The success of any surgical intervention on the liver and bile ducts is totally dependent on a thorough working knowledge of their anatomy. As more and more patients are now being considered for liver resection this anatomy should now be within the understanding of all surgeons with an interest in the gastrointestinal tract. Furthermore, a command of this anatomy is a prerequisite for any interpretation of radiological studies and other imaging of pathology within the liver and biliary system.

When operating on the liver, the surgeon has to obey three basic tenets. First, remove all pathologically involved tissue. Second, preserve the maximal amount of non-pathological liver tissue. Last, perform safe resection without excessive bleeding and impairment of vascularization of the remaining hepatic parenchyma. Similar principles apply to biliary surgery. First, achieve maximal effective drainage of the biliary tree. Second, resect all diseased tissue while protecting and maintaining the vascularity of the residual bile ducts thus allowing successful long term biliary enteric drainage.

**Anatomy of the liver**

Historically, the liver has been described according to its morphological appearance, but hepatic resection is wholly dependent on the functional and surgical anatomy of the liver.
Morphological anatomy

At laparotomy the liver is divided by the umbilical fissure and falciform ligament into a larger ‘right’ lobe and a smaller ‘left’ lobe (Figs 1.1 and 1.2). Situated on the inferior surface of this right lobe is the transverse hilar fissure which constitutes the posterior limit of this lobe. That portion of the right lobe lying anterior to this fissure and to the right of the umbilical fissure is referred to as the quadrate lobe. The right side margin of the quadrate lobe is determined by the gallbladder fossa. Posterior to the hilum, lying between the portal vein and the inferior vena cava (IVC) is the caudate lobe, which is anatomically and functionally separate from the rest of the liver. This anatomical approach is only adequate for left lateral segmentectomy (see below) and is of no use in any other form of liver resection.
Functional anatomy

Francis Glisson of Cambridge first described the segmental anatomy of the liver in 1654, but this work remained largely forgotten for nearly 300 years. In 1888, Rex reported a ‘new’ arrangement of the right and left lobes of the liver and further refined our understanding of lobar anatomy. The modern first attempt to define the functional anatomy of the liver was made by Cantlie in 1898 while working as a pathologist in Hong Kong. Cantlie made a number of dissections of the livers of

Figure 1.4 Venous drainage of the liver.

Figure 1.5 Functional sectoral anatomy and relationship to hepatic scissurae.
condemned prisoners following their execution in a Hong Kong jail. He made vascular casts of the liver to demonstrate that the main lobar fissure is oblique and extends from right to left and from the visceral to the parietal surface at an angle of about 70°. From these studies, Cantlie demonstrated that the main division between the right and left lobe extends from approximately the bed of the gallbladder anteroinferiorly to the right side of the IVC posteroinferiorly (Figs 1.2 and 1.3). Thirty years later, Cantlie’s work was verified by McLndoe and Counsellor and Hjorstjo. In 1939, Ton That Tung described the role of the venous drainage of the liver in relationship to the functional lobar anatomy (Fig. 1.4), and in 1953 Healey and Schroy, while constructing casts of the biliary tree, were able to show that the right lobe was further divided into an anterior and a posterior segment. These studies also demonstrated that the left lobe was divided into a medial and lateral segment by the line of the falciform ligament (Fig. 1.5). From these descriptions, Goldsmith and Woodburne were able to recommend anatomical planes through the liver parenchyma for performing a right lobectomy (right hepatectomy), a left lobectomy (left hepatectomy) and a left lateral segmentectomy (Fig. 1.6).

Early application of the functional anatomy

Although successful surgical treatments of isolated liver wounds had been described in the early seventeenth century by Hildanus and Berta, and subsequent series of battlefield injuries described during the Napoleonic and Franco-Prussian Wars, the first attempt at resection of a liver tumour was not made until 1886 by Luis. In November of that year, he excised a solid liver tumour by ligating and cutting through a pedunculated left lobe ‘adenoma’. Attempts to suture the severed pedicle were unsuccessful, and the stump was returned to the peritoneal cavity. Not surprisingly, the patient succumbed some 6 hours later, after continuing haemorrhage from the stump.

The first successful elective liver resection is attributed to von Langenburch, who excised a 370 g portion of the left lobe of the liver containing an adenoma in 1888. Unfortunately, he had to reopen the abdomen several hours after the operation because of reactionary haemorrhage, but was able to ligate the bleeding vessels and return the oversewn liver to the abdomen. Two years later, the Baltimore surgeon McLane Tiffany reported the successful removal of a benign liver tumour, and the following year Lucke described the successful resection of a cancerous growth of the liver. In 1911, Wendel reported the first case of right lobectomy for a primary tumour, and in 1940 Cattell was first to remove successfully a colorectal hepatic metastasis. In 1943, Wangensteen performed a coincidental partial hepatectomy while performing a gastrectomy for a carcinoma with direct extension into the left lobe of the liver.

The first left lateral segmentectomy was probably performed by Keen in 1899, but because of a lack of understanding of anatomical planes was described as a left hepatic lobectomy. The first anatomically correct description of a left lateral segmentectomy was made by Raven in 1948 while resecting metastatic colon cancer. An anatomical resection was performed in which the triangular and coronary ligaments were divided, and the left portal vein, left hepatic artery and left hepatic ducts were ligated within the hepatoduodenal ligament. The left hepatic vein was then isolated extrahepatically and then divided before the parenchyma was transected. Four years later, Lortat-Jacob and
Robert described a similar approach to right hepatic lobectomy (Fig. 1.6).

**Figure 1.6** Formal hepatectomies: (A) right hepatectomy; (B) left hepatectomy; (C) left lateral segmentectomy; (D) extended left hepatectomy; (E) extended right hepatectomy.
Appreciation of segmental anatomy

Probably the most important anatomical contribution to modern liver surgery comes from the work of Claude Couinaud, who in 1957 published the findings of a large number of vasculobiliary casts made by plastic injection followed by corrosion of the surrounding parenchyma. These studies followed on 5 years after his demonstration of a right paramedian and latero-inferior sectors, which paralleled the work of Healey and Schroy. Couinaud was able to demonstrate that the liver consists of eight segments, each of which can potentially be separately resected. Couinaud redefined the caudate lobe as segment I and Goldsmith and Woodburne’s left lobe as segments II and III. The quadrate lobe is now segment IV and more recently has been further subdivided by its portal blood supply into segments IVA lying superiorly and IVB interiorly. The right liver consists of segments V (anteroinferiorly), VI (posteroinferiorly), VII (posterosuperiorly) and VIII (anterosuperiorly) (Fig. 1.7). Couinaud later suggested a further clarification of the

Figure 1.7 Functional division of the liver and of the liver segments according to Couinaud’s nomenclature: (A) as seen in the patient and (B) in the ex vivo position.
caudate lobe in which the part to the left of the IVC remains segment I and that to the right is redefined as segment IX. 25

Resections based on these segments would minimize residual functional hepatic impairment. The description of Couinaud is the most complete and exact and also the most useful for the operating surgeon, and it is this description which will be used throughout this book.

Resection of segment I usually requires a preliminary left lobectomy to facilitate access and this procedure was first described by Ton That Tun, who was also the first to describe resection of segment VIII. 26 The first description of resection of segment IV was by Caprio in 1931, but in essence this was a resection of the inferior part of what was then the quadrate lobe. 27 Bismuth was first to report isolated resection of segment VI, 28 and in parallel with Ton That Tun described bisegmentectomy of segments VI and VII (right posterior sectorectomy). 26 , 28 Bisegmentectomy of segments V and VI (right inferior hepatectomy) was described in 1955 by Mancuso and colleagues, 29 while in 1957 Couinaud was proposing en bloc resection with the gallbladder of segments IV, V and VI for carcinoma of the gallbladder (Fig. 1.8). 23

The study of the functional anatomy of the liver allows us to describe hepatic segments based upon the distribution of the portal pedicles and the location of the hepatic veins (Fig. 1.5). The three main hepatic veins (right, middle and left) divide the liver into four sectors, each of which receives a portal pedicle of hepatic artery, hepatic duct and portal vein, thus producing an alternation between hepatic veins and portal pedicles. These four sectors demarcated by the hepatic veins are the portal sectors, since each sector receives an independent portal supply. For the same reason, the scissurae containing the hepatic veins are called portal scissurae, while the scissurae containing portal pedicles are the hepatic scissurae (Fig. 1.5). Thus the liver is divided by the main portal scissura along the line of the middle hepatic vein into two discrete hemilivers, the line previously described by Cantlie. 3 We prefer to refer to these hemilivers as right and left livers, rather than right and left lobes, to avoid confusion with the anatomical lobes, particularly since there is no visible surface marking that permits individualization of a true lobe.

As described by Cantlie, the main portal scissura runs posteriorly from the middle of the gallbladder fossa to the right side of the IVC (Fig. 1.5). This scissura describes an angle of 75° with the horizontal plane opened to the left. Therefore, the right and left livers individualized by the main portal scissura are independent as regards their portal and arterial vascularization and biliary drainage.

These right and left livers are both further divided into two by the other two portal scissurae delineated by the right and left hepatic veins. Goldsmith and Woodburne refer to these further divisions as segments, 9 but we will use the more generally accepted nomenclature of Couinaud, which refers to these divisions as sectors. 23 The right liver is divided by the right portal scissura (right portal vein) into an anteromedial (or anterior) sector containing segments V inferiorly and VIII superiorly, and a posterolateral (or posterior) sector containing segments VI inferiorly and VII superiorly (Fig. 1.5). This right portal scissura is inclined 40° to the right (Fig. 1.5). However, when the liver lies in its normal unmobilized position within the upper abdominal cavity, the posterolateral sector
Figure 1.8 Other hepatic sectorectomies: (A) right posterior sectorectomy; (B) right anterior sectorectomy; (C) left medial sectorectomy (segment IVA and IVB); (D) right inferior hepatectomy; (E) right superior hepatectomy.

lies directly behind the anteromedial sector and the scissura is almost in a coronal plane.
Therefore in the clinical setting (particularly when imaging the liver) it is better to speak of the anterior and posterior sectors (Fig. 1.5). The exact location of the right portal scissura is imprecise because it has no external landmarks. According to Couinaud, it extends from the anterior border of the liver at the middle of the distance between the right angle of the liver and the right side of the gallbladder bed to the confluence between the IVC and the right hepatic vein posteriorly. In Ton That Tung’s description of 1939, this scissura follows a line that runs parallel to the right lateral edge of the liver, some three fingers’ breadth anteriorly.

The venous drainage of the right liver is variable in that in addition to the right and middle hepatic veins, there are often a number of smaller hepatic veins draining directly into the IVC from segments VI and VII. Not infrequently (63–68%) segment VI drains directly into the IVC through a large inferior right hepatic vein, which can be a significant bonus in the preservation of residual hepatic function in extended left hepatectomies (Fig. 1.4). Occasionally the middle and left hepatic veins enter the IVC separately and in 2 of 34 of Couinaud’s casts of the middle-left hepatic veins, the middle vein and left veins joined more than 2.5 cm from the IVC. Such an anomaly must be detected and excluded during isolated resection of segment IV, since if not seen and the last 2 cm of the left vein is damaged, then segments II and III will be needlessly sacrificed.

The left portal scissura, along the left hepatic vein, divides the left liver into an anterior sector containing segments III laterally and IV medially, and a posterior sector containing segment II (Fig. 1.5). Note that the left portal scissura is not the umbilical fissure since this fissure is not a portal scissura; a portal scissura contains a hepatic vein and the umbilical fissure contains a portal pedicle. Therefore the left portal scissura lies posteriorly to the ligamentum teres inside the left lobe of the liver (Fig. 1.5). It is important to note that the middle hepatic vein (defining the main portal scissura) usually enters the left hepatic vein some 1–2 cm before the left hepatic vein joins the IVC (Fig. 1.4). Occasionally the middle and left hepatic veins enter the IVC separately and in 2 of 34 of Couinaud’s casts of the middle-left hepatic veins, the middle vein and left veins joined more than 2.5 cm from the IVC. Such an anomaly must be detected and excluded during isolated resection of segment IV, since if not seen and the last 2 cm of the left vein is damaged, then segments II and III will be needlessly sacrificed.

The caudate lobe (segment I or segments I and IX) is the dorsal portion of the liver lying posteriorly and surrounding the retrohepatic IVC. As a result it lies directly between the portal vein lying anteriorly and the IVC posteriorly. The main bulk of the caudate lobe lies to the left of the IVC, with its left and inferior margins being free in the lesser omental bursa (Fig. 1.2). The gastrohepatic (lesser) omentum separates the left portion of the caudate from segments II and III of the left liver as it passes between them to be attached to the ligamentum venosum. The left portion of the caudate lobe thus traverses inferiorly to the right between the left portal vein and the IVC as the caudate process, which then fuses inferiorly with segment VI of the right liver. This portion of the caudate lobe that lies on the right side is variable but usually small. The anterior surface of the caudate lobe lies within the hepatic parenchyma against the posterior intrahepatic surface of segment IV, demarcated by an oblique plane slanting from the left portal vein to the left hepatic vein.

The caudate lobe must be considered from a functional viewpoint as an isolated autonomous segment, since its vascularization is independent of the portal division and of the three main hepatic veins. It receives both an arterial and a portal blood supply from both the right and left portal structures and this is variable, although the right caudate lobe receives an arterial supply consistently from the right posterior artery. Biliary
drainage is likewise into both the right and left hepatic ducts. However, the left dorsal duct can also join the segment II duct. The small hepatic veins of the caudate lobe drain directly into the IVC. This independent isolation of the caudate lobe is clinically important in BuddChiari syndrome, if all three main hepatic veins are obliterated and the only hepatic venous drainage is through the caudate lobe, which then undergoes compensatory hyperplasia.

Anatomical classification of hepatectomies

We would classify these as ‘typical’ and ‘atypical’. Typical hepatectomies (hepatectomies reglees) are defined by resection of a portion of liver parenchyma following one or several anatomical portal or hepatic scissuræ. These resections are called left or right hepatectomies, sectorectomies and segmentectomies. Atypical hepatectomies involve resection of a portion of hepatic parenchyma not limited by anatomical scissuræ. Such resections are usually inappropriate as they will leave behind devascularized residual liver and will probably also not adequately excise all the pathologically involved parenchyma.

The usual typical hepatectomies can be considered in two groups. First, right and left hepatectomies in which the line of transection is the main portal scissura separating the right and left livers along the middle hepatic vein (as proposed by Couinaud). 23 Second, right and left hepatectomies in which the line of transection commences in the umbilical fissure. For some time the latter definition, proposed by Goldsmith and Woodburne, 9 has been the accepted convention in the Anglo-Saxon literature. We prefer to use the definition of Couinaud, since segment IV (quadrate lobe) is anatomically part of the left liver (Fig. 1.9) and therefore right hepatectomy consists of the resection of segments V, VI, VII and VIII. Left hepatectomy is the removal of segments II, III and IV (Fig. 1.6). In certain pathologies (multiple liver metastases or large tumours transgressing the main portal scissura) hepatectomies can be extended

Figure 1.9 Completion of segment IV resection with portal bifurcation lying inferiorly in front of the inferior vena cava.

to include adjacent segments and sectors of the other liver. Therefore extended right
Hepatectomy will also include resection of segment IV, taking portal structures to the right of the falciform ligament (which Goldsmith and Woodburne describe as a right hepatic lobectomy)⁹ (Fig. 1.6). Similarly, extended left hepatectomy would include resection of segments V and VIII en bloc with segments II, III and IV (Fig. 1.6).

Using this functional approach to liver anatomy, there are numerous other potential liver resections.²⁸ Individual segments can be resected in isolation or in adjacent pairs depending upon the distribution of pathology. This includes complete resection of segment IV, which leaves segments II and III in complete isolation from the right liver (Fig. 1.8). One area of confusion in the definitions of hepatectomies comes in the simultaneous resection of segments II and III (Fig. 1.10). Goldsmith and Woodburne describe this procedure as a left hepatic lobectomy.⁹ However, left lateral segmentectomy is by technical definition wrong since the true left lateral segment (and sector) comprises no more than segment II. However, it is now accepted convention that resection of segments II and III is regarded as a left lateral segmentectomy.

Sectorectomies of the right liver are easier to define. Resection of segments V and VIII between the main portal scissura (middle hepatic vein) and right portal scissura (right portal vein) on their pedicle of the anterior division of the right portal vein is defined as a right anterior sectorectomy, while resection of segments VI and VII posterior to the right portal scissura (on the pedicle of the posterior division of the right portal vein) is a right posterior sectorectomy (Fig. 1.8). Similarly, segments V and VI can be resected en bloc (right inferior hepatectomy) and if there is a significant right inferior hepatic vein draining segments V and VI, then segments VII and VIII can be resected with the right hepatic vein (right superior hepatectomy) (Fig. 1.8).

**Figure 1.10** Left lateral segmentectomy immediately prior to division of the portal structure lying inferiorly and the left hepatic vein lying superiorly.

draining segments V and VI, then segments VII and VIII can be resected with the right hepatic vein (right superior hepatectomy) (Fig. 1.8).

**Surgical approach to the caudate lobe (dorsal sector)**

This is initially achieved by dissection of the coronary ligament up to the right of the IVC, but avoiding the right hepatic vein. The falciform ligament is then dissected to the IVC and the lesser omentum incised close to the liver. Opening the left coronary ligament
allows ligation of the inferior phrenic vein. The caudate veins to the IVC are now exposed and can be divided between ligatures as they run up the back of the caudate lobe. After the hilar plate is lowered to expose the right and left portal pedicles, the portal inflow to both the right and left caudate segments can be identified, ligated and divided. The caudate lobe is now isolated and the main portal fissure is divided to separate segments IV, VII and VIII. However, the caudate segment is not defined macroscopically from segment VI.

The biliary tract

Accurate biliary exposure and precise dissection are the two most important steps in any biliary operative procedure and are both totally dependent on a thorough anatomical understanding of these structures. Several authors have thoroughly described the anatomy of the biliary tract, but unfortunately the surgical implications have been incompletely described and continue to be misunderstood by many surgeons.

Figure 1.11 Exposing the hilar plate by raising the inferior surface of segment IVB, thus demonstrating the condensation of Glisson’s capsule which will cover the extra hepatic confluence of the right and left hepatic ducts.

Intrahepatic bile duct anatomy

The right liver and left liver are respectively drained by the right and the left hepatic ducts, whereas the caudate lobe is drained by several ducts joining both the right and left hepatic ducts. The intrahepatic ducts are tributaries of the corresponding hepatic ducts which form part of the major portal tracts invaginating Glisson’s capsule at the hilus and penetrating the liver parenchyma (Fig. 1.11). There is variation in the anatomy of all three components of the portal triad structures, hepatic ducts, hepatic arteries and portal vein, but the latter of these shows the least anatomical variability. In particular, the left portal vein tends to be consistent in location. Bile ducts are usually located above the portal vein whereas the corresponding artery will lie below. Each branch of the intrahepatic portal vein corresponds to one or two intrahepatic bile ducts which converge
outside the liver to form the right and left hepatic ducts, in turn joining to form the common hepatic duct.

The left liver is divided between segments III and IV by the umbilical fissure, although this division may be bridged by a tongue of liver parenchyma of varying depth. The ligamentum teres passes through this umbilical fissure to join the left portal vein within the recessus of Rex (Figs 1.12 and 1.13). However, all these biliary and vascular elements are liable to anatomical variation. The left hepatic duct drains segments II, III and IV which constitute the left liver. The duct draining segment III is found a little behind the left horn of the umbilical recess, from where it passes directly posteriorly to join the segment II duct to the left of the main portal branch to segment II. At this point the left branch of the portal vein turns forward and caudally in the recessus of Rex (Fig. 1.14).

As the duct draining segment

Figure 1.12 Exposing the recessus of Rex by distraction of the falciform ligament to demonstrate the bifurcation of segment III and segment IV bile ducts.

Figure 1.13 Demonstration of the right hepatic duct lying within the gallbladder fossa.
Figure 1.14 Biliary and vascular anatomy of the left liver. Note the position of segment III duct above the corresponding vein and its relationship to the recessus of Rex.

Figure 1.15 Biliary and vascular anatomy of the right liver. Note the horizontal course of the posterior sectoral duct and the vertical course of the anterior sectoral duct.

III begins its posterior course it lies superficially in the umbilical fissure, often immediately under Glisson’s capsule. As such it is usually easily accessible at surgery to allow a biliary-enteric (segment III hepaticojejunostomy) anastomosis for biliary drainage if such access is not possible at the porta hepatis. The left hepatic duct then
passes beneath the left liver at the posterior base of segment IV, lying just above and behind the left branch of the portal vein. After the left duct crosses the anterior edge of that vein it joins the right hepatic duct to form the common duct at the hepatic ductal confluence. In this transverse portion, where it lies below the liver parenchyma, it receives one to three small branches from segment IV. 23

The right hepatic duct drains segments V, VI, VII and VIII and arises from the convergence of the two main sectoral (anterior V and VIII and posterior VI and VII) tributaries. The right posterior sectoral duct runs almost horizontally 26 and comprises the confluence of the ducts from segments VI and VII (Fig. 1.15). The posterior duct joins the anterior sectoral duct (formed by the confluence of the ducts from segments V and VIII) as it descends vertically. 26 This anterior sectoral duct lies to the left of the right anterior sectoral branch of the intrahepatic portal vein as it ascends within the parenchyma (Fig. 1.15). The junction of the two main right biliary ducts usually occurs immediately above the right branch of the portal vein. 23 The right hepatic duct is considerably shorter than its counterpart on the left, which it joins to form the common hepatic duct in front of the right portal vein (Fig. 1.15).

The caudate lobe (segment I) has its own separate biliary drainage. This segment comprises two anatomically and functionally distinct portions, a caudate lobe proper (which consists of a right and left part) located at the posterior aspect of the liver and a caudate process passing behind the portal structures to fuse with the right liver. In nearly half of individuals, three separate bile ducts drain these distinct parts, while in a quarter of individuals there is a common bile duct between the right portion of the caudate lobe proper and the caudate process, while the left part of the caudate lobe is drained by an independent duct. However, the site of drainage of these ducts is variable. In over three-quarters of individuals, the caudate lobe drains bile into both the right and left hepatic ducts, but in the rest, the caudate lobe drains exclusively into the left (15%) or right (7%) hepatic duct. Many authors now advocate en bloc resection of the caudate lobe during resection of hilar cholangiocarcinoma, 31 since the tumour usually infiltrates these ducts draining the caudate lobe. Certainly these authors have demonstrated that in 88% of cases of hilar cholangiocarcinoma coming to resection there is histological evidence of tumour infiltration of the caudate lobe along these ducts.

**Extrahepatic biliary anatomy**

The detail of this section will be confined to the upper part of the extrahepatic biliary tree, above the common bile duct, since the common bile duct is also covered in Chapter 2. The right and left hepatic ducts converge at the right of the hilum of the liver, anterior to the portal venous bifurcation and overlying the origin of the right portal vein. The biliary confluence is separated from the posterior aspect of the base of segment IV by a fusion of connective tissue investing from Glisson’s capsule to form the fibrous hilar plate. This hilar plate has no vascular interposition and, when opened behind the posterior aspect of the base of segment IV, will display the extrahepatic confluence of the right and left hepatic ducts (Fig. 1.16).
Figure 1.16 Demonstration of the relationship between the posterior aspect of the base of segment IV and the biliary confluence. Note the extension of Glisson’s capsule to invest the portal structures at the hilum (hilar plate) and extending over the hepatic surface of the gallbladder (cystic plate). Exposure of the extrahepatic left hepatic duct is achieved by incising the hilar plate at the base of segment IV medially as far as the umbilical fissure.

The main bile duct is divided into its upper part, the common hepatic duct, and lower part, the common bile duct, by the entry of the cystic duct from the gallbladder. This point of entry is widely variable. The main bile duct normally has a diameter of 6 mm and passes downwards anterior to the portal vein in the right free border of the lesser omentum. The bile duct is closely related to the hepatic artery as it runs upwards on its left side before dividing into its left and right branches, the right hepatic artery usually passing posteriorly to the bile duct. The cystic artery which usually arises from the right hepatic artery crosses the common hepatic duct as frequently anteriorly as it does posteriorly (Figs 1.17 and 1.18).

Calot’s triangle was originally defined by the common hepatic duct lying medially, inferiorly by the cystic duct and superiorly by the cystic artery. However, the usually accepted surgical definition of Calot’s triangle defines the upper border as the inferior surface of the liver. The junction of the cystic duct and common hepatic duct varies widely and may even occur behind the pancreas. The retropancreatic portion of the bile duct approaches the duodenum obliquely, accompanied by the terminal part of the duct of Wirsung (see Chapter 2). These two ducts join to enter the duodenum through the sphincter of Oddi at the papilla of Vater.
Figure 1.17 Anterior aspect of biliary anatomy. Note the hepatic duct confluence anterior to the right hepatic artery and origin of the right portal vein. Note also the course of the cystic artery, arising from the right hepatic artery and passing posteriorly to the common hepatic duct.

The gallbladder lies within the cystic fossa on the underside of the liver in the main liver scissura at the junction between the right and left livers. It is separated from the hepatic parenchyma by the cystic plate, which is an extension of connective tissue from the hilar plate (described previously). The relationship of the gallbladder to the liver ranges from hanging by a loose peritoneal reflection to being deeply embedded within the liver substance. The gallbladder varies in size and consists of a neck, body and fundus which usually reaches the free edge of the liver, still closely applied to the cystic plate. Large gallstones impacting within the neck of the gallbladder may create a Hartmann’s pouch, and inflammation secondary to this can obscure the anatomical plane between the gallbladder and the common hepatic duct leading to damage of the latter during cholecystectomy. Other structures similarly threatened during this manoeuvre include the right hepatic artery and occasionally the right hepatic duct.

The cystic duct arises from the neck of the gallbladder and descends to join the common hepatic duct in its supraduodenal course in 80% of people. Its length varies widely but its lumen is usually between 1 and 3 mm. The mucosa of the cystic duct is arranged in spiral folds (valves of Heister). In a small number of cases the cystic duct joins the right hepatic duct or a right hepatic sectoral duct.
Figure 1.18 The eight most common variations in the anatomy of the arterial supply (cystic artery) to the gallbladder.

Figure 1.19 (A) Venous drainage of the gallbladder. (B) The lymphatic drainage of the gallbladder towards the coeliac axis.
Gallbladder and cystic duct

The gallbladder receives its blood supply by the cystic artery, the anatomy of which varies widely (Fig. 1.18). The most common variant arises directly from the right hepatic artery and then divides into an anterior and posterior branch. The venous drainage of the gallbladder is directly through the gallbladder fossa to the portal vein in segment V (Fig. 1.19).

Biliary ductal anomalies

The biliary anatomy described above, comprising a right and left hepatic duct joining to form a common hepatic duct occurs in between 57% \( ^{23} \) and 72% \( ^{8} \) of cases. This variance may be because Couinaud \( ^{23} \) specifically identified a triple confluence of right posterior sectoral duct, right anterior sectoral duct and left hepatic duct in 12% of cases, which Healey and Schroy do not describe. Furthermore, Couinaud also describes a right sectoral duct joining the main bile duct in 20% of individuals (right anterior sectoral in 16%, right posterior sectoral in 4%). In addition, a right sectoral duct (posterior in 5%, anterior in 1%) may join the left hepatic duct in 6% of cases. In 3% of cases there is an absence of a defined hepatic duct confluence with all the sectoral ducts joining separately and in 2% the right posterior sectoral duct may join the neck of the gallbladder or be entered by the cystic duct \( ^{23} \) (Fig. 1.20).

Similarly, there are common variations of the intrahepatic biliary anatomy. Healey and Schroy \( ^{8} \) describe the classical intrahepatic biliary arrangement (described above) in 67% of cases, with ectopic drainage of segment V in 9%, segment VI in 14% and segment VIII in 20% of cases. In addition, they describe a subvesical duct in 20–50% of cases. \( ^{8} , ^{37} \) This subvesical duct may lie deeply embedded in the cystic plate and can join either the common or right hepatic ducts. This duct does not drain any specific area of the liver and never communicates with the gallbladder, but may be damaged during cholecystectomy and therefore contribute to postoperative biliary leak. On the left side the commonest anomaly is a common union of segment III and IV ducts in 25% of cases, and in only 2% does the segment IV duct independently join the common hepatic duct (Fig. 1.21).

Anomalies of the accessory biliary apparatus

Gross described a number of anomalies of the accessory biliary apparatus in 1936. \( ^{38} \) These include bilobed and duplicated gallbladder, \( ^{39} , ^{40} \) septum and diverticulum of the gallbladder and variations in cystic duct anatomy including a double cystic duct. \( ^{41} \) More rare is agenesis of the gallbladder \( ^{42} , ^{43} \) (Fig. 1.22). Furthermore, the gallbladder may be abnormally positioned, either lying deep within the liver parenchyma or lying under the left liver. \( ^{44} \)
Figure 1.20 Main variations of the hepatic duct
Figure 1.21 Variations of the intrahepatic biliary confluence. anatomy.
Figure 1.22 Main variations in gallbladder and cystic duct anatomy: (A) bilobed gallbladder; (B) septum of gallbladder; (C) diverticulum of gallbladder; (D) variations in cystic duct anatomy.

Figure 1.23 Different types of union of the cystic duct and common hepatic duct: (A) angular (75%); (B) parallel (20%); (C) spiral (5%).

The union of the cystic duct with the common hepatic duct may be angular, parallel or spiral. The most frequent union is angular (75%), while the cystic duct may run parallel with the hepatic duct in 20%, both encased in connective tissue. In 5% of cases the cystic duct may approach the hepatic duct in a spiral fashion, usually passing posteriorly to the common hepatic duct before entering on its left side (Fig. 1.23).
The arterial blood supply of the liver and bile ducts

The hepatic artery

The hepatic artery usually arises as one of the three named branches of the coeliac trunk along with the left gastric and splenic arteries (Fig. 1.24). The first named branch of the hepatic artery is the gastroduodenal artery and either of these arteries may then give rise to the right gastric and retroduodenal arteries (Fig. 1.24). The hepatic artery then divides into right (giving rise to the cystic artery) and left hepatic arteries. This arrangement holds true for 50% of cases.

Figure 1.24 (A) The biliary duct blood supply; (B) conventional arterial anatomy of the liver (50%).
In nearly 25% of cases the right hepatic artery arises separately from the superior mesenteric artery, indicative of the joint fore and midgut origin of the liver (Fig. 1.25), and in nearly another 25% of cases the left hepatic artery arises from the left gastric artery. In a small number of people other variations of these arrangements will occur (Fig. 1.25). However, these variations will be readily apparent to an experienced surgeon at operation and the authors do not advocate preoperative visceral angiography to delineate these anomalies before routine hepatectomy.

**The blood supply of the extrahepatic biliary apparatus**

The extrahepatic biliary system receives a rich arterial blood supply, which is divided into three sections. The hilar section receive arterioles directly from their related hepatic arteries and these form a rich plexus with arterioles from the supraduodenal section. The
blood supply of the supraduodenal section is predominantly axial, most vessels to this section arising from the retroduodenal artery, the right hepatic artery, the cystic artery, the gastroduodenal artery and the retroportal artery. Usually, eight small arteries, each 0.3 mm in diameter, supply the supraduodenal section. The most important of these vessels run along the lateral borders of the duct and are referred to as the 3 o’clock and 9 o’clock arteries. Of the arteries supplying the supraduodenal section, 60% run upwards from the major inferior vessels while 38% run downwards from the right hepatic artery. Only 2% are non-axial, arising directly from the main trunk of the hepatic artery as it runs parallel to the bile duct. The retropancreatic section of the bile duct receives its blood supply from the retroduodenal artery.

The veins draining the bile duct mirror the arteries and also drain the gallbladder. This venous drainage does not enter the portal vein directly but seems to have its own portal venous pathway to the liver parenchyma. 

It has been proposed that arterial damage during cholecystectomy may result in ischaemia leading to postoperative stricture of the bile duct, although it seems unlikely that ischaemia is the major mechanism in the causation of bile duct stricture after cholecystectomy. Although intraoperative ultrasound has made easier the location of dilated intrahepatic biliary radicals, surgical exposure of the extrahepatic biliary confluence and the segment III duct demands knowledge of precise anatomical landmarks. Biliary-enteric anastomosis necessitates precise bile duct exposure to facilitate the construction of a mucosa to mucosa apposition.

To expose the extrahepatic biliary confluence, the base of the quadrate lobe (segment IV) is lifted upwards and Glisson’s capsule is incised at its base (see Fig. 1.16). This technique is also sometimes referred to as lowering the hilar plate. In only 1% of cases is this made difficult by any vascular imposition between the hilar plate and the inferior aspect of the liver. This manoeuvre will expose considerably more of the left hepatic duct than the right, which runs a shorter extrahepatic course. Contraindications to this approach include patients with a very deep hilum which is displaced upwards and rotated laterally, and those patients who have undergone removal or atrophy of either the right or left livers resulting in hilar rotation. In this situation the bile duct may come to lie behind the portal vein.
The anatomy of biliary exposure

When approaching the segment III duct (segment III hepaticojejunostomy), follow the round ligament (in which runs the remnant of the obliterated umbilical veins) through the umbilical fissure to the point where it connects with the left branch of the portal vein within the recessus of Rex. This junction may sometimes be deeply embedded within the parenchyma of the fissure. The bile ducts of the left liver are located above the left branch of the portal vein, whereas the corresponding arteries lie below the portal vein. Dissection of the round ligament on its left side allows exposure of either the pedicle or anterior branch of the duct from segment III. This is achieved by mobilizing the round ligament and pulling it downwards, thereby freeing it from the depths of the umbilical fissure. This procedure usually requires the preliminary division of the bridge of liver tissue which runs between the inferior parts of segments III and IV. The umbilical fissure is then opened and with downward traction of the ligamentum teres an anterior branch of the segment III duct is exposed on its left side.

Sometimes it may be necessary to perform a superficial liver split to gain access to this duct. In the usual situation of chronic biliary obstruction with dilatation of the
intrahepatic bile ducts, the segment III duct is generally easily located above the left branch of the portal vein. However, in the situation of left liver hypertrophy, it may be necessary to perform a more extensive liver split to the left of the umbilical fissure in order to widen the fissure to achieve adequate access to the biliary system.

Access to the right liver system is less readily achieved than to the left as the anatomy is more imprecise. However, intraoperative ultrasonography greatly enhances the ability of the surgeon to locate these ducts at surgery. The ideal approach on the right side is to the segment V duct, \(^{52}\) which runs on the left side of its corresponding portal vein. \(^{23}\) The duct is exposed by splitting the liver over a short distance to the right of the gallbladder fossa, commencing at the right side of the porta hepatis. The segment V duct should lie relatively superficially on the left aspect of the portal vein to that segment.

**Key points**

- A full understanding of the lobar, sectoral and segmental anatomy of the liver and biliary system is an essential prerequisite for successful liver surgery.
- The surgeon must appreciate the wide variation in extrahepatic biliary anatomy.

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Microanatomy

Exocrine

The acinus is the secretory unit for digestive enzymes. The glandular or acinar cells of the pancreas form the major part of the lining of the acini and are the most abundant cells within the exocrine lobule (Fig. 2.1). The acinar cells are pyramidal in shape and contain prominent endoplasmic reticulum, golgi apparatus and zymogen granules which correspond to their main function of digestive enzyme secretion. These cells are interspersed with epithelial cells which are cuboidal or flat and are termed centroacinar cells. The epithelial cell lined ductules drain the acini and coalesce to form intralobular and interlobular ducts. The epithelial cells lining the centroacinar and interlobular ducts are flat and have interdigitating lateral basement membranes. This structure corresponds to their function of fluid and ion transport including the secretion of bicarbonate. The interlobular ducts are lined by pyramidal cells with microvilli and mucoprotein containing secretory granules. The main pancreatic duct is lined by columnar cells interspersed with goblet cells.
Endocrine

Pancreatic islet cells make up only 2% of the weight of the pancreas but receive 20% of its blood flow. The islets of Langerhans are essentially clumps of hormone secreting cells, including 25% \( \alpha \) cells, 60–80% \( \beta \) cells and 15% \( \delta \) cells. These proportions vary within the regions of the pancreas, for example the majority of \( \beta \) cells are located within the tail. Within each islet the \( \beta \) cells lie centrally, the \( \delta \) cells surround these and the \( \alpha \) cells lie at the perimeter. The portal drainage of the islets is arranged such that the acinar cells have greater contact with this draining blood than does any other cell in the body. Acinar cells in the peri-insular regions are larger and have more insulin receptors. This structure is thought to reflect an interaction between the endocrine and exocrine systems.

Ductal anatomy

A brief review of the embryology of the pancreas is required for an understanding of normal ductal anatomy and its variants. The pancreas begins as dorsal and ventral buds arising from the duodenum, each with its own duct. The ventral bud rotates posteriorly and to the left to become the uncinate process, while the dorsal bud becomes the head, body and tail (Fig. 2.2). The dorsal and ventral ducts carry the eponyms Santorini and Wirsung, respectively. In 70% of the cases these two ducts fuse and the connection of both ducts to the duodenum disappears (see Fig. 2.3A). In these cases the

![Figure 2.2 Embryology of the pancreas: position of pancreatic ducts before fusion and after rotation.](Image 121x198 to 311x326)
Figure 2.3 Variations in the pancreatic ducts: (A) Normal configuration (60% of population): major and minor ducts empty into duodenum through the major and minor papilla respectively—connection between ducts is maintained. (B) The accessory duct is suppressed and loses its connection to the duodenum (30% of population). (C) The main duct is suppressed and loses its connection to the accessory duct (pancreas divisum: 10% of population).

opening of the dorsal duct of Santorini into the duodenum is termed the minor papilla (Fig. 2.3A). When this is combined with failure of fusion of the two ducts, the situation is termed pancreas divisum (Fig. 2.3C). The other variations of ductal anatomy include either the suppression or the absence of the accessory or dorsal duct. The exact incidence of these variants is unknown, but they are thought to be present in between 15% and 30% of the population. The incidence of pancreas divisum is higher in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) for idiopathic pancreatitis, but whether pancreas divisum is aetiologic in this condition remains controversial.

The relationship of the main pancreatic duct and common bile duct is also variable. The two join to form a common channel within the wall of the duodenum in the majority of normal subjects (see Fig. 2.2). This is because the ventral pancreatic duct originates as a branch of the bile duct embryologically (Fig. 2.4C). The common channel is termed the ampulla of Vater. This common channel has been shown to be longer (>5 mm) in patients who have had acute pancreatitis. In these patients this anatomical situation is associated with reflux of bile from the bile duct into the pancreatic duct. The pancreatic duct of such patients has also been found to sit at a wider angle in relation to the bile duct.
and tends to have a greater diameter, although this latter finding may well be secondary to the pathological process. In a smaller percentage of patients the common channel is completely resorbed into the duodenal wall, resulting in separate openings of the pancreatic duct and bile duct into the duodenum. In each of these configurations both ducts or their common channel are surrounded in their most distal extent by a muscular sphincter termed the sphincter of Oddi. This circular smooth muscle is of a variable length of 6 to 30 mm and lies largely within the duodenal wall. It is, in fact, a sphincter complex made up of four different sphincters: the sphincter pancreaticus encircling the pancreatic duct, the superior and inferior choledochal sphincters around the bile duct and the sphincter ampullae around the ampulla. It is this muscle which must be divided during endoscopic sphincterotomy or surgical sphincteroplasty. The bulge seen at the papilla is due to these fibres.

The relationship of the distal common bile duct to the head of the pancreas is also variable. It most commonly lies within the pancreatic tissue, but may also lie posteriorly within a groove in the pancreatic tissue. There are multiple variations between these extremes, including cases where the duct is intrapancreatic superiorly but lies extrapancreatic distally before joining the pancreatic duct and duodenum.

The dimensions of the main pancreatic duct have been defined in ERCP studies by several authors. Its length varies from 175 to 275 mm. The diameter is greatest in the pancreatic head at 3 to 4 mm and

![Figure 2.4A](image-url) Normal pancreatic duct as seen at ERCP.
decreases to 1 to 2 mm in the tail. A gradual increase in ductal diameter occurs with age. A natural narrowing may be present at the point of fusion of the ventral and dorsal ducts. Knowledge of normal ductal dimensions is helpful in identifying pathological states such as small tumours in the head of the gland, intraductal tumours and chronic pancreatitis. The normal pancreatic duct is smooth and tapered with side branches that are also smooth and tapered. Shortening, irregularity or dilatation of these ducts correlates with disease states such as chronic pancreatitis. Evidence from endoscopic ultrasound studies indicates that changes in the ducts are preceded by morphological changes within the pancreatic parenchyma. The main ultrasonographic features of these parenchymal changes are alternating echo-poor and echo-rich areas and an irregular pancreatic margin rather than the usual uniform echogenicity and smooth margin.
Vascular anatomy

**Venous anatomy of the pancreas and duodenum**

Attention to the portal venous system in and around the pancreas is the most important aspect in preventing blood loss during pancreatic surgery (Fig. 2.5). These high flow vessels are situated in awkward positions and if they are torn the application of proximal and distal vascular control is often neither advisable nor possible.

The portal vein itself can be further defined as the hepatic portal vein and the pancreatic portal vein. The latter runs behind the neck of the pancreas and

![Venous anatomy of the head of the pancreas.](image)

the former extends from the superior border of the pancreas to its bifurcation into the right and left portal vein branches. The pancreatic portal vein sits within a groove in the back of the gland. This groove may be further accentuated by the presence of a tumour within the head of the pancreas. It is formed from the confluence of the splenic and superior mesenteric veins. The inferior mesenteric vein may also contribute to this junction, although it classically joins the splenic vein and occasionally joins the superior mesenteric vein directly. Ligation of the inferior mesenteric vein is often a necessary step in mobilization of the body and tail of the pancreas. The venous drainage of the head of the pancreas and duodenum is via an anterior and a posterior arcade termed the anterior superior and inferior pancreaticoduodenal veins (ASPD-V and AIPD-V) and the posterior superior and inferior pancreaticoduodenal veins (PSPD-V and PIPD-V). It is important to recognize the common sites at which these vessels join the portal vein when performing a resection of the pancreatic head. The posterior superior vein commonly drains directly into the portal vein near the superior border of the pancreas after crossing anterior to the bile duct. 13 The anterior superior vein drains directly into the loop of Henle, or gastrocolic trunk. This latter vessel is both a common landmark and a source of trouble if
not dealt with carefully. It is formed by the confluence of the right gastroepiploic vein and an unnamed middle colic vein. It joins the superior mesenteric vein just below the neck of the pancreas. Ligation of the gastroepiploic vein near this junction facilitates exposure of the superior mesenteric vein and pancreatic portal vein. Some studies seem to indicate that an anterior superior vein may not be present in all cases and that venous drainage in the corresponding region is directly into the gastrocolic trunk. Both the anterior and posterior inferior veins drain directly into the first jejunal tributary to the SMV after it passes posterior to the SMV itself, although an anterior inferior vein is not always identified.

**Arterial anatomy**

The arterial supply to the head of the pancreas is through an anterior and a posterior arcade. The anterior superior and posterior superior arteries arise from the gastroduodenal artery (GDA), the posterior being the last branch after the right gastroepiploic artery. The gastroduodenal in turn is a branch of the common hepatic artery and arises within the porta hepatis, where it marks the transition to the hepatic artery proper. It runs in the same general direction as the latter vessel, but when viewed from behind the mobilized and anteriorly retracted pylorus appears to run transversely. Ligation of the gastroduodenal artery is a necessary step for pancreaticoduodenectomy and can be helpful in controlling bleeding from difficult duodenal ulcers. The right gastric artery is the first branch of the hepatic artery proper, but often appears to arise at the same point as the GDA and runs in the same general direction as the GDA, and can therefore sometimes be confused with it. According to some authors, preservation of the right gastric artery is crucial during a pylorus preserving pancreatico-duodenectomy. Some surgeons, however, do not preserve it on the basis that its preservation may not allow adequate lymph node clearance.

The anterior and posterior inferior pancreaticoduodenal arteries form the inferior blood supply to the head of the pancreas and duodenum. They arise either as a single trunk or separately directly from the superior mesenteric artery. The anterior arcade follows the course of the duodenal wall, passing posterior to the inferior pancreatic head as it overhangs the duodenum. The posterior arcade passes anterior to the common bile duct before it enters the pancreas and follows the margin of the head of pancreas posteriorly. It is relatively easy to detach from the pancreatic head.

The most frequent arterial anatomical variant related to the head of the pancreas is a replaced or accessory right hepatic artery arising from the superior mesenteric artery (25% of the population) (Fig. 2.6A). In 2–4.5% of cases, the main hepatic artery arises aberrantly from this position and its branches therefore arise behind the pancreas and pass to the liver posterior to the portal vein (Fig. 2.6B). Much more rarely, an aberrant left hepatic can arise from the superior mesenteric artery (SMA) (Fig. 2.6C). The presence of one of these variations, such as a left hepatic artery arising from the left gastric artery, makes the presence of another more likely. The pulse of an accessory or replaced right hepatic can normally be palpated in the porta hepatis posterior to the bile duct. Failure to identify such a vessel can result in ligation of part of the hepatic blood supply during pancreaticoduodenectomy.
With respect to the identification of vascular variants, some surgeons have advocated preoperative angiography. However, angiography can be misleading. Trede reports examples of its failure to demonstrate an accessory right hepatic artery and points out that when such an artery is identified its position anterior to, posterior to or within the head of the pancreas cannot be ascertained. Angiography can also identify vascular abnormalities which may not be significant. One example is atherosclerotic stenosis of the coeliac axis. Very rarely this condition can be associated with collateral blood flow to the liver provided by the superior mesenteric artery through the pancreaticoduodenal arcade, thus precluding pancreaticoduodenectomy. However, this rare situation can be identified intraoperatively when blood flow to the liver ceases upon temporary occlusion of the gastroduodenal artery.

The blood supply to the body and tail of the pancreas is through a number of collateral branches running posteriorly to the pancreas arising principally from the dorsal pancreatic artery. The origin of this artery is variable, arising from the splenic artery in 38%, directly from the coeliac trunk in 22%, the common hepatic in 22%, the superior mesenteric artery in 12.7% and the gastroduodenal artery in 5%. The splenic artery...
also gives rise separately to a caudal pancreatic artery.

Nerve supply to the pancreas

The pancreas receives both sympathetic and parasympathetic input. The parasympathetic input to the pancreas is by way of vagal fibres passing through the right and left coeliac ganglia which are situated adjacent to the coeliac axis. The sympathetic input is from the greater and lesser splanchnic nerves which are formed by branches from the T4 through T10 and T9 through L2 sympathetic ganglia, respectively. These then synapse in the coeliac plexus and ganglia. Sympathetic and parasympathetic fibres then enter the pancreas by several routes. The supply to the pancreatic head is by way of the plexus pancreaticus capitalis I, which runs directly from the right coeliac ganglion to the posterior pancreatic head, the plexus pancreaticus capitalis II, which runs from both coeliac ganglia to the left margin of the uncinate process by way of the plexus surrounding the superior mesenteric artery, and through the plexus surrounding the common hepatic artery and the gastroduodenal artery to the anterior region of the head of the pancreas. The supply to the body and tail is from the left coeliac ganglion via the plexus associated with the splenic artery and directly from the left ganglion and coeliac plexus to the posterior body.

The significance of the nerve supply clinically is in the relationship to the control of endocrine and exocrine function, to the perineural spread of pancreatic malignancies and to strategies for the control of the pain of chronic pancreatitis and pancreatic malignancy. The parasympathetic nerves along the arteries enter the pancreatic parenchyma along with the arteries and end on intrinsic ganglia which lie near the parenchyma, in keeping with their role in stimulating secretion of pancreatic juice. Parasympathetic afferents provide feedback through the same routes. The sympathetic fibres also enter the pancreas with the arterial branches. They are distributed to the vascular plexus and the islets. With regard to pain control, the approach used has been the destruction of the splanchnic nerves, either within the thorax where they are formed from the sympathetic chain or by way of ablation within the abdomen as they enter through the hiatus and the horn of the semilunar ganglia. The right and left semilunar ganglia are located in the retroperitoneum, the left lying caudal to the splenic artery and the renal vein with the aorta to the right and the left adrenal to the left, the right lying anterior to the aorta superior to the left renal vein.

Anatomy in relation to surgical access

Relations and attachments of the pancreas and duodenum

The pancreas is a retroperitoneal structure (Fig. 2.7). The head of the pancreas is defined as that portion to the right of the left border of the superior mesenteric and portal vein. It sits within the loop of the
duodenum, by which it is partly covered anteriorly. The uncinate process is the extension of the head posterior to the portal vein and superior mesenteric artery and normally lies caudal to the pancreatic head. The pancreatic neck is that portion lying directly over the portal vein and superior mesenteric artery. It is covered anteriorly by the pylorus. The body and tail extend obliquely in a cranial direction toward the hilum of the spleen. The area anterior to the body and tail is termed the lesser sac and is bordered by the body of the stomach and gastrocolic ligament anteriorly and the transverse mesocolon and the transverse colon inferiorly. The pancreas is contained within the retroperitoneal space, which is bordered anteriorly by the visceral peritoneum and posteriorly by the transversalis fascia. The fusion of visceral peritoneum to the posterior parietal peritoneum fixes the pancreas in the retroperitoneum. This ‘fusion fascia’ is termed the fascia of Treitz in the region of the head and neck and the fascia of Toldt in the region of the body and tail.

Surgical access to the pancreatic head and duodenum

Mobilization or Kocherization of the duodenum and head of pancreas is a familiar manoeuvre used in many upper gastrointestinal procedures. The plane of dissection and the extent of mobilization will vary with the procedure. When mobility only is needed, the peritoneal fusion fascia can be separated from the duodenum using sharp dissection, leaving the fascial sheath overlying the inferior vena cava and aorta. For more extensive mobilization or more radical surgery, the fascia overlying the vena cava is divided and mobilized medially along with the duodenum and pancreatic head. This mobilization of the pancreatic head and neck may be carried to the left far enough to expose the anterior aorta. Such a manoeuvre is part of a radical pancreaticoduodenectomy as it is thought to provide more adequate posterior clearance of tumour and the opportunity for dissection of lymph nodes in the retropancreatic region. Further exposure of the head of pancreas
and duodenum in the region of the uncinate process requires division of attachments between the third part of the duodenum and transverse mesocolon, thus exposing the right side of the root of the mesentery containing the portal vein. Careful dissection of the portal vein allows exposure of the posteriorly lying uncinate in some cases, but full exposure for resection usually requires transection of the proximal jejunum with division of its most proximal arterial and venous branches. Further exposure of the head of the pancreas in its anterior aspect is achieved by opening the lesser sac by separation of the omentum from the transverse mesocolon or by division of the gastrocolic ligament. This dissection will reveal a right middle colic vein which leads to the gastrocolic trunk (loop of Henle), formed by its junction with the right gastroepiploic vein. Ligation of the right gastroepiploic vein will facilitate further dissection along the gastrocolic trunk, which then joins the superior mesenteric vein on its anterior aspect. This point in turn defines the neck of the pancreas and serves as a starting point for the dissection of a tunnel anterior to the portal vein during pancreaticoduodenectomy. To complete exposure of the anterior pancreatic head the pylorus and first part of the duodenum can be mobilized by division of small mesenteric vessels. This manoeuvre is used in pylorus preserving resections of the pancreatic head.

**Surgical access for pancreatic necrosectomy**

Several descriptions of the technique of necrosectomy have been published. All include the exposure and debridement of the contents of the lesser sac. The group in Verona have consistently used a technique of more extensive mobilization and drainage, with excellent results. Highlights of that technique will be described here. The aim of the technique is to expose the entire pancreas anteriorly and posteriorly as well as the entire upper abdominal retroperitoneum. An extended Kocher’s manoeuvre is performed. The lesser sac is entered by opening the gastrocolic omentum. The anterior pancreatic capsule is removed. In the healthy state this capsule consists of a peritoneal layer overlying a layer of fatty tissue. In the diseased state it may consist of necrotic or saponified peripancreatic fat. Posterior mobilization of the body and tail is achieved by finger dissection, beginning behind the pancreas and the splenic vessels at the ligament of Treitz and extending toward the pancreatic tail. Irrigation drains are then placed posterior to the head and the tail and in the lesser sac for continuous lavage.

**Staging of pancreatic and periampullary tumours**

The TNM staging of pancreatic and periampullary adenocarcinomas refers to the systems published by the International Union against Cancer (UICC) and to other similar systems such as the Japanese system. The UICC TNM system was modified in 1997 for both tumour types (Table 2.1).
T Staging

The T stage defines the primary tumour with respect to size and its relationship to pancreatic and peripancreatic structures. Pancreatic exocrine tumours are defined as those arising from the pancreatic ducts (although the cell of origin has been debated) and most commonly arise in the pancreatic head. Periampullary tumours are those arising from the ampulla or common channel of the pancreatic and main bile duct. In practice this is not always an easy differentiation to make. For pancreatic tumours confined to the pancreas, those less than 2 cm are designated T1 (previously T1a) and those greater than 2 cm are designated T2 (previously T1b). T3 tumours are those extending into the duodenum, bile duct, retroperitoneal fat, mesenteric fat, mesocolon, omentum or peritoneum.

<table>
<thead>
<tr>
<th>T Stage</th>
<th>1987</th>
<th>1997</th>
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<tr>
<td>&lt;2cm</td>
<td>T1a</td>
<td>T1</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>T1b</td>
<td>T2</td>
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<tr>
<td>Invasion of duodenum, bile duct or peripancreatic tissues</td>
<td>T2</td>
<td>T3</td>
</tr>
<tr>
<td>Invasion of major vessels, stomach, spleen or colon</td>
<td>T3</td>
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N Staging

The various staging systems for pancreatic cancer differ mostly in the classification of lymph node metastases. The UICC system is the simplest in this regard as only regional
lymph nodes are included. For tumours of the pancreatic head these are classified as superior, inferior, anterior, posterior and coeliac. For body and tail tumours splenic hilum nodes are included as well. Within this system the only differentiation regarding the extent of lymph node involvement is between no involvement, single node involvement and multiple node involvement. The Japanese system is more detailed, giving specific numerical designations to specific lymph node stations (Fig. 2.8). Such designations have been shown to be clinically important as some of these sites harbour metastases in a high percentage of cases, whereas others rarely do so.

The progression of nodal metastases from tumours of the head of the pancreas begins in the anterior and posterior pancreaticoduodenal nodes, areas 17 and 13, respectively. These regional nodes then drain into the inferior head nodes (areas 15b, c, d, v) and from there into the juxta-aortic nodes (areas 19, 14a) and the para-aortic group (area 16). The juxta-aortic nodes most commonly involved are those in area 16b which lie between the aorta and the inferior vena cava from the level of the coeliac axis to the superior mesenteric artery. Because of the clinical utility of the Japanese system a recent European consensus conference on pancreatic resection has recommended definitions of standard, radical and extended resections based largely on this system (personal communication). Lymph nodes which are removed in a standard Whipple’s resection

![Figure 2.8 Regional lymph nodes of the pancreas according to the Japanese staging system.](image)

according to this system are considered regional lymph nodes and those removed with a more radical lymphadenectomy are considered to be level 2 or 3 in the Japanese system and juxtaregional in the new European designation. The UICC system does not make
such a differentiation, although there is an option within that system of considering certain node sites as distant metastases.

**M Staging**

This aspect of staging is fairly straightforward as it relates to the presence of disseminated disease, most commonly in the form of peritoneal or liver deposits. There is some discussion over whether lymph node involvement at certain sites should be considered as distant metastases.

**Staging modalities**

The main aim of staging of pancreatic cancer currently focuses on the question of resectability. The emphasis is therefore on M stage and T stage. CT scanning has been the mainstay of such assessments in recent years and indeed some reports using techniques such as dual phase contrast injection and fine cut imaging intervals have shown excellent results. Nevertheless, this type of experience with CT scanning is not universal. Even in specialist centres, pancreatic surgeons have seen both false positive and false negative predictions of resectability from this investigation. For this reason other modalities for staging have been developed. Endoscopic ultrasound has been shown by some groups to provide excellent local tumour staging. Nevertheless, the technique does not overcome one of the main shortcomings of CT which is the failure to detect small peritoneal and liver deposits. Laparoscopic staging has been used to address this problem. The addition of laparoscopic ultrasound has been found by some groups to increase the sensitivity for detecting intraparenchymal liver deposits and to provide very accurate local tumour staging. Despite some excellent reports of CT staging, comparative studies have so far shown laparoscopic ultrasound to provide more accurate overall staging. The hallmark of such staging is a positive predictive value of 100% for predicting unresectable disease. This reflects the certainty of assessment which laparoscopic ultrasound provides, which so far has not been provided by other techniques. None of the techniques mentioned has so far demonstrated sufficient accuracy in lymph node staging to be of clinical value.

The examples (Fig. 2.2B) show the relationships between tumour, portal vein, pancreatic duct and common bile duct which can be demonstrated using laparoscopic ultrasonography and intraoperative ultrasonography. With the addition of the colour flow Doppler technique, disturbances of flow within the portal vein may help to determine whether a tumour is resectable.

**Key points**

- Attention to vascular anatomy is essential for low blood loss during pancreatic surgery.
- Most frequent arterial variant is the origin of the right hepatic artery from the superior mesenteric in 25% of cases.
- Staging modalities of pancreatic tumours include:
Spiral CT
ERCP and endoscopic ultrasound
Laparoscopy with peritoneal cytology and laparoscopic ultrasound.

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Introduction

The caudate lobe, deeply situated and surrounded by major vascular structures, is an area of the liver often seen as forbidding and dangerous. The pioneering work of Couinaud \(^1\) provided a much clearer understanding of hepatic anatomy and allowed a safer, anatomically-based approach to hepatic resectional surgery. As hepatic surgery has advanced, surgeons have increasingly and successfully pursued resection of caudate lobe lesions. The caudate lobe is not infrequently involved in primary and secondary malignancies. While rarely

![Figure 3.1](image_url)

**Figure 3.1** Schematic view of the caudate lobe (segment I, shaded), looking from above with the left lateral segment (segments II/III) retracted to the patient’s right. The caudate is bounded anteriorly by the left portal vein (LPV) and posteriorly by the inferior vena cava (IVC). The principal portal venous supply, arising from the LPV, is indicated by the arrow. The ligamentum venosum runs along the anterior border of the caudate, from the LPV to the base of the left hepatic vein (LHV). PV, main portal vein; RPV, right portal vein; MHV, middle hepatic vein.
performed as an isolated procedure, caudate lobectomy is most often included in conjunction with other hepatic resections to achieve complete tumor clearance. A thorough understanding of the caudate lobe anatomy is necessary for safe resection.

Anatomy

**Landmarks**

The caudate lobe (segment I) is that portion of hepatic parenchyma situated posterior to the hilum and anterior to the inferior vena cava (IVC) \(^2\) (Fig. 3.1). In many respects, the caudate is an independent anatomical segment composed of three distinct parts. \(^3\) The caudate lobe proper, or Spiegel lobe, lies

![Cross-sectional view looking from below upwards. The caudate (segment I, shaded) is situated between the left portal vein (LPV) and the inferior vena cava. The main portal venous supply from the LPV and the caudate veins draining into the inferior vena cava are clearly shown. The lesser omentum separates the caudate from the left lateral segment (segments II/III). The posterior aspect of segment IV and the medial surface of segment VII mark the rightward extent of the caudate, which is in close proximity to the middle hepatic vein (MHV).](image-url)
Figure 3.3 Two views of the caudate lobe, from above (A) and from the left with the left lateral segment retracted upwards and to the patient’s right (B). The extent of the caudate from the hilum to the insertion of the hepatic veins is clearly shown. A plane from the origin of the right posterior sectoral portal vein (p.br.PV) to the confluence of the right hepatic vein (RHV) and inferior vena cava approximates the right border of the caudate (right). The ligamentous attachment, or dorsal ligament (DL), extending from the caudate to the IVC and segment VII is shown (left). CL, caudate lobe; PV, main portal vein; MHV, middle hepatic vein; LHV, left hepatic vein; LV, ligamentum venosum.

to the left of the vena cava and under the lesser omentum, which separates it from segments II and III. The paracaval portion of the caudate lies anterior to the IVC and extends cephalad to the roots of the major hepatic veins. The caudate process is located between the main right Glissonian pedicle and the IVC and fuses with segment VI of the right lobe $^3-^5$ (Fig. 3.2).

The caudate lobe is bounded posteriorly, along its entire length, by the retrohepatic vena cava, and superiorly by the left and middle hepatic veins at their insertion. Its anterior border is formed by the left portal vein, the hilum and the base of segment IV (Figs 3.1–3.3). The ligamentum venosum, the obliterated ductus venosus, courses along the medial aspect of the caudate from the umbilical portion of the left portal vein to the inferior border of the left hepatic vein (Figs 3.1–3.3). The rightward extent of the caudate is variable, but is usually small and is indistinctly delimited by the posterior surface of segment IV and the medial surfaces of segment VI and VII $^2,^5-^7$ (Fig. 3.2). A plane passing from the origin of the right posterior sectoral portal vein to the confluence of the right hepatic vein (RHV) and IVC serves as a useful approximation of the right border $^2$ (Fig. 3.3). The middle hepatic vein is adjacent to the right portion of the caudate, and may be the source of significant hemorrhage if damaged during resection $^6$ (Figs 3.2 and 3.3). The posterior edge of the caudate on the left has a fibrous component that attaches to the crus of the diaphragm and extends posteriorly behind the vena cava to join segment VII (Fig. 3.4). In up to 50% of patients, this fibrous band
Figure 3.4 View of the caudate from the left. The left lateral segment is retracted upwards and to the patient’s right. The ligamentous attachment extending from the caudate to the inferior vena cava (IVC) and segment VII is indicated (large arrowhead). The principal portal venous branch to the caudate arises from the left portal vein (small arrow), while a smaller branch arises from the right (small arrowhead). LV, ligamentum venosum; RL, round ligament; LHV, left hepatic vein; IVC, inferior vena cava.

may be replaced by hepatic parenchyma, so that the caudate lobe may completely embrace the vena cava at this level. 6

Blood supply and biliary drainage

Both the left and right portal pedicles contribute to the blood supply and biliary drainage of the caudate. 2, 5, 6, 8 – 10 Portal venous blood is supplied by 2–3 branches from the left portal vein and the main right or right posterior sectoral portal vein. From a practical standpoint, the left branch is much more constant and supplies a greater proportion of the lobe than the right branch(es) 2, 9 (Figs 3.1 and 3.2). It is important that the left branch be identified and preserved during conventional left hepatectomy (i.e., without concomitant caudate resection). 6 The right posterior sectoral portal vein provides a branch to the right caudate in approximately 50% of patients. 9 The arterial anatomy is much more variable than the portal venous supply. The most common pattern is one branch from the main left hepatic artery and a second, smaller branch from the right posterior sectoral hepatic artery. Three branches may be seen in up to one-third of patients. 9 The principal biliary drainage of the caudate is through one or, less commonly, two branches that empty into the left main duct. A much smaller branch drains the right caudate and caudate process via the right posterior sectoral duct. 2, 8, 9 Failure to recognize and ligate these branches often results in troublesome biliary leak after caudate lobe resection. 6
Hepatic venous drainage

The caudate lobe is the only hepatic segment that does not drain into one of the main hepatic veins. The hepatic venous drainage of the caudate is accomplished by a variable number of short venous branches that enter directly into the anterior and left aspect of the vena cava. Branches draining into the back of the vena cava may be encountered if there is a significant retrocaval caudate process. Approximately 20% of patients have a solitary venous branch, but most patients have multiple branches and over one-third will have more than three. This independent venous drainage allows continued decompression of the caudate in patients with complete hepatic venous outflow obstruction (Budd-Chiari), resulting in increased perfusion and compensatory hypertrophy.

Embryogenesis

Many anatomical features of the caudate are thus unique relative to the other hepatic segments. Although often considered a left-sided structure, the caudate maintains physical attachments to the right liver, from which it derives some of its blood supply and biliary drainage. Consideration of its embryogenesis may provide a clearer understanding of the caudate lobe anatomy in the adult. During the second trimester of fetal life, the persistent left umbilical vein enters the liver via the...
umbilical fissure and empties into the left portal vein (Fig. 3.5). The ductus venosus is suspended within the dorsal mesentery of the liver, shunting placental blood from the left portal vein directly into the vena cava. With hepatic enlargement and counterclockwise rotation, a small portion of the right liver inserts behind the ductus venosus mesentery, anterior to the IVC. The extrahepatic portion of the ductus venosus and its mesentery progressively shorten, and the future caudate lobe comes to rest between the IVC and the left portal triad. The ductus venosus obliterates shortly after birth and persists as the ligamentum venosum 7 (Fig. 3.5).

Surgical approaches

Surgical approaches to the caudate are critically dependent on the size and location of the tumor(s) and the type of associated resection. Caudate lobectomy may be undertaken as an isolated procedure or, more often, in conjunction with a right or left hepatic resection. 2, 6 Bulky tumors, even though limited to the caudate, may be difficult to remove without associated left or right hepatectomy, as this may provide safer access without compromising the resection margin. 6, 11 Other situations that require more extensive resection in addition to caudate lobectomy include: (1) tumors that arise from other segments and extend into the caudate, or vice versa; (2) primary or secondary tumors involving multiple segments, including the caudate; (3) hilar cholangiocarcinoma involving the caudate ducts.

General principles

The techniques of liver resection favored by the authors have been previously published and are described elsewhere in this book. 12 Full examination of the abdomen, pelvis, retroperitoneum and porta hepatis is performed to exclude the presence of extrahepatic disease. The lesser omentum is incised and the caudate is inspected and palpated. The liver is mobilized sufficiently to allow intraoperative ultrasound. The central venous pressure (CVP) is carefully controlled and not allowed to rise above 5 mmHg until the parenchymal transection is completed. Maintaining a low CVP greatly facilitates mobilization of the liver off the vena cava and control of the retrohepatic vena caval branches, and minimizes blood loss from small tears in hepatic venous branches. The possibility of air embolization is minimized by keeping the patient in a 15° Trendelenburg position. Parenchymal transection is accomplished with a Kelly clamp to expose ducts and vessels, which are then clipped or ligated. The authors make liberal use of vascular staplers for major pedicle and hepatic venous structures, 13 and favor intermittent rather than continuous portal triad clamping (Pringle maneuver).

Because of their location, tumors within the caudate often compress the IVC. Preoperative imaging often cannot distinguish tumor invasion from compression, and an attempt at resection should not be denied based solely on this radiographic finding. 6 Many tumors can be dissected free of the vena cava, and in selected cases vena caval resection can be performed. A short segment of resected vein may be amenable to primary repair or may require autogenous graft. On the other hand, a chronically
occluded vena cava can often be resected without the need for reconstruction, since collateral flow has usually been established. 6

Isolated caudate resection

Many of the critical maneuvers required for isolated caudate lobectomy apply also to combined resections. The caudate may be approached from the left or the right, depending on the size and location of the tumor. Often, dissection from both sides is necessary. 2, 6, 11, 14 The essential elements of the procedure can be summarized in three steps. 6 First, control of the inflow blood supply is achieved by lowering the hilar plate and exposing the principal branches of the left and right hepatic artery and portal vein. As described above, the branches from the left are usually the most prominent. Second, the posteriorly draining caudate veins must be divided. A substantial tumor will often render the caudate stiff and difficult to manipulate, making exposure of these veins difficult. Third, after complete devascularization, the hepatic parenchyma between the base of segment IV and the left border of segment VII must be transected. During this phase of the dissection, one must always consider the close proximity of the middle hepatic vein and the possibility of major hemorrhage from inadvertent injury. 6

Lowering the hilar plate is a necessary initial step for exposing the caudate blood supply and biliary drainage. Cholecystectomy may improve access to the base of segment IV and should be considered. The principal branches, arising from the left at the base of the umbilical fissure, are readily identified and divided (Fig. 3.6). The right sided branches must also be identified and controlled 2, 6 (Fig. 3.7). The left lobe of the liver is mobilized and retracted upwards, exposing the ligamentous attachments to the IVC on the left (Fig. 3.8). If parenchyma is found to completely encircle the IVC, as discussed above, then complete mobilization from the left side may be difficult and an approach from the right should be considered. 6, 11 When this ligament is divided, the caudate can

Figure 3.6 Dissection at the base of the umbilical fissure reveals the principal portal venous branch to the caudate (elevated on the clamp) arising from the left portal vein. The caudate lobe is being retracted to the patient’s left and the right lobe upwards and to the patient’s right.
be elevated and the hepatic venous branches safely controlled with clips or ligatures (Fig. 3.9).

**Figure 3.7** Portal venous branch to the right portion of the caudate and caudate process (large arrow), arising from the right portal vein (small arrow), is controlled and divided.

**Figure 3.8** The ligamentous attachment extending from the caudate lobe to the inferior vena cava (IVC) is divided (small arrow). The caudate lobe is retracted upwards and to the patient’s left. The IVC is indicated by the large arrow.
Figure 3.9 The caudate is retracted upwards and to the patient’s left, exposing the inferior vena cava (IVC). A venous branch draining directly into the IVC is prepared for ligation and division.

Figure 3.10 Cross-sectional view of the partially mobilized caudate lobe. The ligamentous attachments and the portal venous inflow have been divided. The posteriorly draining hepatic veins can be controlled and divided from the left or right.

Complete or nearly complete mobilization of the caudate can often be achieved in this manner, working from the left (Fig. 3.10). However, in the presence of a large, bulky tumor or retrocaval hepatic parenchyma extending from the caudate to segment VII, an initial approach from the right side is safer. This requires complete mobilization of the right lobe from its diaphragmatic and retroperitoneal attachments, as well as from the right adrenal gland. The right lobe is rotated upwards and to the left, and the retrohepatic veins are serially divided, starting at the level of the caudate process and continuing upwards to the hepatic veins (Fig. 3.11). The ligamentous or parenchymal attachments to segment VII can also be divided working from the right (Fig. 3.12). As the dissection progresses, it is usually a simple matter to continue across the anterior surface of the IVC and gain control of the caudate veins on the left.

At this point, the caudate is devascularized, leaving only its parenchymal attachments
to segment IV and segment VII to be divided (Fig. 3.10). The possibility of vigorous bleeding from a posterior tear in the middle hepatic vein makes this part of the procedure particularly hazardous. 6 This is especially true for a large tumor that extends anteriorly and to the right. When caudate resection is combined with right or left hepatectomy, this danger is reduced by controlling the vein prior to this portion of the procedure,

![Figure 3.11](image)

**Figure 3.11** Mobilization of the right hepatic lobe off the vena cava. The diaphragmatic attachments have been divided, and the liver is retracted upwards and to the patient’s left. A large retrohepatic vena caval branch is prepared for ligation and division (arrow).

either extrahepatically or within the hepatic parenchyma. Likewise, for isolated caudate lobectomy, the authors have found it valuable to isolate the middle and left hepatic veins at their insertion into the suprahepatic IVC. 6 This allows temporary control with a vascular clamp during parenchymal transection. An alternative approach has been described, which entails partial occlusion of the vena cava at the confluence of all three hepatic veins.5 Others have described splitting the hepatic parenchyma in the interlobar plane, separating the right and left hemilivers along the right border of segment IV 15 (Fig. 3.13). This transhepatic approach allows the transection of the remaining caudate parenchyma under direct vision of the middle hepatic vein, thereby minimizing the risk of injury. Total vascular isolation for caudate resection has also been described, but is usually unnecessary. 11

**Caudate resection with left hepatectomy**

This technique is indicated for large caudate lesions where isolated resection is not safe, tumors that involve other segments of the left liver in addition to the caudate, and for cholangiocarcinoma of the hepatic duct confluence with extension into the left hepatic duct. In the latter case, tumor often extends into the principal caudate duct, arising from the left hepatic duct, and caudate resection is necessary to achieve tumor clearance. 2 , 6 , 16 , 17

The left and right lobes should be mobilized completely. The falciform ligament is divided to the level of the suprahepatic vena cava. The hilar plate should be lowered and
the left aspect of the caudate

Figure 3.12 Division of the ligamentous attachment to segment VII. The liver has been mobilized and retracted upwards and to the patient’s left. A clamp is passed between the inferior vena cava and the fibrous ligament (arrow), which in this case contains no hepatic parenchyma.

Figure 3.13 Cross-sectional view of the devascularized caudate lobe, which is attached only by its right border to segment VII medially and segment IV superiorly. As an alternative approach, the liver parenchyma may be split in the interlobar plane (black arrow), allowing the remaining caudate attachments to be divided under direct vision of the middle hepatic vein (MHV). LHV; left hepatic vein; IVC, inferior vena cava.
exposed as described above. The left portal vein and hepatic artery are exposed within the porta hepatis and divided at a point proximal to the principal caudate branches. Similarly, portal venous and hepatic arterial branches arising from the right should be sought and controlled. It is the authors' practice to control and divide the hepatic venous outflow, if feasible, before starting parenchymal transection. Dissecting from the left, the root of the left hepatic vein can be identified at the cephalad extent of the ligamentum venosum. Careful dissection in this area, anterior to the caudate, and above the liver along the anterior surface of the suprahepatic IVC, usually exposes the vein. Commonly, the left and middle hepatic veins enter the IVC as a common trunk, which can be exposed in a similar fashion. Once adequately exposed, the common trunk may be divided with a vascular stapler or oversewn. Alternatively, the left and middle veins may be divided separately. If extrahepatic control of the hepatic veins is not feasible, this may be accomplished during the parenchymal transection phase. The posteriorly draining caudate veins are then exposed and divided. The retrohepatic veins coursing from the right into the IVC should also be divided, as this makes transection of the right portion of the caudate easier. The liver tissue is then divided along the principal resection plane, encompassing the middle hepatic vein. The left hepatic vein may be divided during the hilar dissection or during parenchymal transection. It is essential to avoid narrowing the biliary confluence when the left hepatic duct stump is oversewn.

The approach to the bile duct is much different when this procedure is performed for hilar cholangiocarcinoma. In this circumstance, the entire supraduodenal bile duct and lymphatic tissues are reflected upwards early in the procedure and included with the specimen. Also, the right hepatic duct should be divided at a point beyond the tumor and before dividing the liver. It may be necessary to divide the duct at the level of the right anterior and posterior sectoral hepatic ducts. The bile duct margins should be sent for frozen section histology to ensure complete tumor clearance.

Extended left hepatectomy with caudate lobectomy is one of the more complex and technically challenging of all hepatic resections. This procedure is indicated for multiple tumors that also involve the caudate or large central hepatic tumors of the left lobe that extend into the caudate and the right anterior sector. Tumors situated high in the liver, involving the left and middle hepatic veins and extending into segment VIII, may also involve the caudate and require this type of resection. Adding caudate lobectomy requires exposing and mobilizing the caudate, as described above for left hepatectomy. With the left liver and caudate completely prepared, the line of parenchymal transection is oblique from the right, anterior to the right hepatic vein and then carried posteriorly along the right border of the caudate.

This procedure is typically indicated for solitary tumors of the right hepatic lobe that extend into the caudate (Fig. 3.14) or multiple tumors of the right lobe and caudate. Occasionally, this procedure is necessary for cholangiocarcinoma of the hepatic duct confluence with extension into the right hepatic duct. Often, however, these tumors spare the principal caudate duct, and caudate resection is not necessary. This is in contrast to cholangiocarcinomas of the left hepatic duct, which nearly always involve the orifice of the principal caudate duct and usually require caudate resection.
Figure 3.14 Computed tomographic scan showing a metastatic tumor within the right portion of the caudate lobe and extending into segment IV superiorly and segment VII medially (arrow). The tumor extended very near to the insertion of the middle and right hepatic veins. Complete removal required an extended right hepatectomy and caudate lobectomy en bloc.

**Caudate resection with right hepatectomy**

Caudate resection is somewhat easier to perform in conjunction with right hepatectomy, mainly because the potentially hazardous disconnection of the right portion of the caudate is avoided. The right and left lobes should be fully mobilized. The gallbladder should be removed and the hilar plate lowered. The right hepatic artery and right portal vein are exposed within the porta hepatis. In situations where the extrahepatic bile duct is not sacrificed, exposing the right portal vein may be difficult. This is especially true when the bifurcation is high. It is usually helpful to first isolate and divide the right hepatic artery. Ligatures left on the divided cystic duct and right hepatic artery

Figure 3.15 The hepatic artery and the divided cystic duct (arrow) are retracted upwards and to the patient’s left, allowing access to the portal vein (right portal vein elevated on the clamp).
can be used to retract the common bile duct and hepatic artery upwards and to the left, allowing access to the portal vein from the right side \(^6\) (Fig. 3.15). Continued cephalad dissection will usually reveal the portal venous bifurcation. A small posterolateral branch to the right portion of the caudate is usually encountered (Fig. 3.7). This branch should be divided early in the dissection to avoid inadvertent injury and to allow better exposure of the right portal vein. \(^6\) Not infrequently, the anterior and posterior portal vein branches arise separately, requiring that they be divided individually. With the inflow to the right lobe controlled, a clear line of demarcation should be evident along the principal resection plane. Dissection of the left portal vein at the base of the umbilical fissure exposes the principal caudate branch, which is divided (Fig. 3.6). The liver is now fully mobilized off the vena cava by dividing the accessory hepatic veins. The right lobe must be liberated from all of its diaphragmatic and retroperitoneal attachments. The right adrenal may be adherent to the undersurface of the liver, just lateral to the vena cava, and may be the source of troublesome bleeding if dissection is not pursued in the proper tissue plane. The falciform ligament should be divided to the level of the suprahepatic vena cava, and the origin of the right hepatic vein identified. With the liver retracted upwards and to the left, ligation of the retrohepatic veins should commence from below and proceed to the level of the hepatic vein \(^2\cdot^6\) (Fig. 3.11). It is often possible to extend this dissection across the anterior surface of the vena cava and control some or all of the caudate veins. \(^2\cdot^6\) As the dissection proceeds cephalad, the ligamentous attachments along the lateral aspect of the vena cava are encountered and divided to allow access to the right hepatic vein. In approximately one half of patients, parenchymal tissue from the caudate will extend behind the vena cava and attach to segment VII. \(^6\) This tissue, if present, must be carefully separated from the right hepatic vein and divided. Continued dissection from below and at the level of the suprahepatic vena cava exposes the right hepatic vein, which may be divided at this point (Fig. 3.16).

The left liver is now retracted upwards and to the right, and mobilization of the caudate

![Figure 3.16](image) The staple line of the divided right hepatic vein is shown (black arrow). A clamp has been passed around the common trunk of the middle and left hepatic veins (white arrow).
lobe is completed. Any remaining caudate veins are divided. The hepatic parenchyma may be divided just to the right of the middle hepatic vein. As the dissection proceeds posteriorly, the surgeon’s left hand is placed anterior to the vena cava, retracting the left portion of the caudate toward the right. The remaining parenchyma can then be divided along the right lateral aspect of the middle hepatic vein. When necessary, the middle hepatic vein may be divided, either extrahepatically or from within the liver parenchyma. This can be done without fear of causing venous congestion of segment IV, since drainage will continue via the umbilical vein.

It should be noted that the right hepatic duct need not be divided during the hilar dissection. It is safer and easier to control the right duct by dividing and oversewing the main right portal pedicle, which is encountered early during parenchymal transection (Fig. 3.17). When this procedure is performed for hilar cholangiocarcinoma, the bile duct must be approached as discussed above.

It is usually a straightforward matter to extend this resection to include most or all of segment IV as an extended right hepatectomy. The procedure is carried out as described above, except that the segment IV pedicles are ligated at their origin within the umbilical fissure. Alternatively, these pedicles may be isolated and divided during the parenchymal transection phase. Likewise, the middle hepatic vein may be divided extrahepatically or from within the parenchyma.

**Figure 3.17** Hepatic parenchymal transection during right hepatectomy and caudate lobectomy. A sling has been placed around the portal triad. The main right pedicle is exposed (white arrow) and is prepared for ligation and division. Note the close proximity of the middle hepatic vein (black arrow).

Results of caudate lobectomy

Much of the published literature on caudate resection consists of case reports or small series (three or less). These reports provided important insights into the technical aspects of caudate resection and documented its feasibility. Since 1990,
however, many centers have reported their experience with an increasingly larger number of procedures (Table 3.1), allowing a more thorough analysis. 4, 6, 11, 16, 17, 22, 23

It is readily apparent from these studies that caudate resection represents a small percentage of the total number of hepatic resections from any one center, generally 10% or less. In one of the largest series of partial hepatectomy for hepatocellular carcinoma, caudate lobectomy was performed in less than 1% of patients. 24 Moreover, isolated caudate resection is performed even less frequently. While some authors have reported a greater incidence of complications associated with caudate resection, 4 most series cite morbidity and mortality figures that are comparable to those of standard hepatic resection. 6, 11, 16, 22, 23 These results suggest that caudate resection, either alone or in conjunction with a larger resection, can be performed without excessive risk.

Some authors have suggested that isolated caudate resection for metastatic tumors or hepatocellular carcinoma may not provide adequate tumor clearance. Two studies have documented narrow resection margins and early recurrences in patients undergoing isolated caudate resection for hepatocellular carcinoma and metastatic tumors. 4, 11 However,

Table 3.1 Selected series of caudate resections, diagnoses and procedures performed. The numbers in parentheses indicate the frequency of caudate resection as a percentage of all hepatic resections

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>Diagnoses</th>
<th>Procedures</th>
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<tbody>
<tr>
<td>Nimura et al. 16</td>
<td>45</td>
<td>Cholangiocarcinoma (45)</td>
<td>En bloc complete caudate resection (42)</td>
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<td></td>
<td></td>
<td></td>
<td>Isolated complete caudate resection (3)</td>
</tr>
<tr>
<td>Elias et al. 11</td>
<td>20 (9.4%)</td>
<td>Metastatic tumors (16)</td>
<td>En bloc complete caudate resection (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Isolated complete caudate resection (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma (3)</td>
<td></td>
</tr>
<tr>
<td>Nagasue et al. 22</td>
<td>19 (4%)*</td>
<td>Cholangiocarcinoma (1)</td>
<td>Partial caudate resection (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>En bloc complete caudate resection (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Isolated complete caudate resection (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial caudate resection (10)</td>
</tr>
<tr>
<td>Yang et al. 23</td>
<td>6</td>
<td>Hepatocellular carcinoma (6)</td>
<td>En bloc complete caudate resection (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial caudate resection (3)</td>
</tr>
<tr>
<td>Shimada et al. 4</td>
<td>9</td>
<td>Hepatocellular carcinoma (9)</td>
<td>Isolated complete caudate resection (2)</td>
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</table>
many of these resections were partial or wedge excisions. Moreover, studies containing a greater number of complete resections also report adequate tumor clearance and acceptable recurrence rates.\(^6\),\(^{22}\) Reasonable judgment must be exercised in selecting patients for isolated caudate lobectomy. The cumulated evidence supports the efficacy of isolated complete caudate lobectomy for small or medium sized tumors. Certainly, large tumors usually require a more extensive resection in order to achieve clear margins, and wedge resections, except for very small tumors, should be avoided.\(^6\)

Several studies have documented the relatively frequent involvement of caudate lobe ducts in patients with hilar cholangiocarcinoma. Nimura et al. reported involvement of the caudate ducts in 44 of 46 patients in whom caudate resection was performed.\(^{16}\) In a separate study by Ogura et al., microscopic tumor involvement of the caudate lobe was less common (9 of 21 patients).\(^{17}\) It would seem clear that, in light of the predominant biliary drainage pattern of the caudate lobe, tumors of the left hepatic duct almost always require caudate lobectomy. Tumors involving the right hepatic duct, by contrast, do not always require complete caudate resection.\(^{20}\) Indeed, the ducts draining the caudate process will likely be involved, but this portion of the liver and the associated bile ducts are usually included with the resection. The results of several large series of resections for hilar cholangiocarcinoma, including a report from the authors, support this policy of selective caudate resection.\(^{25 – 27}\)

<table>
<thead>
<tr>
<th>Surgical approach to caudate resection</th>
<th>Number and Percentage</th>
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</thead>
<tbody>
<tr>
<td>Bartlett et al.(^6)</td>
<td>21 (7.5%)</td>
</tr>
<tr>
<td>Metastatic tumors (9)</td>
<td>Partial caudate resection (7)</td>
</tr>
<tr>
<td>Other, not specified (12)</td>
<td>En bloc complete caudate resection (17)</td>
</tr>
<tr>
<td>Ogura et al.(^{17})</td>
<td>39</td>
</tr>
<tr>
<td>Cholangiocarcinoma (39)</td>
<td>En bloc complete caudate resection (34)</td>
</tr>
</tbody>
</table>

\(^{*}\)2.2% of all patients with primary HCC had caudate involvement; of those resected, 4% of patients with primary HCC and 11% of patients with recurrent HCC underwent caudate resection.

**Summary**

Resection of the caudate lobe is occasionally necessary for primary or secondary hepatic tumors. While some lesions may be excised with an isolated caudate lobectomy, the majority will require right or left hepatectomy and caudate resection en bloc. The addition of caudate lobectomy does not significantly increase the morbidity above that expected for major hepatectomy. In properly selected patients, isolated caudate resection can achieve adequate tumor clearance without excessive morbidity. The surgical approach to caudate resection is critically dependent on the size and location of the
tumor. The surgeon should be completely comfortable with the relevant anatomy and the common variations, as well as the standard techniques of hepatic resection.

Key points

- Caudate lobectomy is rarely performed as an isolated procedure.
- A thorough understanding of the anatomy of the caudate lobe is essential for safe resection.
- Tumors of the caudate lobe often involve the inferior vena cava.
- Caudate lobectomy is often performed in conjunction with other major liver resections.
- Resection margins of 1 cm may not be possible with caudate lobectomy in view of caval proximity.

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Ex-vivo resection for liver tumours

J Peter A Lodge

Introduction

These days it seems that virtually no liver tumour should be considered to be unresectable, even though the majority of patients continue to present at a late stage in their disease. Many experts have challenged the old dogma relating to hepatic resection and candidates with multiple and bilobar hepatic tumours as well as patients with limited extrahepatic tumour infiltration are now considered for resection. In addition, patients with metastases from tumours other than colorectal cancer are also regularly undergoing liver resection.

Improvements in anaesthesia have been integral to the success of hepatic surgery, primarily through the use of low central venous pressure techniques for liver resection. In this author’s centre only 30% of cases require blood transfusion. This is despite the fact that 85% of our current resection practice is hemihepatectomy or more and the majority is trisectionectomy (extended hepatectomy) and bilateral resection work. In the majority of hepatobiliary centres, Pringle’s manoeuvre and total vascular isolation (hepatic vascular exclusion) are used routinely, and this short-term warm ischaemia is reported to be well tolerated. However, it has been our preference in recent years to avoid ischaemia whenever possible as we had noticed an increased postoperative morbidity and longer hospital stay in those patients in whom vascular isolation techniques had been used for prolonged periods.

In our experience, the use of hepatic ischaemia techniques and blood transfusion is more often necessary for the more complex resections. Whereas right and left heptectomy and right hepatic trisectionectomy (right trisegmentectomy, extended right heptectomy—resection of hepatic segments IV, V, VI, VII, VIII) should be regarded as routine and only rarely require transfusion, left hepatic trisectionectomy (left trisegmentectomy, extended left heptectomy—resection of hepatic segments II, III, IV, V, VIII), for example, is more challenging. Recent internal audit of the first 22 left hepatic trisegmentectomies carried out by this author has shown that 11 required Pringle’s manoeuvre and five needed a period of total vascular isolation. In 14 cases the caudate lobe (segment I) was also resected. Eleven of the 22 patients required blood transfusion, although the median requirement was only 1.5 units. This may partly be explained by a high proportion of cholangiocarcinoma cases (32%) in this series as resection of these tumours is associated with a greater degree of operative difficulty. In this group of 22 patients, six of the seven patients with major postoperative morbidity had required either Pringle’s manoeuvre or total vascular isolation, confirming our previous observation. It is also true to say that increasing experience helps to reduce the use of
ischaemia and blood transfusion, and there has been little morbidity in a further 15 left trisectionectomies carried out recently by this author.

Although orthoptic liver transplantation and cluster resection are the most radical forms of tumour clearance, results for otherwise unresectable tumours have been uniformly disappointing. Tumours account for only 3% of our liver transplant programme in terms of primary indication. However, transplantation remains a valuable option for patients with tumours as secondary indications: principally small hepatomas within cirrhosis. Our centre has been investigating cluster resection and multivisceral grafting as an alternative for extensive tumours and the neuroendocrine group lends itself neatly to this concept. These are most often tumours of midgut origin with foregut metastases and adequate lymphadenectomy involves both the coeliac and superior mesenteric arterial distributions, and if purely foregut (pancreatic tail) then a lesser cluster resection can also be appropriate. These concepts will be discussed at the end of this chapter as they are helpful in defining the place of ex-vivo liver resection in the spectrum of hepatic surgical techniques. In addition there are many lessons to be learnt from the practice of liver transplantation, not least anaesthesia and the role of veno-venous bypass.

The short-term survival of untreated patients with both primary and secondary liver tumours, the unpredictability of chemotherapy response on an individual patient basis and the disappointing results of transplantation for cancer provide adequate impetus for attempts to extend the boundaries of liver resection as far as possible. Hilar involvement can be adequately dealt with by short periods of vascular isolation and warm ischaemia and this can often be done without caval or hepatic vein isolation. Portal vein and hepatic artery resection and reanastomosis or replacement now accounts for 40% of this author’s experience of primary hepatic resection for cholangiocarcinoma. Inferior vena cava (IVC) involvement can often be dealt with by simple venous side-clamping or in more extensive cases by total hepatic vascular isolation with IVC clamping and the selective use of veno-venous bypass. IVC resection accounts for 4% of this author’s metastatic work, and replacement by graft has been necessary in most. This fraction is expected to increase as more advanced cases are being considered and it accounts for 6% of cases during the past 12 months in our centre. Tumours involving all of the major hepatic veins with or without IVC invasion, and particularly tumours involving the hepatocaval confluence and needing IVC replacement, continue to pose a surgical challenge, particularly if portal hilar structures are involved bilaterally (Fig. 4.1). Ex-vivo resection offers a potential lifeline for this group of patients and this technique deserves discussion, although it accounts for less than 2% of this author’s total hepatic resection experience. The processes of patient selection and operative assessment of operability by more conventional yet advanced techniques have meant that we have found ex-vivo resection to be necessary in only five of 28 cases (21%) considered during the past 7 years.

Before considering a surgical procedure of this scale it is essential to be as sure as possible that the patient is fit enough to withstand the operation. It is important to take a detailed history of previous cardiovascular disease, including myocardial infarction, angina pectoris and hypertension. Clearly, a history of smoking or peripheral vascular disease should raise the clinical suspicion of coronary artery disease. Respiratory diseases, particularly emphysema and chronic bronchitis, are quite prevalent in the
elderly population and clinical examination with chest radiology can be helpful.

Figure 4.1 This MRI scan demonstrates a typical case for ex-vivo liver resection. The patient had liver metastases from colorectal cancer. The tumour is closely applied to the hepatocaval confluence, the IVC and the portal triad structures. At ex-vivo resection, a section of IVC was resected and replaced with a prosthetic graft. The patient survived for 12 months but died with bone metastases.

Patient selection

Cardiorespiratory assessment

Resting and exercise electrocardiography are the standard cardiological objective assessment tests in our centre. Failure to achieve an adequate heart rate for true stress testing can be a problem in the elderly population, most often due to osteoarthritis of the hips and knees. In this situation a great deal of useful information can be gained from echocardiography, with measurement of end diastolic and systolic volumes to calculate left ventricular ejection fraction, or by radioisotope assessment with dobutamine stress.
Failure to complete these investigations or a significant depression of the S-T segment on the exercise EGG is a clear indication for coronary artery angiography. This procedure is carried out in 10% of major liver surgery candidates in our experience, ruling out surgery in 3% but providing reassuring information in the rest. Only five patients in our experience have been suitable for preoperative coronary artery angioplasty, stenting or bypass grafting prior to liver surgery, but these are clearly potential treatment options to consider.

Routine lung function tests including vital capacity and forced expiratory volume form part of our standard assessment as well as chest radiology. Useful information is also gained from the chest CT, which is done primarily to look for lung metastases and diaphragm involvement by the hepatic tumour. The CT appearances of emphysema in particular are characteristic. In our northern UK population, because of the high incidence of emphysema and chronic obstructive airways disease, we often consider blood gas sampling preoperatively. In cases where severe pulmonary hypertension is suspected a pulmonary artery wedge pressure line is placed at the commencement of anaesthesia before definitely deciding to proceed with the resection. If there is a very high index of suspicion then we prefer to check the pulmonary artery pressures as a day case procedure in advance of the planned surgical date so that the patient can be advised more accurately about operative risk.

**Hepatic reserve**

Preoperative blood tests necessary before proceeding to major resection include full blood count, urea and electrolytes, liver function tests, clotting screen and tumour marker studies. Prothrombin time, bilirubin and albumin give a fairly accurate indication of global hepatic function, but in some cases a liver biopsy of the residual tumour-free liver will also be necessary if there is a doubt about hepatic reserve, in particular in hepatoma. This is particularly important in the group of patients with a previous history of excess alcohol consumption or if there is serological evidence of hepatitis B or C. It is also useful when dealing with cholangiocarcinoma, as there may be underlying sclerosing cholangitis.

Some consideration needs to be given to the number of viable tumour-free hepatic segments that will be reimplanted, but this should not usually be less than two, unless there is considerable hypertrophy of the tumour-free liver (Fig. 4.2). Although it has not been our practice to use detailed CT-based volumetric analysis of the planned residual hepatic volume, careful review of preoperative imaging is clearly important to make the decision for surgery. It is inevitable that a degree of temporary hepatic failure will be induced in some patients undergoing very major resection. More work needs to be done in this interesting area. If the tumour-free segments are affected by biliary obstruction, it is our current practice to attempt biliary decompression by endoscopic or percutaneous techniques a few days in advance of surgery as this may speed up the postoperative recovery.
Tumour type

It is reasonable to consider any malignant tumour of the liver, primary or secondary, for ex-vivo liver resection if there is an acceptable chance of clearance of all the disease. It is not our routine to biopsy the tumour unless there is a serious doubt about the diagnosis after radiological assessment. There is a potential for peritoneal tumour spread from the biopsy site and if a tumour biopsy is absolutely necessary then it is best done under ultrasound or CT guidance, traversing a section of normal liver as this may prevent tumour cell spillage. A biopsy can be useful if a benign tumour is suspected, for example hepatic adenoma occurring as a result of a glycogen storage disease, as liver transplantation may be more appropriate in that case.

Radiology assessment

Although MRI is the imaging method of choice for the liver in our centre, other groups routinely use CT arteriopangeography with similar results. Three-dimensional CT and MRI imaging technology continues to improve and may be of value in planning the surgical approach. Hepatic angiography with portal venography may also be useful. Small metastases or hepatomas not detected by other methods will rule out some candidates and variations in hepatic arterial anatomy can be helpful in some cases, particularly in cholangiocarcinoma. For example, an aberrant left hepatic artery from the left gastric artery can enable radical right hepatic trisectionectomy with bilateral portal vein resection and left portal vein reconstruction without interruption of the hepatic arterial supply to segments II and III at any stage of the operation. Venography to examine the inferior vena cava and hepatic veins is occasionally useful if all three major hepatic veins are involved with tumour as an adequate inferior or middle right hepatic vein (Fig. 4.3) may obviate the need for ex vivo venous reconstruction. It is our current practice to use CT scanning of chest, abdomen and pelvis to exclude extrahepatic disease for all tumour types. Screening for primary site recurrence (e.g. colonoscopy) is also clearly important. An isotope bone scan may be useful in hepatoma, cholangiocarcinoma and some metastatic tumours, and we have recently found it to be of use in colorectal metastatic disease. This is at variance with our usual practice for patients with hepatic metastases from colorectal cancer and may reflect the late stage of presentation of the ex-vivo candidates.

Can it be avoided?

New surgical techniques such as resections that rely on the presence of an inferior or middle right hepatic vein and the possibility of hepatic venous reconstruction in situ will mean that ex-vivo liver resection will rarely be performed. In-situ hypothermic perfusion and the ‘ante situm technique’, which do not require hepatic arterial or biliary reconstruction, may be preferable in some cases where it is anticipated that the parenchymal dissection will be difficult. Careful thought must be given to these techniques both preoperatively and during the eventual operation as these methods are
widely thought to have a greater applicability than the ex vivo technique. However, the only disadvantage of the ex-vivo method is the number of necessary vascular anastomoses and the associated thrombotic risk and in this author’s opinion this is outweighed by the advantages of superb exposure and adequate hypothermic protection in some cases.

**Figure 4.2** Considerable hypertrophy of the uninvolved hepatic segments can occur as demonstrated on this CT scan (A, B). In this case, in-situ hypothermic perfusion was used to preserve parts of segments II and III with left hepatic vein reconstruction using a flap from the IVC (C: schematic diagram of resection, D: operative photograph following reperfusion). The patient had undergone 6 months of preoperative chemotherapy. At the time of writing he was alive and disease-free at 4 months postoperatively.
In this patient with a large hepatocellular carcinoma (A: MRI) a large inferior right hepatic vein is evident on venography (B) and in-situ resection was possible despite involvement of the three major hepatic veins.

**In-situ hypothermic perfusion**

The techniques involved in in-situ hypothermic perfusion (Fig. 4.4) are very similar to those employed in total vascular isolation. The aim is to provide a bloodless field combined with hypothermic cellular protection, allowing a prolonged and more precise dissection. It is thought to be more straightforward than hepatic excision and reimplantation (ex-vivo method), but it should be noted that cooling may not be even and difficulties remain when considering access to the IVC and hepatic veins. It may be performed without portal or systemic venous bypass. Cooling can be achieved by portal vein or hepatic artery perfusion and a small dose of heparin is usually given before arterial and portal vein clamping. The IVC should be dissected enough to be clamped above and below the liver and the right suprarenal (adrenal) vein is slung as this will usually need to be clamped. The IVC is clamped above and below the liver (and also the right suprarenal vein if necessary) and the infrahepatic IVC is incised above the lower clamp. Perfusion is started with a cold hepatic preservation solution and the venous effluent is actively sucked from the IVC to prevent excessive body cooling. Liver cooling can be maintained by continuous slow perfusion during the resection or by repeated cooling by perfusion every 30 minutes. A practical point is to avoid rewarming by inadvertently allowing portal perfusion to continue: in a recent case we perfused and established veno-venous bypass through the cut end of the right portal vein and some blood flowed past the cannula from the main portal vein to the left liver.

**The ante situm procedure**

The ante situm procedure combines in-situ hypothermic perfusion with separation of the suprahepatic IVC to allow mobilization for dissection of the cranial and posterior parts of the liver under direct vision. It is usual to ligate and divide the right suprarenal vein in order to gain adequate rotation of the organ. In our experience, it has been necessary also
to divide the infrahepatic IVC, with replacement by a prosthetic graft or by venous patches. This should allow the whole upper part of the liver to be moved onto the abdominal wall in order to allow access to the cranial and posterior aspects of the liver. Veno-venous bypass may be an advantage. Hepatic perfusion is as for the in-situ technique, although the liver can be placed on a heat exchange plate to help keep it cool during the resection. 18

**Figure 4.4** In-situ hepatic perfusion is summarized in this line drawing.

**Patient preparation**

**Counselling**

Preoperative counselling is one of the most important aspects of modern medical practice. When considering ex-vivo liver resection, the patient must be warned that worldwide experience is small. It is appropriate to explain the reasons behind this option and the risks and results of alternative operative and chemotherapeutic strategies. It is our unit’s practice to give each patient being assessed for liver surgery a patient information booklet. This booklet details preoperative investigations, basic anatomy and pathophysiological aspects and the impact of hepatic surgery in broad terms. It includes a review of possible postoperative complications and a description of dietary recommendations and an integrated exercise programme to aid recovery. It is written in a reassuring but realistic fashion so that patient’s expectations are not too high and so that they have stages in recovery to aim for. This booklet is given to each patient prior to
assessment as it provides a useful basic knowledge for the patient before detailed discussion on an individual basis. The individual patient also requires a face-to-face discussion with the operating surgeon and anaesthetist to run over concerns including operative risk and it is our practice to overstate this aspect and to do this in the presence of the patient’s next of kin. For ex-vivo liver resection candidates we suggest a potential inoperability rate of 20% and potential mortality risk of 20%, tending to exaggerate the risk when compared to standard liver resection or transplantation work. We suggest that our hope is that about 40% of survivors should expect to be cured by either conventional or ex-vivo liver surgery, but that it is difficult to make an accurate judgement before laparotomy. We explain that unfortunately statistics mean little to an individual and that if things go wrong then the outcome can result in a disadvantage in terms of survival. It is important that the patient is given an adequate amount of time to make his/her decision and also to discuss things with their family. Having made a decision to go ahead, the patient should clearly be supported in this decision by the medical and nursing team as a positive psychological approach to the surgery will influence the recovery time.

**Preoperative preparation**

Routine blood tests in our unit include full blood count, urea and electrolytes, liver function tests, coagulation screen and tumour marker studies (primarily carcinoembryonic antigen—CEA, CA19–9 and alpha fetoprotein) immediately before surgery as a baseline. A 10 unit blood cross match is our routine and 4 units of fresh frozen plasma are available at the start of surgery to prevent abnormalities in coagulation during the anhepatic phase. It is our routine to use some mechanical bowel preparation as this may help to reduce postoperative encephalopathy, but this is not excessive as it is important to avoid dehydration. A low molecular weight heparin is administered on the night before surgery to reduce the risk of deep vein thrombosis and pulmonary embolism. Broad spectrum antibiotics are given at the time of anaesthetic induction.

**Setting up**

**Time factors**

We have found that ex-vivo liver resection surgery can take up to 12 hours to perform. Consideration must be given to the time needed for each phase of the surgical procedure: anaesthesia, assessment of operability, veno-venous bypass, hepatectomy, liver cooling and preservation, bench resection and reconstruction, reimplantation and patient recovery. Clearly some surgical teams are quicker than others, but in comparison we would normally allow about 2 to 3 hours for a routine hemihepatectomy, 4 to 5 hours for a routine liver transplant and 9 hours for a more complex liver transplant in our centre.
Practice

For any new surgical procedure it is best to have a well-rehearsed team approach. Ex-vivo liver resection involves a combination of the techniques used in liver resection and transplantation, so a centre where these are routine should be able to proceed without special consideration. This is especially true in centres where cut-down and split liver transplantation is practised as there is no fundamental difference in the approach. Valuable lessons about the tolerance of cold ischaemia by the liver can be extrapolated from the data provided by these units, but it would be unusual for the ischaemic period to be longer than 4 hours as there is no requirement for organ transport.

Surgery with a liver available

For conditions where liver transplantation is a realistic and sensible option, it may be reasonable to consider listing the patient for major hepatic resection to be done as an emergency when a suitable donor becomes available. We have used this technique on occasion in our centre but have not applied it to the ex-vivo group. A back-up liver recipient is brought into hospital to receive the liver if the resection/transplant candidate is found to be resectable by conventional or ex-vivo means. The major drawback is the potential for a long cold ischaemia time for the donor liver if the decision for operability is difficult and it is our practice to begin the surgery whilst the donor team is at the donor site so that the delay is reduced to a minimum. Ideally, a second surgical team should be standing by to carry out the transplant on the second patient once the decision is taken. Patients assessed for exvivo surgery are probably not applicable to this situation at this time. If a tumour is not resectable by an ex-vivo technique it will not be a tumour that is treatable by transplantation. In our programme we have used this back-up technique for severe benign diseases, particularly intrahepatic biliary strictures, and it is mentioned here only for completeness.

Anaesthesia

A standard liver resection anaesthetic becomes a liver transplant anaesthetic if the ex-vivo dissection proceeds. It is our routine to place a central venous line, pulmonary artery wedge pressure catheter, arterial line, an oesophageal temperature probe and urinary catheter for careful monitoring. In the near future we plan to add to this by also using transoesophageal echocardiography. A warm air flow device covers the patient as well as a standard warming blanket underneath. We use an air-oxygen-desflurane-based anaesthesia which has been shown to minimize the derangement of postoperative liver function, with infusions of N-acetyl cysteine and antioxidants to confer hepatic protection. Veno-venous bypass lines are inserted percutaneously into the internal jugular and femoral veins as the morbidity associated with this technique is lower than with the classical surgical method.

It is sensible to begin using accepted methodology for low central venous pressure anaesthesia as in most cases the surgery will proceed in situ. In our centre we use an
epidural catheter for central venous pressure manipulation as well as postoperative analgesia, although vasodilators are sometimes necessary in addition. Inotropic support, primarily with adrenaline, is often necessary for the elderly patient in particular to maintain an adequate blood pressure during the low venous pressure phase.

If the ex-vivo operation proceeds then veno-venous bypass with high central venous pressure will be necessary. The bypass lines are heparin bonded so no additional anticoagulation should be used. The use of fresh frozen plasma early in the procedure is sensible to limit clotting abnormalities during the anhepatic phase, and cryoprecipitate and platelets should be given around about the time of reperfusion. Tranexamic acid or aprotinin is often necessary to prevent fibrinolysis and to maintain platelet function after reperfusion of the ischaemic liver. In our practice, the mean arterial blood pressure is maintained above 50 mmHg by the use of a phenylephrine infusion and after reperfusion of the liver dopexamine is infused to optimize hepatosplanchnic blood flow. Despite these manoeuvres, it would be unwise to proceed without adequate availability of cross-matched red blood cells as sometimes transfusion will be necessary. It is not our practice to use a cell saver or other blood recycling device as there is a theoretical risk of tumour cell dissemination into the blood stream.

Assessment of operability

Surgical assessment

The initial phase of surgery is full laparotomy to determine operability. In this author’s opinion, there seems little role for an initial laparoscopy except to exclude peritoneal disease and usually these cases have had major abdominal surgery in the past so adhesions may prevent a full assessment. It is our practice to use an incision that will give adequate access for assessment, whilst being fairly minimalist initially in case there are clear signs of inoperability. It is often possible to make use of an old incision site from previous surgery, but inevitably a variety of approaches are satisfactory and depend on surgeon preference and the availability of mechanical retractors. Transverse, midline, rooftop and Mercedes incisions are most usual. Adhesions should be divided to assess the primary tumour site and a careful examination of all peritoneal surfaces is carried out. Doubtful areas should be sampled for frozen section histopathological analysis and samples should also be taken from the coeliac nodes as this may suggest a more conservative approach for metastatic disease. The liver should be fully mobilized to allow adequate examination of the tumour and non-involved liver. It is usual to sling the portal triad structures individually and the inferior vena cava above and below the liver. In addition, one must decide whether to divide the right suprarenal vein or not and this will depend on the position of the tumour in relation to the inferior vena cava.

Intraoperative ultrasound

The use of intraoperative ultrasound can provide additional information about the relationship of the tumour to portal triad and hepatic venous structures, and may detect
small metastases not seen on the preoperative CT or MRI.

**Blood vessel and biliary involvement**

Although much information will have been gained by preoperative radiology, careful dissection to examine the hepatic artery and portal vein in cholangiocarcinoma or the inferior vena cava in metastatic disease or hepatoma is sensible. This can normally be done without taking any irreversible steps, although we have found that final decisions about the degree of vessel invasion will need to be made once the liver has been removed. For example, we have found that in cases where only parts of segments II and III are to be reimplanted, close application of the tumour to the portal bifurcation may necessitate resection to the level of the segmental divisions of the left portal vein. In addition, involvement of the biliary tree by metastatic tumours can necessitate a cholangiocarcinoma style approach, with resection of the biliary tree to the segmental level in order to gain a margin of surgical clearance.

**Conduits**

Major blood vessel involvement should not prevent successful surgical resection as there are many strategies for vessel repair and conduit formation. Often an adequate repair can be created by a simple suture technique or end-to-end anastomosis. We have found that a satisfactory angioplasty/venoplasty patch can be created using vein remnants from the excised portion of the liver. Alternatively, the saphenous vein can be used to replace the hepatic artery, or opened out sections can be sutured together to create a wider vessel to repair the portal vein or inferior vena cava. The internal jugular vein, internal iliac vein or common iliac vein can be used to replace a section of portal vein without long-term detriment as collateral channels should open up. If a wide area of inferior vena cava must be excised then it is our preference to use a prosthetic graft. Some experience with vascular conduits made from vessels retrieved along with donor organs has also been reported but there is a theoretical risk of allograft rejection and stricture formation. It has been our practice to use a jejunal Roux loop for biliary diversion to reduce the chance of ischaemic stricture formation following biliary reanastomosis.

**Surgical techniques for ex-vivo liver resection**

**Liver mobilization and excision**

The liver needs to be completely separated from the posterior abdominal wall and any lumbar veins draining into the IVC between the diaphragm and the right renal vein must be ligated and divided so that the IVC can be encircled in slings in these two positions. In addition, in most cases it is necessary to ligate and divide the right suprarenal vein in order to gain adequate clearance of the tumour. The common bile duct is divided and ligated. The portal vein and hepatic artery should be mobilized so that they can be clamped individually, maximizing lengths for subsequent reanastomosis. The femoral
(IVC) bypass is begun at this stage and heparin (5000 units intravenously) can be given before vascular clamps are applied to the portal vein, hepatic artery and the superior and inferior levels of the IVC to be excised. The liver is now ischaemic and it should be rapidly removed to the bench. The portal limb of the bypass is inserted and secured with a snugger technique, and once portal and systemic veno-venous bypass has been established the patient should remain stable for several hours.

**Hepatic perfusion and preservation**

Once the liver has been removed it must be flushed (down the portal vein for cooling then down the hepatic artery and biliary tree) with a suitable organ preservation solution and cooled to 0–4°C as in liver transplantation (Fig. 4.5). University of Wisconsin (UW) solution is the current ‘gold standard’ for liver preservation and is our choice for ex-vivo work, although it is certainly possible to preserve a whole liver adequately for a few hours with several other preservation fluids such as HTK solution. 28 – 31 It is not yet known how long a liver can be preserved during bench dissection, but in the accepted practice of cut-down and split liver transplantation most groups report bench times of 2–5 hours, with good results after reimplantation following total cold ischaemic times of more than 12 hours. In our own practice, the median bench time for ex-vivo resection for tumour is 2 hours and the longest has been 4 hours, although the total ischaemic time was a little over 5 hours up to reperfusion.

![University of Wisconsin solution](image)

**Figure 4.5** University of Wisconsin solution is flushed first through the portal vein for rapid cooling and then via the hepatic artery and biliary tree.

**Bench resection and reconstruction**

Hepatic parenchymal fracture techniques or ultrasonic dissection may be used without the fear of blood loss, but great care must be taken to ligate or clip all visible vessels or ducts to avoid significant haemorrhage at reperfusion (Fig. 4.6). It is our practice to use a tissue sealant such as fibrin glue at the end of dissection. The most common reason for ex-vivo hepatic work will be extensive involvement of the IVC or hepatic veins by tumour. Although the major hepatic veins are quite thick walled near the IVC, more peripherally they are very friable and great care needs to be taken with the choice of suture material.
and technique. In our three most recent resections, where parts of hepatic segments II and III have been reimplanted, we anastomosed the left hepatic vein stump to a 20 mm ringed Gore-Tex graft with a 4–0 Gore-Tex suture.

**Figure 4.6** Bench dissection is performed without fear of blood loss. (A) Resection of all except parts of segments II and III; (B) reconstruction of IVC by anastomosis of left hepatic vein to 20 mm ringed PTFE graft; (C) resection of all except segments IVb, V and VI, with subsequent reanastomosis of right and middle hepatic vein stumps to a vascular graft.

**Hepatic reimplantation and reperfusion**

The reimplantation technique is identical to that used in orthoptic liver transplantation. After the upper IVC and 75% of the lower IVC have been sutured, the liver remnant should be flushed via the portal vein with a rinse solution (as UW solution contains a high concentration of potassium and adenosine). The lower IVC is then completed and the portal vein bypass is stopped and the portal vein reanastomosed. The IVC and portal vein clamps are removed for reperfusion. It is sensible to stay on systemic venous bypass via the femoral vein cannula until after reperfusion as this lowers the IVC pressure and may help to prevent rapid blood loss at this stage. Once haemostasis has been achieved, the bypass can be stopped and a further period aimed at control of haemorrhage follows. A direct hepatic artery to hepatic artery anastomosis will usually be possible, although a saphenous vein conduit may be needed, and if so this is most easily anastomosed first to the liver end on the bench. It is likely that a direct biliary anastomosis will be under some
tension so it has been our choice to use a Roux loop to create an hepaticojejunostomy to the residual biliary tree, in our most recent cases to the segment II/III duct.

**Figure 4.7** A Roux loop of jejunum for biliary anastomosis may prevent stricture formation. In this case the hepaticojejunostomy is to the segment II/III duct (A) following reimplantation of the liver remnant (B).

(Fig. 4.7). There is no need for a t-tube or other biliary stent. Other authors have used a duct-to-duct anastomosis but reported a high incidence of biliary stricturing. 20

Finally, in our most recent cases we have used a 4 mm PTFE graft to create an arteriovenous fistula in the iliac vessels to increase the blood flow in the IVC graft. We have chosen 4 mm as this is unlikely to cause heart failure and we have used PTFE to prevent expansion of the fistula, which may occur with direct anastomosis or with venous conduits. It is our hope that the use of a small arteriovenous fistula may reduce the chance of IVC graft thrombosis and may obviate the requirement for long-term anticoagulation.

**Postoperative care**

The postoperative care of the ex-vivo liver resection patient should be similar to any major liver resection or liver transplant candidate. Nursing care should be initially on a high dependency ward or intensive care unit. Although inpatient care will usually be required for between 10 days and 3 weeks, our most recent case was fit for discharge at 6 days despite being 75 years old and having only parts of segments II and III reimplanted. Short stays can be anticipated in cases where there has been significant preresection hypertrophy because of the size of the tumour, as in this case where the major tumour was 17 cm diameter and the resected specimen weighed in excess of 2 kg. It is our practice to use intravenous antibiotics for the first 5 days whilst assessments for liver failure are being made. A period of enteral supplementation may be useful in addition. Gastric acid secretion suppression with a proton pump inhibitor or H₂ antagonist is sensible as there is often an associated acute portal hypertension which may be additive to postoperative stress ulceration.

The prothrombin time seems to be most predictive of hepatic functional recovery. A
daily requirement for fresh frozen plasma and 20% human albumin solution (200 ml/day) can be calculated from the blood results. The ALT is inevitably high (300–1000 IU/1) for the first few days and reflects the period of hepatic ischaemia. Our group uses N-acetyl cysteine by intravenous infusion for major hepatic resection cases as we have found it to be useful in our fulminant hepatic failure programme. In addition, there is usually a requirement for potassium, magnesium and phosphate supplementation intravenously following very radical resection. Low dose intravenous infusion heparin (40 unit/kg/24 hours) is used in our unit to help prevent hepatic arterial thrombosis in our live transplant and exvivo resection programme and the haematocrit is kept low at 25–35%.

In the long term, we have chosen to anticoagulate all of our ex-vivo liver resection patients with warfarin, aiming for a prothrombin time of two to three times normal to prevent IVC thrombosis. The use of a small arteriovenous fistula, as described above, may obviate the need for long-term anticoagulation. However, if the warfarin is not causing any significant problems then it will provide an extra safeguard against thrombosis so it is likely that the majority of our patients will continue on this drug in the long term.

Complications of ex-vivo liver resection

**Vascular thrombosis and stenosis**

A sudden rise in ALT postoperatively should be an indication for Doppler analysis of the portal vein and hepatic artery, and if there is any doubt then arteriography should be performed. In our experience, if a thrombosis occurs more than 7 days postoperatively after major liver resection it can be managed conservatively. Anticoagulation with intravenous heparin and then by warfarin for 3 months should allow portal vein recanalization or arterial collateral formation. Dopexamine appears to increase splanchnic blood flow and we have used this with both portal vein and hepatic artery thrombosis. This is at variance with experience in liver transplantation where regrafting is almost always required if early arterial thrombosis occurs. Unfortunately, in addition, significant stenosis can occur in any of the vascular anastomoses. They are usually detected by Doppler ultrasound in response to abnormalities in liver function tests, particularly a rise in ALT. Radiological intervention can solve most problems by balloon angioplasty or the use of endovascular stents.

**Biliary strictures**

There is a theoretical risk of biliary or biliaryenteric stricture formation. We have not experienced any difficulty in this regard and this may be because of our preference to hepaticojejunostomy. Strictures of the external biliary tree should be dealt with in standard fashion. Intrahepatic strictures as a result of preservation injury or arterial thrombosis are much more difficult to deal with and some consideration would have to be given to liver transplantation in order to correct this. We have used liver transplantation in one patient following a failed biliary reconstruction after the development of severe
intrahepatic stricturing as a result of a right hepatectomy for colorectal metastases 18 months previously: at 5 years he is tumour free.

Long-term follow-up

Long-term follow-up after ex-vivo liver resection for tumour should be designed to examine the patients primarily for tumour recurrence, but also for complications related to the extensive hepatic resection and vascular replacement. Tumour marker studies (CEA, CA19–9, AFP) may indicate recurrent disease, although we have found CA19–9 to be often more related to biliary obstruction and it is more difficult to interpret than the other tumour markers. Regular CT of chest, abdomen and pelvis forms the basis of follow-up for complications and tumour recurrence at our centre, at 3, 6, 12, 18 and 24 months and then annually thereafter, but there are no clear cut guidelines. Isotope bone scans may also play a role in some tumour types. Regular blood tests for liver enzymes and bilirubin are helpful. A progressive rise in ALT may indicate a vascular stenosis impeding hepatic inflow or outflow. Doppler ultrasound should usually be diagnostic, with rapid recourse to arteriography and venography when necessary for consideration of endovascular correction. A rise in alkaline phosphatase or bilirubin may indicate an ischaemic biliary stricture or recurrent disease causing biliary obstruction.

Long-term results

There are very few series of ex-vivo liver resection in the world literature. Published cases and small series have concentrated on surgical technique and even perioperative mortality risk appears to be of the order of 10–40%, but these patients have been in the terminal phase of their illness at the time of surgery. Disease recurrence is inevitable for some of the surviving patients as the tumours have been so extensive at the time of presentation. Our experience does suggest, however, that a significant period of good quality palliation can be achieved by these elaborate techniques. In addition, as these techniques become more common place, the risk should reduce. This is exemplified by our most recent case where there was no requirement for blood transfusion and the patient was fit enough for discharge from hospital by day 6 despite being 75 years of age. At the time of writing this patient is alive with asymptomatic recurrent disease at 33 months from surgery.

Considering this author’s direct experience to date with IVC resection and ex-vivo liver resection for malignant tumours, we have dealt with 12 cases to date of whom 10 had colorectal metastases. In five cases, ex-vivo resection was necessary and two of these patients died within 30 days from multiorgan failure. One of the other seven patients, in whom insitu IVC resection was carried out, also died from multiorgan failure. This high mortality rate is comparable to that in other series and reflects the gravity of the surgery combined with the late stage of disease in these patients.

In the long term, disease recurrence has been a problem. Our longest surviving ex-vivo
patient is alive at 33 months. A second patient lived for 30 months, and although the resection had been carried out for colorectal metastases, she died from complications relating to the development of a renal cell carcinoma. The other three ex-vivo patients have died with recurrent disease within 2 years. These data lend support to arguments for the use of adjuvant therapies despite the potential risk of systemic sepsis associated with the use of prosthetic graft material, and again relate to the late stage at presentation.

Prospects for transplantation

There is much experience in transplantation for hepatoma. There is no doubt that it is a suitable therapy for patients with small hepatomas in cirrhotic livers, where the cirrhosis is the primary indication for the transplant. Unfortunately, however, where the hepatoma is the primary indication for liver transplantation because of the enormity of the lesion, the results of transplantation have been almost universally poor. Similar experience is reported for cholangiocarcinoma and for colorectal metastases. This is probably related to the necessary immunosuppression used following organ transplantation, and the development of more specific immunosuppressive agents may enable transplantation to be used in the future for these tumours.

Our group has been investigating the use of cluster resection and multivisceral grafting as an alternative for neuroendocrine tumours. These are most often tumours of midgut origin with foregut metastases and adequate lymphadenectomy involves both the coeliac and superior mesenteric arterial distributions, so surgery involves excision of all organs supplied by these arteries: stomach, duodenum, liver, pancreas, spleen, jejunum, ileum and large bowel as far as the descending/sigmoid colon. This approach provides superb access to the para-aortic lymph nodes for adequate lymphadenectomy. This is followed by implantation of a multiorgan block of liver, pancreas, duodenum, jejunum and ileum. We have used a Roux loop (created from the transplanted jejunum) to the oesophagus, as gastric stasis can be a problem for several weeks following stomach transplantation. An ileostomy is used to provide access for regular endoscopic biopsies for careful monitoring for rejection and cytomegalovirus infection during the first few months, but it is our practice to reverse this at about 6 months if graft function is stable. We have found that the donor innominate artery forms an ideal conduit for anastomosis of the donor coeliac and superior mesenteric arteries to the recipient aorta. If purely a foregut neuroendocrine tumour (arising in the pancreatic tail), then a lesser cluster resection can also be appropriate to take the stomach, duodenum, liver, pancreas and spleen, with subsequent implantation of a liver-pancreas block. Our early results with neuroendocrine disease are more encouraging than with other tumours, but long-term analysis is necessary. This may be related to the more extensive resection or, more probably, to the tumour type.

We have also investigated the effect of liver transplantation and resection on the growth of a colorectal cancer cell line in an attempt to examine the links between cancer regrowth, hepatocyte growth factor (HGF) and immunosuppressed and nonimmunosuppressed controls. Serum samples were taken before and after operation (days 1, 4 and 30) from patients undergoing hepatic resection and liver transplantation,
and from three control groups: major abdominal surgery, renal transplantation and normal volunteers. The human colonic cancer cell line LoVo was incubated for 4 days in a 5% concentration of the patient’s serum in a medium. Tumour cell proliferation was measured by tritiated thymidine incorporation and an ELISA assay was used to measure hepatocyte growth factor (HGF). The immunosuppressed and non-immunosuppressed control groups showed no significant differences from normal. Serum from liver resection patients stimulated tumour cell growth throughout the experiment and this was associated with high levels of HGF. Serum from liver transplant recipients did not stimulate tumour cell line growth, but had high levels of HGF before and immediately after surgery, with rapid resolution after successful transplantation. This experiment, therefore, has not demonstrated a link between the HGF response of liver regeneration or recovery and cancer growth. An alternative growth factor may be active in the resection group both before and after resectional surgery. Our results supported the hypothesis that rapid tumour recurrence following liver transplantation is the result of the necessary immunosuppression. The development of more specific immunosuppressive agents may enable transplantation to be used in the future for more hepatic tumours, but for the moment the role of transplantation remains very limited.

Summary

Techniques for hepatic resection continue to advance and the involvement of liver transplant teams has aided the development of new types of resection and anaesthetic techniques. Short-term warm hepatic ischaemia is practised widely but there is often a necessity to hurry during this demanding surgery as prolonged warm ischaemia can result in irreversible liver failure. Transplant experience, particularly relating to cut-down and split liver techniques, has demonstrated that bench dissection and reimplantation after long periods of cold ischaemia can be successful in the majority of cases. Tumours involving all three major hepatic veins and IVC invasion continue to pose a surgical challenge and the combined techniques of hepatic resection and transplantation offer a potential lifeline for this unfortunate group of patients. Exvivo liver resection for tumour therefore deserves consideration.

Summary panel

The short-term survival of untreated patients with both primary and secondary liver tumours, the unpredictability of chemotherapy response on an individual patient basis and the disappointing results of transplantation for cancer provide adequate impetus for attempts to extend the boundaries of liver resection as far as possible. Major improvements in hepatic surgery have occurred during the past few years and improvements in anaesthesia have been integral to this success. Pringle’s manoeuvre and total vascular isolation (hepatic vascular exclusion) are used widely, and this short-term warm ischaemia appears to be well tolerated. Tumours involving all of the major hepatic veins with or without IVC invasion, and particularly tumours involving the hepatocaval
confluence and needing IVC replacement, continue to pose a surgical challenge. Ex-vivo resection offers a potential lifeline for this group of patients.

Key points

• Hepatic resections involving IVC and portal structure reconstructions are occurring with increasing frequency.
• When considering patients for ex-vivo resection, a full cardiorespiratory work-up is mandatory.
• Careful consideration must be given to residual hepatic reserve.
• Patients and relatives must be counselled preoperatively with regard to the limited world experience and operative risk.
• Anaesthesia for ex-vivo liver resection: A standard liver resection anaesthetic becomes a liver transplant anaesthetic if the ex-vivo dissection proceeds.
• Phases of ex-vivo liver resection surgery:
  Liver mobilization and excision
  Hepatic perfusion and preservation
  Bench resection and reconstruction
  Hepatic reimplantation and reperfusion
  A Roux for biliary anastomoses may prevent stricture formation
  Consider a small a-v fistula if a prosthetic IVC graft has been used.

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Further reading

5

Resection of smal hepatocellular carcinoma in cirrhosis

Claude Smadja and Giacomo Borgonovo

Introduction

There is some discrepancy in the literature regarding the definition of small hepatocellular carcinoma (HCC). In surgical practice, 5 cm has emerged as the most suitable cut-off between small and large HCCs when a surgical approach is contemplated, despite the fact that transplant surgeons consider 3 cm as the upper limit of small HCCs. Although ablation by thermal injury and ethanol injection has gained a wide success, at present partial liver resection and liver transplantation still offer the best chance for cure. Neither adjuvant therapy with chemotherapy nor preoperative chemoembolization has been shown to be of any benefit in reducing the risk of recurrence or improving survival. Despite the growing role and the encouraging results of liver transplantation in the treatment of HCC in cirrhosis, and in view of the shortage of organs, partial liver resection remains the therapy of choice. Over the last two decades, increased screening of patients with chronic liver disease has led to a rise in the number of resections of HCC in cirrhosis. In specialized centres, noteworthy progress in operative techniques and improvements in the surgical care of patients with liver cirrhosis have been achieved. However, while the risk of hepatic resection in cirrhosis has decreased dramatically during the last 15 years, the operation remains an arduous one in some cases. Nevertheless, it is imperative that we demystify this procedure, which can be relatively safe provided that some rules are respected. In other words, careful and precise preoperative evaluation is paramount in order to select those patients who might benefit from liver resection or liver transplantation.

Pathological classification of HCC

The recent increase in the number of resections performed for HCC in cirrhosis has allowed pathologists to establish prognostic factors, especially those indicating liver resection. In Western countries, indications for resection of HCC are less frequent than in the East. It is, however, essential to use a very simple classification that permits comparison of the results from different teams. In our centre, HCCs are divided into three groups: group I corresponds to an expanding tumour which is defined as a round, well-demarcated tumour, compressing the adjacent liver parenchyma and surrounded by a capsule which may be visible on gross examination (Fig. 5.1), and which is often...
infiltrated by tumour cells but never ruptured; group II corresponds to an expanding HCC, but in which the capsule has been ruptured in some regions (Fig. 5.2). In our experience, tumour spreading to distal portal vein branches and satellite nodules was significantly less frequent in group I than in group II HCCs; 5 group III is an infiltrating tumour (Fig. 5.3), which is defined as a tumour with no precise landmarks, where the normal parenchyma bordering the HCC is continuously replaced by neoplastic tissue. The prognosis of infiltrating tumour is poorer than expanding tumour. 6 This classification is simple and carries the major advantage over other classifications that HCC characteristics can be accurately detected by preoperative radiological imaging (Fig. 5.4).

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**Figure 5.1** Group I HCC. The tumour is surrounded by a complete and thick capsule.

**Figure 5.2** Group II HCC. The tumour is expanding, but the capsule is incomplete with a rupture (white arrow) and intrahepatic metastases (black arrows).
The tumour is infiltrating the adjacent liver parenchyma, without capsular interposition.

**Figure 5.3** Group III HCC. The tumour is infiltrating the adjacent liver parenchyma, without capsular interposition.

**Natural history of small HCC in cirrhosis**

Precise knowledge of the natural history of the underlying disease is of major importance in the management of HCC, since more than 80% of patients suffering from HCC have associated cirrhosis. Ginès et al. studied the natural history of compensated cirrhosis, irrespective of its origin. They showed that 5 years after the diagnosis of cirrhosis the probability of developing decompensated cirrhosis was 35% and the survival rate probability was 70%. These data should be taken into account when adopting a therapeutic choice and in the analysis of the results of liver resection for small HCC in cirrhosis. Therefore, to evaluate the efficacy of surgical therapy, it is essential to know the natural history of small HCC in cirrhosis. There are limited data in the literature concerning this topic. Ebara et al. evaluated the outcome of 22 patients with untreated small HCCs (<3 cm). Patients were followed for 6 to 37 months without therapy. The mean 1-, 2-, and 3-year survival rates were 90.7%, 50.0% and 12.8%, respectively. In parallel, when taking into account also the severity of the liver disease, Barbara et al. showed that cirrhotic patients with a good liver function (i.e. Child-Pugh’s class A) and those with an impaired liver function (i.e. Child-Pugh’s class B or C) had an estimated 3-year survival rate of 62% and 0%, respectively.
Figure 5.4 CT scan aspect of the different anatomic types of HCCs. (A) Group I: expanding HCC, note the presence of a complete and thick capsule; (B) group II: expanding ruptured HCC, (1) rupture of the capsule (arrowhead) and thrombosis of the feeding portal branch (arrow), (2) rupture of the capsule (arrowhead) and intrahepatic metastases (arrow); (C) group III: infiltrating HCC, (1) portal venous phase study, (2) late phase study.

respectively. In this last series, the overall 3-year survival rate was 21%. Moreover, Llovet et al. \textsuperscript{11} have shown that patients with HCC but without an extrahepatic spread or a poor liver function had a spontaneous survival at 1 and 3 years of 80% and 50% respectively. Given the results of these studies, the operative mortality of small HCCs treated by partial liver resection or liver transplantation should be less than 10% and the 3-year survival rate equal to or greater than 60% for the patients with good liver function.
Screening for HCC and preoperative radiological investigations

There is potential interest in screening cirrhotic patients, in order to detect symptomless HCCs of small size, which are more accessible to surgical therapy than symptomatic tumours. Indeed, the annual risk of developing HCC in cirrhosis is estimated at 5%; chronic hepatitis B and C are recognized as the major factors increasing the risk of HCC. The most commonly used screening tests are serum α-fetoprotein and ultrasonography (US). Serum α-fetoprotein has low sensitivity and is not specific for small HCC, since it rises with flare-ups of active hepatitis. However, a serum α-fetoprotein level >400 ng/ml is generally considered as diagnostic of HCC. Ultrasonography is used as a first step in the diagnostic work-up of cirrhotic patients. Its accuracy has increased since the availability

Figure 5.5 Helical CT scan assessment of a small HCC in cirrhosis located in segment VI. (A) Arterial phase study showing a hypervascular nodule, and the lack of intrahepatic metastases. (B) Portal vein phase study demonstrating the patency of the portal branch of segment VI (arrow). (C) Late phase study highlighting the presence of a thin capsule.
of broadband transducers and the introduction of new signal processing algorithms. The sensitivity of US in the detection of HCC in cirrhosis is 78% and the specificity 93%. The use of ultrasound hepatospecific contrast medium seems to further ameliorate these percentages. On the other hand, US is relatively poor at identifying small multifocal lesions in cirrhotic patients. As a consequence, in order to confirm US findings and to assess the resectability of the tumour, other radiological investigations are used. Helical biphasic CT scans are the most used technique of imaging for diagnosis and staging of HCC. This investigation must be performed by a very precise technique (Fig. 5.5), in order to specify the characteristics of the tumour and to detect some prognostic factors, such as the presence of a capsule and its rupture, satellite nodules, and vascular involvement, which can be confirmed by a percutaneous biopsy of the thrombosed vessel. The sensitivity of CT scanning in detecting nodules in the cirrhotic liver is proportional to the size of the lesion. Nodules larger than 3 cm are identified in 95% of cases, but this percentage drops to 80% for nodules of 1–3 cm. Even less successful is the detection of small and hypovascular lesions whose identification is still very difficult. In these cases the place of magnetic resonance imaging in the diagnosis of HCC is still under discussion.

Whenever the diagnosis is questionable a fine needle biopsy is mandatory. It can, nevertheless, be difficult to distinguish large cirrhotic nodules from well differentiated HCC or low-grade dysplastic nodules from HCC, using either needle or wedge biopsy. Moreover, liver biopsy carries the risk of tumour spread, although it is worth mentioning that one technique of tumour biopsy may obviate this risk. In a recent prospective study, conducted by Maitre and undertaken at the Hôpital Antoine Béclère, comparing the preoperative radiological findings and the pathological data obtained from the resected liver, helical CT scanning turned out to be the most accurate investigation to determine the tumour characteristics and to assess correctly its resectability (unpublished data).

Factors influencing recurrence of HCC after partial liver resection

Following liver resection for HCC in cirrhosis, tumour recurrence is the main cause of poor prognosis. The risk of intrahepatic tumour recurrence after resection ranges from 70 to 100% at 5 years. Most of these recurrences are the result of growth of HCCs, different to those of the resected tumour, as documented by studies showing a different clonal origin between the initial and recurrent HCC. Thus initial tumours that relapsed exhibited more profound genomic abnormalities than tumours followed by de novo neoplasms. Precise knowledge of the preoperative factors that influence recurrence after resection and, in turn, postoperative survival, is of paramount importance, since it helps surgeons to select patients with the best prognosis after liver resection. Also, scores based on the histopathological examination of the resected specimen, such as the invasiveness scoring system based on pathological criteria, may be useful for the selection of the potential candidates for adjuvant therapy studies. The risk of postoperative recurrence depends on tumour characteristics and decreases in the presence of a small, single and encapsulated HCC, in the absence of capsule rupture,
portal vein invasion or intrahepatic metastases. Hepatitis status has also been incriminated as a significant risk factor for tumour recurrence, as well as the severity of liver fibrosis. The underlying liver disease seems to have a greater influence on 5-year and long-term survival after liver resection than the characteristics of the initial tumour.

Therapeutic options for HCC in cirrhosis

Partial liver resection and liver transplantation seem to offer the best chances of cure for small HCCs. However, the lack of controlled data for most therapeutic modalities, including chemoembolization and percutaneous ethanol injection, thermal ablation by radiofrequency and cryotherapy, makes it difficult to assess whether any of these therapies is associated with a significantly improved survival. The development of surveillance programmes has allowed the detection of small asymptomatic HCCs which are amenable to surgical therapy. Nevertheless, it must be stressed that the prognosis of HCC is largely dependent on the underlying liver cirrhosis. This suggests that liver transplantation and nonsurgical treatments should be included in the therapeutic armamentarium. Percutaneous ethanol injection and radiofrequency ablation have gained wide popularity. Both techniques are highly effective and safe in the treatment of single small (<3 cm), encapsulated tumour, but their palliative role is confirmed by the high rate of local and distant recurrence. Moreover, in patients with subcapsular tumour and poor degree of differentiation the risk of tumour seeding after percutaneous radiofrequency is augmented. As far as transplantation is concerned, even if indications based on tumour size and the number of nodules seem to be slightly expandable, only a fraction of patients with small HCCs have the opportunity to receive a transplant, since demand exceeds the number of donor organs and, as a consequence, in the centres where the therapy is available the waiting lists grow longer. All efforts must therefore be made to evaluate fully the possibilities of partial liver resection.

Partial liver resection in cirrhosis

Surgical anatomy

Modern hepatic surgery is based upon functional liver anatomy, according to the vascular architecture of the organ. The liver is schematically divided into three major portions: the right liver, the left liver and the dorsal sector (Figs 5.6 and 5.7). According to Couinaud, the three hepatic veins (i.e. right, middle and left) divide the right and left livers in four sectors called portal sectors, each of which receives a portal pedicle. The limit between the right and left livers is represented by the main portal scissura (Cantlie’s line) in which the middle hepatic vein runs. Each hemiliver includes two portal sectors. The left liver (Fig. 5.6) is divided by the left portal scissura containing the left hepatic vein into an anterior sector which includes two segments, III and IV, and a posterior sector
represented by segment II. The quadrate lobe (segment IVB), located in front of the hilum, corresponds to the anterior part of segment IV, the posterior part corresponding
to segment IVA. The anatomy of the right liver should be described with the liver in its normal place in the abdominal cavity (see Fig. 5.6). Indeed, the classic lateral right sector (i.e. segments VI and VII) is posterior and lies behind the median sector (i.e. segments V and VIII) which is in fact anterior. This in vivo anatomic description is clearly demonstrated by an analysis of the morphological appearance of the liver on CT scanning.
This information is of paramount importance for the practice of liver resection in cirrhotic patients for several reasons. First, atrophy or hypertrophy of the right liver currently observed in cirrhotic patients may alter the normal anatomy and should be taken into consideration for the type of resection to be performed: for example, major atrophy of the right liver should warrant formal right hepatectomy for HCC located in this hemiliver rather than segmentectomy or sectorectomy. Second, the difficulty of fully mobilizing the right liver in cirrhosis because of the presence of a right liver hypertrophy should be taken into account when resection is to be performed for HCC located into the right posterior sector. Third, the major anatomical alterations sometimes encountered in cirrhosis render the location of the surgical limit of a segment or a sector difficult to delineate. Each sector of the right liver (Fig. 5.6) is finally divided by the plane of the portal bifurcation into segments. The superior portion of the anterior sector is called segment VIII and the inferior portion segment V. For the posterior sector, the superior portion corresponds to segment VII and the inferior portion to segment VI. The dorsal sector is made up of two segments separated by the middle hepatic vein, left (segment I or caudate lobe) and right (segment IX), incorporated in the posterior portion of the right liver 46 (Fig. 5.7). This segment IX is a separate entity located behind the hilum and covering the inferior vena cava. The dorsal sector is tightly connected with the right liver without precise anatomic landmarks. It receives its own vessels from the right and left branches of the portal vein and hepatic artery. Its hepatic veins drain directly into the inferior vena cava and represent an important pathway of venous drainage into the inferior vena cava. Finally, it should be mentioned that, following Couinaud’s study, Makuuchi et al. 47 confirmed the ultrasonic presence of a significant inferior right hepatic vein in about 10 to 20% of cases, the existence of which offers new surgical possibilities. Indeed, tumours located in the superior portion of the posterior sector (i.e. segment VII) may lead to the performance of a bisegmentectomy VII–VIII and those encasing the right hepatic vein distally.

**Specific risks linked to partial liver resection in cirrhosis**

Liver resection is sometimes poorly tolerated by cirrhotic patients, with the potential risk of death by liver failure jeopardizing the overall clinical picture. The presence of portal hypertension may initiate postoperative complications such as variceal rupture and the development of ascites. Finally, non-specific postoperative surgical complications such as abdominal infection may also precipitate liver failure.
Liver regeneration is altered in cirrhosis. Therefore, in patients with good preoperative liver function, postoperative liver failure is mainly related to the volume of non-neoplastic liver parenchyma removed during the resection. Liver failure may be induced by intraoperative bleeding. Indeed, there is a direct relationship between intraoperative bleeding and supervening liver failure. Noteworthy are findings that, despite selection of only Child’s A patients for hepatic resection, the presence of a significant portal hypertension was the best predictive factor of unresolved postoperative liver decompensation.

Complications of portal hypertension

Although there are no controlled data, and no clear relationship has been established, the risk of variceal rupture after liver resection is obviously increased. It seems logical to postulate that the extent of parenchymal resection might influence the occurrence of this
serious complication, which is related primarily to the diminution of the liver vascular bed after hepatic resection, which leads to an increase in portal pressure. In our experience, intractable ascites occurred in 6% of cirrhotic patients undergoing liver resection for HCC. It has been shown that the presence of significant portal hypertension was the best predictor of postoperative ascites following hepatic resection for a small HCC. Ascites occurred in 55% of cases and had a severe influence on prognosis. Ascites formation has serious adverse effects, distends the abdominal cavity, has repercussions on the ventilatory function and may jeopardize the abdominal incision with wound dehiscence, resulting in ascitic leak and subsequent infection. Leakage of ascites through drains may result in major fluid loss and electrolyte imbalance.

Preoperative nutritional status, postoperative complications and infection

The prevalence of malnutrition in hospitalized cirrhotic patients varies from 30 to 70%. Factors associated with an increased risk of postoperative complications are weight loss >10% of current weight and a serum albumin level <30 g/l. Whether patients undergoing hepatic resection benefit from preoperative artificial nutrition is a matter of debate. Some insight into the issue comes from the prospective randomized study of Fan et al. who showed that perioperative total parenteral nutrition reduced postoperative morbidity, weight loss and liver failure. Cabre et al. have shown that in selected malnourished patients a short course of enteral nutrition is able to ameliorate malnutrition or a hypercatabolic state. It often occurs that in our clinical practice these patients are unfit for hepatic surgery. In most cases, in our opinion, a short work-up readily allows prompt surgery without any form of preoperative nutrition.

The risk of septic complications is high in cirrhotic patients, due to defects in cellular and humoral immunity, and a deficiency in the non-immune acute infectious mechanism. Moreover, total and prolonged hepatic pedicle clamping during hepatic resection might facilitate bacterial translocation from the gut to the blood. Prevention of intraoperative bleeding and contamination of the peritoneal cavity by drains, and the use of perioperative short-term antibiotic prophylaxis in patients at risk should improve the results.

Selection of patients

Indications of partial liver resection in cirrhotic patients are dictated by the characteristics of the tumour and the hepatic reserve status. Patients with a single and small encapsulated nodule are the best candidates for liver resection. In any case, if doubts exist about the nature of an associated portal vein branch thrombosis, there is an indication to perform a fine needle guided biopsy. When two nodules are present, great care should be taken to determine whether localized portal spreading has occurred. In such a case, resection is still possible, but should be extended to the territory supplied by the feeding portal branch. It is a matter of debate, in view of the very poor prognosis and the significant risk of surgery, whether infiltrating tumours deeply located in the parenchyma should be removed. In our experience, even extensive removal of non-neoplastic liver parenchyma
around the tumour did not reduce recurrence, and no patient lived more than 2 years after radical resection. 6

Liver function status is crucial to the prognosis of cirrhotic patients undergoing liver resection. There is no single biochemical value that is predictive of postoperative liver failure, even if serum bilirubin of greater than 34 µmol/1 (twice the normal value) is generally considered as an ominous sign and excludes the patient from surgery. 61, 62 Pugh’s modification of Child’s classification is a simple, reproducible and reliable method to determine preoperatively the hepatic functional reserve. There is consensus that only patients with a score under 7 (i.e. Child-Pugh’s class A) should be resected. The use of this criterion showed prospectively that the risk of hepatic resection was extremely low in patients with a good liver function (i.e. Child-Pugh’s A patients; mortality 3.7%) and significant in cases of moderate liver failure or poor liver function (i.e. Child-Pugh’s B and C patients; mortality 16.7%). 6 In no case are patients with ascites candidates for partial liver resection. It is our opinion that young cirrhotic patients with ascites and a small HCC should always be considered for liver transplantation.

Many sophisticated tests have been proposed for improved measurement of residual hepatic function, the most validated of them being indocyanine green clearance at 15 minutes. 3, 62–64 When the retention rate is less than 10%, any type of resection is possible; for values between 10 and 20% a bisegmentectomy is well tolerated, while for values between 20 and 29% only a unisegmentectomy is indicated. The use of a combination of indocyanine green clearance, serum bilirubin level and the presence or absence of ascites has enabled Japanese surgeons to reduce operative morbidity to 1%. 65 Later, the assessment of wedged hepatic pressure was suggested as a means to improve the selection of patients for liver resection. 53 This last study suggests that hepatic resection should be proposed only in patients with a hepatic venous gradient below 10 mmHg. Information on the volume of the hepatic remnant measured by CT scanning may enhance the accuracy of assessment. The formation of monoethylglycinexylidide, the main lidocaine metabolite, might also provide an additional tool to assess preoperative liver function. 66 The potential usefulness of this test seems to be confirmed by the fact that formation of the metabolite decreases as liver disease evolves, probably because of a reduction in the cellular mass. 67 A further simplification in the preoperative assessment of liver function comes from the use of the C13-aminopyrine breath test that reproduces the results obtained by the monoethylglycinexylidide (MEGX) test. 68 Important signs of portal hypertension or previous haemorrhage from variceal rupture should be viewed as a relative contraindication to liver resection, although preoperative variceal eradication has been suggested to reduce the risk of bleeding.

Finally, given the current epidemiology of hepatitis C virus infection in Western countries, we should expect that most of the patients with HCC who are candidates for surgery will, in the future, be aged over 70 years. This implies that age should also be taken into account in the selection of patients for surgery, even though it has been shown that the treatment policy for HCC in the aged patient should be identical to that adopted in the young subject. 69, 70
General guidelines for liver resection of HCC in cirrhosis

Resection is more difficult in patients with cirrhosis than in those with a normal liver parenchyma. Perioperative bleeding is frequent. Difficulties are mainly related to the presence of portal hypertension and to the distortion of anatomy induced by the process of atrophy-hypertrophy and fibrosis. Haemorrhage and lymphatic spillage occur mainly during severance of the liver ligaments and the posterior peritoneum. These are usually thickened and contain dilated lymphatic and venous vessels; therefore, the simple dissection and mobilization requires careful haemostasis to avoid insidious perioperative bleeding and postoperative collection or ascites. The intense fibrosis that occurs in cirrhosis makes it difficult to identify intraparenchymal vascular structures and is, in association with portal hypertension and fragility of hepatic veins, the main cause of haemorrhage during parenchymal transection. In recent years, liver resections have been performed using minimally invasive techniques. In cirrhotic patients, this approach may be used only for small tumours located anteriorly (i.e. segments III, IVB+V), or for HCCs requiring a bisegmentectomy II–III.

Anatomical resection

As a consequence, the treatment of choice for small HCC in cirrhosis is limited resection which has the following advantages: (1) removal of a small amount of functioning parenchyma, but a free margin of 10 mm should be respected; (2) since HCC spreads through the regional portal system, anatomical resection allows for the complete removal of the tumourrelated domain, including possible microscopic daughter nodules around the mass; (3) dissection through the known anatomical planes prevents accidental injury to vascular structures and, consequently, potential major bleeding. By contrast, although proven feasible and safe in cirrhotic patients with large tumours, major hepatic resections should be avoided in the case of small HCC, because of the risk of postoperative hepatic failure and portal hypertension complications. Nevertheless, it should be mentioned that it has been reported recently that preoperative portal vein embolization in cirrhotic patients might allow atrophy of the liver to be resected with compensatory hypertrophy of the remaining liver, thus increasing the safety of liver resection.

Non-anatomical resection (atypical resection)

This is indicated only in cases of tumours confined at the boundaries of two or three adjacent segments when an anatomical resection is not feasible, mainly because of atrophy of the liver to be left after liver resection. Transection through non-anatomical planes exposes the patient to continuous haemorrhage during parenchymal transection, and prolonged total blood inflow clamping (with its attendant risk to parenchymal function) is often required to control major blood loss.
Liver exposure

Position of the patient

The patient is positioned supine, turned 30° to the left on his sagittal axis with the right arm along the body. Tilting the table will give an adequate view, even for posteriorly located tumours. When a bisegmentectomy of segments II–III has been planned, the patient is left supine. A crossbar or special device should be fitted at the head of the table for two self-retaining retractors in order to widen the laparotomy, by elevating the costal margin.

Incision

For most hepatic resections a right S-shaped subcostal incision extending from the midaxillary line to the external margin of left rectal muscle enables good liver exposure. Also the incision popularized by Hasegawa et al. might be used. For tumours located in the left lateral segments (i.e. segments II and III), the right portion of the incision should be reduced or the subcostal incision replaced by an upper midline laparotomy. Once the peritoneum is entered, the round ligament (ligamentum teres) is not systematically divided in order to avoid suppression of possible collateral circulation through a recanalized umbilical vein that might augment portal hypertension.

Exploration and liver mobilization

Most of the information concerning morphology and location of the tumour is obtained from preoperative imaging; rarely does manual exploration add further information, in particular for deeply located tumours. Variations of arterial anatomy (which are detectable by CT scan) are preliminarily sought out in order to avoid accidental ligation and consequent ischaemia during liberation of the liver. The most common findings are a right hepatic artery originating from a superior mesenteric artery, and a left hepatic artery from a left gastric artery. The former runs on the right border of the hepato-duodenal ligament, the latter in the lesser omentum. Mobilization should be as minimal as possible, to avoid fluid spillage and haemorrhage. For anteriorly located tumours (segments III, IVB, V) sectioning of the falciform ligament (while preserving the ligamentum teres) usually suffices. In the other locations, division of the triangular and coronary ligaments on the side of the lesion is mandatory. For right-sided nodules the posterior peritoneum is divided as well. This manoeuvre, associated with division of the triangular ligament, allows the liver to be turned to the left, with initial exposure of the inferior vena cava that is fixed in its upper portion to the liver by the suspensor caval vein ligament. This ligament is particularly thickened in cirrhotic livers and its division should only be performed after having meticulously secured haemostasis. The retrohepatic vena cava is only completely free after careful ligation and division of all short accessory hepatic veins. This manoeuvre is mandatory for tumours located in the right posterior (i.e. segments VI–VII) and dorsal (i.e. segments I–IX) sectors. For tumours arising in the left
segments of the liver and the dorsal sector, the lesser omentum is opened and the falciform, left triangular and coronary ligaments are divided. The round ligament is divided in the case of left hepatectomy (i.e. segments II–III–IV), but can be preserved in case of bisegmentectomy II–III.

**Intraoperative ultrasonography**

Although preoperative work-up provides most of the information needed for a correct surgical strategy, intraoperative US still plays an important role in defining intrahepatic anatomy and, in some cases, serves as a complement to diagnosis. In cirrhosis, the difficulty of finding the usual superficial landmarks makes US an indispensable tool for segmental resection. 76 Through systematic examination of the liver, the surgeon can easily identify segmental distribution of portal pedicles that are recognized because they are enveloped in a hyperechogenic fibrous sheath. The hepatic veins and their branches are also readily identified because of their thin wall, which is much less echogenic than that of the portal vessels. Hepatic veins are studied from their confluence with the inferior vena cava to their peripheral branches in order to detect their relationships to the territory to be removed. Therefore, the exact location of the lesion and its relationship with the vascular distribution make it easier to perform anatomically and oncologically correct, segmental resections. When re-resection is performed, US is mandatory for detection of the modified anatomy created by the previous surgery. This prevents both vascular injury and excessive parenchymal removal. Finally, US is a great aid for the surgeon who performs anatomic resection either under the guidance of tattooing, after injection of the dye into the segmental portal branch, or under selective segmental vascular occlusion through the introduction of a balloon into the segmental portal branch. 60

The role of US in the diagnosis of a liver mass in cirrhosis is limited. Nevertheless, US may in some instances detect small additional nodules in the liver substance, resulting in major modifications of the surgical strategy.

**Liver blood flow control, parenchymal transection and hepatic stump**

**Liver blood flow control**

Because of associated portal hypertension and the characteristics of liver parenchyma, the risk of bleeding is generally considered to be higher in cirrhosis than in normal liver, although, we have not been able to confirm these data in a univariate analysis. 77 Many procedures have been suggested to prevent this complication.

**Temporary total hepatic blood inflow occlusion**

The Pringle’s manoeuvre is the commonest of these procedures. It entails encircling the hepatic pedicle at the foramen of Winslow with a vascular tape, and then occluding the entire hepatic pedicle with a vascular clamp. This results in a critical reduction in bleeding, and if bleeding is persistent, it must originate from the hepatic veins. The tolerance of prolonged normothermic ischaemia in cirrhotic patients is good, 78 and this
allows the performance of complex liver resections in cirrhotic patients. Clamping of the portal triad can be continuous or intermittent. At present, most surgeons are used to performing intermittent clamping (alternating 15 minutes of occlusion with 5 minutes of re-circulation in order to reduce the period of liver ischaemia). It has been shown that continuous occlusion of the hepatic inflow is also well tolerated. 79

**Selective clamping**

In order to avoid prolonged liver ischaemia due to total inflow occlusion, selective clamping has been proposed. This can be achieved at either the hilar or suprahilar level. In the former, main portal and arterial branches are dissected and occlusion is obtained by bulldogs, vascular clamps or special balloon catheters. In the latter, occlusion of sectoral portal branches is more difficult because dissection must be pursued deep within the liver substance, which may be the source of bleeding. In order to obviate this risk, selective occlusion of a segmental portal branch by a specially devised balloon catheter introduced into the vessel under ultrasonic guidance has been proposed. 60, 80 The dissection and clamping of the ipsilateral hepatic artery better delineates the limits of dissection and further reduces bleeding during parenchymal transection. While the duration of portal occlusion is indefinite, arterial clamping should last no longer than that needed during Pringle’s manoeuvre. This procedure, however, should be reserved only for experienced teams, as it is expensive, time-consuming and demands skill in intraoperative interventional US.

**Total hepatic vascular exclusion**

This procedure entails the concomitant occlusion of the inferior vena cava below and above the liver together with the hepatic pedicle. 81 Tolerance to continuous normothermic ischaemia is poor in cirrhosis, and despite attempts to reduce the risk of postoperative liver failure by inserting a venovenous bypass and reducing total time of clamping, 82 this technique should be used with extreme caution in cirrhotic patients. 83

**Parenchymal transection and hepatic stump**

The line of resection is marked on the liver surface by electric cautery, without penetrating too deeply into the hepatic parenchyma. The hepatic pedicle is then clamped and transection begins. Division of fibrous tissue in cirrhotic livers is made by progressive crushing of the liver parenchyma, using Kelly forceps, allowing skeletonization of the biliavascular structures. Intrahepatic vessels and bile ducts are progressively exposed and occluded by bipolar coagulation if the calibre is less than 1 mm. Larger structures are controlled by resorbable clips (author’s technique) 84 or ligated. No clips are used on the side to be removed. When major branches of the hepatic veins are encountered in the field, great care must be taken to encircle them without tearing their thin wall. The risk of brisk bleeding is high and not controlled by Pringle’s manoeuvre. Every effort has to be made not to place forceps blindly to arrest the haemorrhage; it is preferable to use gentle compression by applying a damp gauze on the
site of bleeding. Division of the hepatic vein is carried out after securing the haemostasis with two forceps, taking care to leave a long stump on the caval side. The vein is then closed by a running vascular suture with a monofilament 5/0. The main portal pedicle of the resected liver is then divided on two forceps and ligated by stout suture.

Parenchymatous division can be also accomplished by an ultrasonic surgical aspirator or by a high velocity water jet dissector. It is our opinion that in cirrhotic livers, transection is better achieved by Kelly crushing. Moreover, an ultrasonic dissector is very useful in the isolation of portal branches, but is potentially harmful when used in the proximity of hepatic veins. A device known as the harmonic scalpel (Ultracision) has been introduced on the market. According to the authors’ experience it is reliable for both haemostasis and bilistasis. The slowness during dissection, poor ergonomy and its cost have so far limited the use of this tool. At the end of liver transection, if this has been carefully conducted, oozing from the liver remnant is minimal. Sources of bleeding are identified, and haemostasis is achieved by absorbable mattress sutures on the raw surface. It is equally important to identify bile leaks. Careful inspection with a clean swab usually facilitates location of the origin of bile leakage. Closure of a bilious leak is achieved by absorbable stitches. To improve further the haemostasis of the cut surface, fibrinogen sealant, microcrystalline collagen powder and argon beam coagulation have all been proposed. However, in our view careful haemostasis and securing of bile ducts during parenchymal transection is the best guarantee against postoperative collection and bile leakage.

**Abdominal drainage**

There is now strong evidence that abdominal drainage can be avoided even after hepatic resection. 85 This would imply that, in cirrhotic patients, prolonged ascitic fluid leakage and exogenous contamination of the abdominal cavity, which result in higher morbidity and prolonged hospital stay, could be prevented. 86 In the very few patients who have symptomatic postoperative collection, we rely on interventional radiological percutaneous drainage.

**Current resections for small HCCs in cirrhosis**

Although resection of each segment has been described, there are procedures that, because of their complexity, should be proposed with caution in cirrhotic patients. This is the case in bisegmentectomy VII+VIII with resection of the right hepatic vein, and venous graft reconstruction. 87 Three segmental resections are routinely performed: segmentectomy IV, V and VIII. Segments V and VIII. Segmentectomy VII is technically feasible, but the posterosuperior location of this segment makes this procedure difficult. The presence of a large right inferior hepatic vein may allow the sacrifice of the right hepatic vein 47, 60 or the performance of a bisegmentectomy VII–VIII, which is technically easier to perform. We seldom perform resection of segment VI, because we have found bisegmentectomy V–VI to be safer and quicker. Likewise, for tumours located in segment II or III, bisegmentectomy II–III, which removes a minor amount of functional liver, is a much simpler operation. Partial or complete resection of the dorsal sector, which some years
ago was considered a hazardous operation, is technically feasible. Finally, small tumours located at the junction of segments II, III and IV or segments IV, V and VIII are a good indication for a left hepatectomy or a central hepatectomy (i.e. trisegmentectomy IV–V–VIII), respectively. It is worth mentioning that parenchymal transection during segmental resection causes more bleeding than during conventional hepatectomy, since there is no previous control of the portal pedicles and the raw surface following sectioning is large.

![Figure 5.9](image1.png)

**Figure 5.9** Complete resection of segment IV. (A) Sketch showing the relationship between the posterior aspect of segment IVB and the hepatic pedicle; the hilar plate (arrow) is formed by the fusion of the connective tissue enclosing the bilio-vascular elements with Glisson’s capsule. (B) Diagram showing the anterior mobilization of the posterior aspect of segment IVB and the parenchymatous split between segment IV and segment I (arrow). (C) Complete segmentectomy IV. Note the site of division of the portal pedicles of segments IVA and IVB, and the relationships with the hepatic pedicle and the middle hepatic vein.

**Segmentectomy IV**

This segmental resection should remove the quantity of liver parenchyma situated between the umbilical fissure and the main portal scissura, up to the union of the middle
and left hepatic veins. The initial step of this procedure entails division of the bridge of parenchyma which joins segments III and IV at the base of the umbilical fissure. Cholecystectomy is performed. Mobilization of the anterior part of segment IV (segment IVB) is then achieved by lowering the hilar plate (Fig. 5.9). This technique has been described in detail elsewhere. 89 Glisson’s capsule is opened just above the fibrous tissue of the hilar plate to separate it from liver tissue. There is an almost avascular plane, with the exception of one artery directed upwards to the liver that has to be ligated. The main portal scissura is opened. Parenchymal division is shifted slightly to the left, thus preserving the middle hepatic vein. Resection is pursued until the level of the hilus. The liver is then divided slightly to the right side of the umbilical fissure. Arterial and biliary branches to segment IVA and segment IVB are ligated and severed. The latter is found to come from the left, some 2 or 3 cm from the falciform ligament, immediately upwards of the left hepatic duct. It is easily recognized because of its horizontal direction and its consistency. The latter is located higher in the parenchyma and should not be searched for at the hilus because of its depth. Once both portal pedicles of segment IV have been divided, transection is begun on the right side following a plane 1 cm from the left side of the right hepatic vein. Portal branches are then divided in a slightly more posterior direction. Liver resection is pursued up to the inferior vena cava or the junction of the middle and left hepatic veins; during this step, collateral branches of these veins draining segment IV are divided. The procedure ends by the separation of segment IV from the dorsal sector (Fig. 5.9). It is worth pointing out that there are no clear guiding landmarks for dividing between these two territories.

**Figure 5.10** (A) Diagram showing a segmentectomy V. Note the location of the portal pedicle of segment V and the proximity of the tip of the right liver from the right area of resection. (B) Postoperative CT scan showing the resected area and the stump of the portal pedicle of segment V (arrow).
**Segmentectomy V**

The limits of segment V are as follows: the main portal scissura on the left and the right portal scissura on the right, which is in the vicinity of the anterior tip of the right liver and the plane of the hilus posteriorly. After cholecystectomy, the main portal scissura is first opened up to the hilum, avoiding injury to the middle hepatic vein. The right portal scissura is then opened. Liver division is slightly displaced to the left in order to preserve the right hepatic vein. This manoeuvre facilitates the division of the posterior boundary of segment V, which has a transverse direction and is located at the level of the plane of the hilum. The main biliovascular pedicle of segment V is divided at the left superior corner of the resected specimen (Fig. 5.10). This step of the procedure should be performed very cautiously, in order to avoid damage to the vascularization of segment VIII.

**Segmentectomy VI**

Segment VI, which is located in the posterior portion of the right liver, is limited on the left by the right portal scissura, which ends posteriorly near the inferior vena cava at the junction of the dorsal sector and the right hepatic vein. The superior limit is the plane of the hilum. After complete mobilization of the right liver, parenchymatous division is performed posteriorly and transversely at the level of the hilum without damaging the right hepatic vein. The right portal scissura is opened on the right side of the right hepatic vein, which marks the anterior limit of the resection. The liver is then divided in the direction of the inferior vena cava. The biliovascular pedicle of segment VI is divided at the junction of both parenchymatous divisions (Fig. 5.11). During this manoeuvre, great care is taken not

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**Figure 5.11** Diagram showing a segmentectomy VI. Note the relationships with the right hepatic vein, segment IX and the site of ligation of the portal pedicle of segment VI.
to damage the blood supply of segment VII.

**Segmentectomy VII**

Removal of segment VII is a difficult procedure because of the posterior and superior location of this segment near the end of the right hepatic vein. Complete mobilization of the right liver up to the inferior vena cava and the distal portion of the right hepatic vein is paramount. The liver is first divided transversely at the level of the hilum. The right portal scissura is then opened and divided in the direction of the inferior vena cava. The right hepatic vein is left intact. The bilio-vascular pedicle of segment VII is divided at the junction of the parenchymal incisions (Fig. 5.12).

**Figure 5.12** Diagram showing a segmentectomy VII. Note the site of ligation of the portal pedicle of segment VII and the relationship with segment IX and the right hepatic vein.

**Segmentectomy VIII**

Medial and lateral limits are the main and right portal scissurae. The boundary between segments V and VIII is given by the projection on the liver surface of the hilar fissure. Division of the right liver and falciform ligaments up to the confluence of the hepatic veins into the inferior vena cava allows exposure of segment VIII. Parenchymatous division is carried out, 1 cm to the right of the main portal scissura, taking care to ligate a large branch of the middle hepatic vein in the cranial portion of the liver division. On the right, the hepatic vein should not be exposed. Only its branches are ligated or, preferably, occluded by clips. The main pitfalls of this resection are injuries to the hepatic veins on the borders of the segment. Resection should be conducted by surrounding the segment on each side. The final shape of the removed liver is that of a truncated pyramid. The natural tendency of coning surgery—the dissection into the axilla of right and middle veins—has to be avoided, as it entails the risk of non-oncological removal of the tumour.
The portal pedicle is ligated intraparenchymally, taking care to avoid the accidental injury to the adjacent pedicles of segment V when dividing the pedicle of segment VIII (Fig. 5.13).

**Figure 5.13** Diagram showing a segmentectomy VIII. Note the large raw liver surface, the vicinity of the middle and right hepatic veins, the site of ligation of the portal pedicle of segment VIII and the size of the resected area.

**Dorsal sectorectomy (segments I and IX)**

This is one of the most challenging operations in cirrhosis. Removal of small tumours located in the left portion of the dorsal sector (segment I) is relatively easy to accomplish after liberation of segment I posteriorly from its connections to the vena cava, by sectioning the accessory veins and, anteriorly, by dividing the arterial and portal vein branches (Fig. 5.14). Much more difficult is the resection of tumours located in the cranial or in the right portion (segment IX) of this sector. In patients with a good liver function, the ablation of the dorsal sector is usually associated with a left hepatectomy or a bisegmentectomy II–III to simplify the procedure. However, similar to what has been suggested in a normal liver, procedures of isolated dorsal sectorectomy have been described also in cirrhosis. Two techniques are available for a complete dorsal sectorectomy. In the first, the liver is completely mobilized on both sides up to the insertion of the three main hepatic veins into the inferior vena cava by sectioning the right and left liver ligaments and dividing the accessory hepatic veins (Fig. 5.15). The dorsal sector is freed from the inferior vena cava posteriorly and from the hilum anteriorly. The posterior branches of the portal vein directed to the dorsal sector are ligated and divided. Because of uncertainty as to the right border of the sector, Japanese authors have suggested injecting dye into the posterior portal branches. The limits of unstained liver posteriorly are traced on the surface by electric cautery. Parenchymatous transaction is carried out with the liver turned medially. The resection starts from the
right limit and advances beneath the hepatic veins up to Arantius’ sulcus on the left, taking care to avoid injury to the main hepatic veins cranially and to the second-order portal branches, anteriorly (Fig. 5.15). In the second technique, dorsal sectorectomy can be performed by using a transhepatic approach, as described by Yamamoto et al. 93 for tumours that displace the middle hepatic vein. The liver is completely freed and transection is carried out along the main portal scissura, thus exposing the middle hepatic vein on most of its length. Two planes of transection are followed on each side of the vein: on the left, following the direction of Arantius’ sulcus, and on the right, behind the middle hepatic vein towards the right side of the inferior vena cava (Fig. 5.16). Once Arantius’ sulcus is joined, the left portion of the dorsal sector is separated from segments II and III. Pulling the resected dorsal sector forwards through the main portal scissura, the resection is ended by division of the portal branches directed towards the dorsal sector.

Central heptectomy (segments IV–V–VIII)

Indications are tumours located at the confluence of the three segments deep within the liver
Figure 5.15 Diagram showing a complete resection of the dorsal sector (i.e. segments I–IX). (A) Note the relationships with the inferior vena cava and the right hepatic vein and the tight connections with the right posterior sector (i.e. segments VI–VII). (B) At the end of the procedure note the numerous ligations of accessory hepatic veins and that the anterior limit of the resection is represented by the segments of the right posterior sector.

substance of patients with a very good hepatic reserve. The volume of non-tumourous liver removed is conspicuous (about 30%) and, therefore, the risks of hepatic failure and worsening portal hypertension are high. Moreover, the raw cut surface is the largest of the different hepatic resections and, as a consequence, postoperative fluid collection is not uncommon. Falciform and coronary ligaments are divided up to the inferior vena cava, whose anterior surface is exposed in order to locate the confluence of the hepatic veins, particularly the middle one, into the vena cava. The limits of the resection are the falciform
Figure 5.16 Sketch showing a representation of complete dorsal sectorectomy according to Yamamoto et al. 93 (A) The liver has been divided through the main portal scissura (arrow). Note the planes of liver division to the left in the direction of Arantius’ sulcus (arrow) and to the right on the right side of the inferior vena cava (arrow), behind the middle hepatic vein. (B) The resected area at the end of the procedure.

Figure 5.17 Diagram showing a central hepatectomy. Note the size of the raw liver surface, the vicinity of the right hepatic vein and the site of
ligation of the portal pedicles of segment IVA and IVB and segment V and VIII. The middle hepatic vein has been divided and occluded by a running suture.

ligament on the left and the right hepatic vein, whose direction has been traced on the surface of the right liver by US. The inferior limit is the hilar plate. The hilar plate is lowered as if for a segmentectomy IV, from the insertion of the ligamentum teres up to the gallbladder fossa. While extending the dissection into the liver substance, although difficult in cirrhosis, it is sometimes possible to identify, isolate and clamp the anterior sectoral portal pedicle for segments V and VIII. It is actually harmful, in most cases, to encircle the pedicle: it is easier and safer to ligate it intraparenchymally during transection. On the left side, there are two portal pedicles, one for segment IVB and one for IVA, that are divided as for a segmentectomy IV. If, for any reason, the right hepatic vein is encountered, the plane of section should be shifted medially. The pedicles of segments V and VIII are separately ligated into the liver parenchyma. In front of the inferior vena cava, the trunk of the middle hepatic vein is easily identified and ligated on a vascular clamp by a running suture. An adequate thickness of liver tissue should be kept posteriorly (i.e. the dorsal sector) (Fig. 5.17).

**Perioperative treatment**

**Antibiotics**

Although some authors argue for the use of antibiotic therapy in cirrhotic patients undergoing liver resection, we do not routinely use this approach. It is worth mentioning that there are no controlled data on the topic. Septic complications seem to be no higher in our patients compared to other series. In at-risk patients, third generation cephalosporins or quinolones are used. In patients in whom a prolonged total portal clamping is foreseen, a preoperative selective intestinal decontamination may be proposed to prevent bacterial translocation.

**Blood transfusion**

The risks entailed in allogeneic blood transfusion are manifest in cirrhotic patients undergoing liver resection, and include worsening of hepatic function, increase in postoperative complications and a higher recurrence rate. Therefore all attempts should be made to identify patients at risk of bleeding in order to minimize the risk of transfusion. As shown in a multivariate study, patients undergoing extended resections or with abnormal coagulation should be specially considered for other procedures, such as autologous blood predeposit, isovolemic haemodilution or intraoperative autotransfusion.

To be effective, autologous blood transfusion requires painstaking organizational efforts prior to the patient’s hospitalization. While the procedure is mandatory in patients with benign tumours, its use in patients with malignant disease is debatable in view of the very high cost/benefit ratio. The best candidates for this procedure are those patients with
haemoglobin concentrations >13 g/dl. Two or three blood units are drawn and stored. Liver resection should be delayed for a period of 2 weeks. When haemoglobin is <11 g/dl, human recombinant erythropoietin and iron may also be effective in cirrhotic patients to accelerate erythrogenesis. However, there is evidence that the use of the human recombinant erythropoietin in cirrhosis can hasten hypophosphataemia and worsening of hepatic function.

Isovolemic haemodilution represents a very inexpensive and reliable method to substitute allogeneic transfusion in cirrhotic patients, provided that contraindications such as major coagulation defects, cardiac disease or anaemia do not co-exist. Haemodilution is probably the best alternative method to allogeneic blood transfusion.

The cell-saver for intraoperative blood recovery is practically unused in elective hepatic resection for malignant tumours because of its costs and the potential risk of tumoural cell dissemination, despite experimental evidence showing that this latter risk is absent.

We have shown that the use of the antifibrinolytic aprotinin during surgery is effective in reducing both perioperative blood loss and the need for blood transfusions in patients undergoing hepatic resection for tumour. Major limitations to its more widespread use are its high cost and the likelihood of allergic reaction.

A policy of fluid and sodium restriction in cirrhotic patients is the best method for preventing ascites formation in the postoperative period. The daily amount of fluid given should not exceed 20 ml/kg and should be based on urinary osmolarity and excretion of sodium. In the case of ascites formation, the intravenous administration of albumin or macromolecules associated with furosemide usually induces a diuresis and a reduction in intraperitoneal fluid accumulation. Paracentesis is mandatory in patients with massive ascites, in order to avoid prolonged leakage of fluid through the abdominal incision. The loss of fluid via abdominal drains must also be compensated.

Postoperative nutritional support is not a common practice after hepatectomy in our experience. Provided that a good selection of patients has been made preoperatively on the basis of residual hepatic function, the appearance of encephalopathy is nearly always exceptional. As a consequence, the use of special formulations, such as branched-chain amino acid enriched solution, does not lead to any clinical advantage over other standard formulations. An early resumption of oral intake in patients without complications is, in our current view, the best way to manage cirrhotic patients.

**Results of partial liver resection for small HCC in cirrhosis**

The results of partial liver resection for small HCCs (<5 cm) in cirrhosis are summarized in Tables 5.1 and 5.2. The average operative mortality is $5.7 \pm 4.9\%$ (range 0–14.6\%). When data from a number of series are collected, the mean 3- and 5-year survivals are $59.2 \pm 15.2\%$ (range 39–79\%) and $48.5 \pm 13.2\%$ (range 37–63.8\%), respectively. In a large series of 1000 patients treated by hepatectomy
for small HCC, 10-year survival has been reported to be 46.3%. Discrepancies between series are probably related to variations in the selection of patients regarding preoperative liver function and tumour invasiveness. Finally, the mean 3-year recurrence rate is 52.2 ± 7.9% (range 43–65%). The high recurrence rate is most likely linked to a small surgical margin, residual neoplastic foci of HCC and the ongoing carcinogenic process.

Table 5.1 Operative mortality following liver resection for small hepatocellular carcinoma in patients with cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Operative mortality (%)</th>
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</thead>
<tbody>
<tr>
<td>Ohnishi et al. 100</td>
<td>34</td>
<td>11.8</td>
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<tr>
<td>Tang et al. 36</td>
<td>132</td>
<td>2.3</td>
</tr>
<tr>
<td>Bismuth et al. 3</td>
<td>46</td>
<td>10</td>
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<tr>
<td>Castells et al. 101</td>
<td>33</td>
<td>9.1</td>
</tr>
<tr>
<td>Kawasaki et al. 38</td>
<td>93</td>
<td>0.9</td>
</tr>
<tr>
<td>Livraghi et al. 102</td>
<td>82a</td>
<td>2.5</td>
</tr>
<tr>
<td>Fuster et al. 103</td>
<td>48</td>
<td>4.2</td>
</tr>
<tr>
<td>Lee et al. 104</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Nagashima et al. 29</td>
<td>41</td>
<td>14.6</td>
</tr>
<tr>
<td>Zhou et al. 105</td>
<td>474</td>
<td>1.7</td>
</tr>
<tr>
<td>Llovet et al. 106</td>
<td>77</td>
<td>4</td>
</tr>
</tbody>
</table>

a Child’s A patients.

Table 5.2 Long-term survival and recurrence rates following liver resection of small hepatocellular carcinoma in patients with cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Survival rate (%)</th>
<th>3-year recurrence rate (%)</th>
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<tr>
<td></td>
<td></td>
<td>3-year</td>
<td>5-year</td>
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<td>Ohnishi et al. 100</td>
<td>34</td>
<td>55a</td>
<td>28b</td>
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<td>Tang et al. 36</td>
<td>132</td>
<td>76.3</td>
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<td>Franco et al. 6</td>
<td>43</td>
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<tr>
<td>Bismuth et al. 3</td>
<td>46</td>
<td>39c</td>
<td>—</td>
</tr>
<tr>
<td>Castells et al. 101</td>
<td>33</td>
<td>44</td>
<td>—</td>
</tr>
<tr>
<td>Kawasaki et al. 38</td>
<td>93</td>
<td>40d</td>
<td>—</td>
</tr>
<tr>
<td>Livraghi et al. 102</td>
<td>82e</td>
<td>79</td>
<td>—</td>
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Liver transplantation for small HCC in cirrhosis

**General considerations**

Liver transplantation has the advantage over partial liver resection of curing the tumour and the underlying liver disease with its potential carcinogenic process which plays a major role in the outcome of patients. Nevertheless, it must be mentioned that reinfection of the transplanted liver by hepatitis B or hepatitis C virus is the rule in cases of viral infection prior to transplantation, which might interfere with the risk of tumour recurrence. Historically, total hepatectomy and liver transplantation have been considered the therapy of choice for HCCs that could not be removed by partial liver resection. The high tumour recurrence rate after liver transplantation in this indication has prompted surgeons progressively to abandon liver transplantation for huge tumours. A 5-year survival rate for small HCCs not exceeding 25% at 5 years has led to the proposal of liver transplantation for small HCCs. However, the shortage in organ donors has hindered the widespread development of such a policy. As regards the operative protocol, a thorough examination of the peritoneal cavity should be carried out before transplantation, and specific operative measures should be respected during the procedure. Very strict selection criteria are essential for the identification of patients who have the best chance of cure following liver transplantation. HCC recurrence following transplantation is largely dependent on the tumour stage, made according to the TNM classification and vascular invasion.

**Indications for liver transplantation**

At present, liver transplantation should ideally be proposed in patients with small HCCs
without vascular invasion (i.e. stage I of the TNM classification) and which are not accessible to a limited curative resection. It is typically the case that HCC centrally embedded in the right liver, at the junction of segments V, VI, VII and VIII, requires a right hepatectomy for a small tumour. In such a situation, despite the presence of a good hepatic function, it seems advisable not to perform a major hepatic resection for a small HCC which could be poorly tolerated, or an atypical resection which might not be curative. However, an alternative therapeutic approach which reduces the operative risk is right hepatectomy, preceded by an embolization of the right branch of the portal vein, provided that a compensatory hypertrophy of the left liver with an atrophy of the right liver has been achieved. The precise staging of HCC, based on the number and size of lesions that predicts recurrence after transplantation, has not yet been defined. However, the indications for transplantation may be expanded. Thus, patients with two or three nodules of HCC, each not exceeding 3 cm in diameter, or patients with their largest nodule ≤4.5 cm and total tumour diameter not exceeding 8 cm, could also be proposed for liver transplantation. Because of the shortage of organs, Majno et al. have studied in selected patients the results of a primary liver resection and salvage transplantation, in patients with single, small HCC and preserved liver function, as against liver transplantation. They showed that life expectancy was similar in both groups. Finally, liver transplantation is strongly indicated in patients with a small asymptomatic HCC and a poor liver function.

Table 5.3 Operative mortality following liver transplantation for small hepatocellular carcinoma in patients with cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Operative mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth et al. 3</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Romani et al. 117</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Schwartz et al. 118</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Mazzaferrro et al. 111</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Collella et al. 119</td>
<td>69</td>
<td>25(^a)</td>
</tr>
<tr>
<td>Otto et al. 120</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Hemming et al. 121</td>
<td>112</td>
<td>13</td>
</tr>
</tbody>
</table>

\(^a\)Within 3 months following liver transplantation.

Results of liver transplantation for small HCCs in cirrhosis

The results of liver transplantation for small HCCs are summarized in Tables 5.3 and 5.4. The operative mortality is quite high, with a mean of 15.6 ± 9.1% (range 5–30%). Three-year survival is 70.1 ± 12.0% (range 54–85%), superior to the results obtained after conventional resection. This last result is most likely related to a more stringent selection
of patients for liver transplantation. The recurrence rate is low when compared to liver resection. Finally, recurrence rate is high, especially in patients with vascular invasion.

Key points

• Precise knowledge of the natural history of HCC in cirrhosis.
• CT scanning assessment:
  - Tumour characteristics
  - Tumour resectability
  - Type of hepatic resection.
• Partial liver resection in cirrhotic patients:
  - Good liver function
  - Economic parenchymal resection
  - Free margin of 10 mm
  - Specific postoperative complications.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>3-year survival rate %</th>
<th>Recurrence rate (%)</th>
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<tr>
<td>Bismuth et al. 3</td>
<td>45</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Romani et al. 117</td>
<td>27</td>
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<td>Schwartz et al. 118</td>
<td>40</td>
<td>66</td>
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<tr>
<td>Mazzaferrro et al. 111</td>
<td>48</td>
<td>85</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Collella et al. 119</td>
<td>69</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15&lt;sup&gt;e&lt;/sup&gt;, 1&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Otto et al. 120</td>
<td>40</td>
<td>54</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Figueras et al. 122</td>
<td>84</td>
<td>77</td>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Hemming et al. 121</td>
<td>112</td>
<td>63</td>
<td>65&lt;sup&gt;g&lt;/sup&gt;</td>
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<sup>a</sup> HCC <3 cm.
<sup>b</sup> At 3 years.
<sup>c</sup> Median follow-up of 26 months.
<sup>d</sup> Disease-free patients.
<sup>e</sup> Median follow-up of 57 months.
<sup>f</sup> During follow-up.
<sup>g</sup> 5-year actuarial tumour recurrence.

- Tumour recurrence after resection: Main cause of poor prognosis In most cases intrahepatic recurrence Anatomic prognostic factors.
- Liver transplantation: Better results than partial liver resection Highly selected patients.
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Small solitary hepatic metastases: when and how?

David L Bartlett and Yuman Fong

Introduction

The management of patients with small hepatic metastases from colorectal cancer and other histologies requires the consideration of many diverse patient and tumor related factors. These factors include the natural history of the tumor type, the expected cure rate after surgical treatment, effectiveness of alternative treatments, and the morbidity of surgical resection. In general, the indications for any major surgical procedure include the potential for cure, prolongation of survival and palliation of symptoms. For metastatic tumors to the liver in selected cases the cure rate may be over 50% for colorectal cancer, but will be exceedingly rare for other histologies such as gastric cases, and melanoma and sarcoma. Small metastases to the liver generally do not cause symptoms (except for hormone secreting neuroendocrine tumors) and, therefore, palliation of symptoms is not a common indication for management of these lesions. Nevertheless, many issues remain unresolved. Does resection of a small solitary hepatic metastasis prolong survival in cases where the patient is likely to develop widespread metastases in the future? Is there any harm in allowing a tumor to go untreated for a period of time, knowing that with close followup the resection option may still be possible in the future? Do metastases metastasize such that a delay in management may obviate the curative option? Unfortunately, all of these difficult issues are only addressed by sparse data in the literature.

The risk and extent of the surgical procedure plays a significant role in the decision making for management of small hepatic metastases. It is more reasonable to excise an enlarged subcutaneous lymph node for metastatic cancer than it is to perform a hepatic lobectomy when the chance of benefit is low in both cases. As other less invasive ablative options become routine therapy, it may be reasonable to consider these options in cases where surgical resection is unreasonable. These alternative options include percutaneous approaches at ablation such as radiofrequency ablation and percutaneous alcohol injection. Laparoscopic procedures may also be an alternative for the management of small hepatic metastases, including laparoscopic resection of tumors and laparoscopically directed ablation such as cryotherapy. If the risks, discomfort, and hospital stay are truly minimal, then it becomes reasonable to consider local treatment of these lesions, even with a small chance of overall benefit to the patient.

This chapter will provide an overview of the data on survival benefit after resection of hepatic metastases and the techniques of surgical management. A brief discussion of minimally invasive and percutaneous procedures for management of small solitary hepatic metastases will follow. In addition, a discussion of the role for adjuvant therapy
after resection or ablation of the hepatic metastases will be included.

Survival results for hepatic metastasectomy

While the purpose of this chapter is not to provide an in-depth review of the results of hepatic metastasectomy, a general sense of expected cure rate and prolongation of survival after hepatic metastasectomy for various histologies is required in order to make an informed decision regarding resection of small hepatic metastases.

Colorectal metastases

Colorectal cancer, compared to other histologies, is more likely to present as disease isolated to the liver. The natural history of unresected solitary hepatic metastases from colorectal cancer was described by Wagner et al. where 39 patients with solitary metastases did not undergo therapy and the median survival was 24 months. 3 Wood et al. described 15 patients with solitary hepatic metastases left untreated with a mean survival of 17 months. 4

There is a considerable body of literature on the results of hepatic metastasectomy for colorectal cancer. The overall 5-year survival ranges from 22% to 39%. 5 In many studies, low number and small size are associated with improved prognosis such that a small solitary metastasis from colorectal cancer has a greater than 50% 5-year survival. Nuzzo et al. report 56% actuarial 5-year survival in patients with solitary metachronous hepatic metastases from colorectal cancer less than 4 cm in size. 1 Table 6.1 reviews the results of the largest series for solitary metastasectomy. After resection of solitary metastases from colorectal cancer, 5-year survival ranges from 30% to 47%. 6 – 10 These reports do not consider the small solitary metastases separately from the entire group of solitary metastases. The size of the lesion is expected to affect prognosis and, therefore, the actual results for small solitary hepatic metastases may be even better than the numbers reported in Table 6.1. Liver resection for hepatic colorectal metastases is, therefore, safe and effective, and may be curative.

Table 6.1 Survival after hepatic resection for a solitary colorectal metastasis

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>N</th>
<th>Actuarial 5-year survival (%)</th>
<th>Median survival (months)</th>
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<tr>
<td>Hughes et al.</td>
<td>6</td>
<td>1988</td>
<td>509 37</td>
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<td>Rosen et al.</td>
<td>7</td>
<td>1992</td>
<td>185 30</td>
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<td>Scheele et al.</td>
<td>8</td>
<td>1995</td>
<td>180 36a</td>
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<tr>
<td>Taylor et al.</td>
<td>9</td>
<td>1997</td>
<td>77 47</td>
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<td>Fong et al.</td>
<td>10</td>
<td>1997</td>
<td>240 47</td>
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</table>

a Actual 5-year survival.
Neuroendocrine metastases

For cancers of other than colorectal origin, patients with hepatic metastases from neuroendocrine tumors have been thought to be the most likely to benefit from surgical resection. Certainly, if the tumor were symptomatic for either hormonal or physical reasons, resection should be considered even though cure is unlikely. Because of the indolent nature of these tumors, durable palliation can be achieved with cytoreduction. Five-year survival rates for untreated hepatic metastases from neuroendocrine tumors have ranged from 13 to 54%. 11 – 15

In patients with no symptoms, the case for surgical resection, or any treatment for that matter, is less clear. We and others 16 have adopted a very aggressive approach even for asymptomatic tumors based only on retrospective data. Chen et al. compared liver resection for neuroendocrine tumors with a retrospectively matched cohort who did not undergo resection, demonstrating improved survival after resection. 17 The general recommendation is for aggressive surgical management of neuroendocrine metastasis. 18 We acknowledge that the variable growth rate and sometimes indolent nature of these tumors make firm conclusions based on retrospective data without a non-treated control group suspect. The rarity of these tumors, however, does not allow for random assignment trials. Certainly for small hepatic metastases, aggressive surgical resection is indicated, while it is acknowledged that definitive proof of its benefit may never be achieved.

Non-colorectal, non-neuroendocrine metastases

For histologies other than colorectal or neuroendocrine cancer, the utility of hepatic metastasectomy is not as obvious. For these tumors the liver is rarely the sole site of disease; liver metastases are rarely the ultimate cause of death, nor does it contribute significantly to symptoms prior to death. Nevertheless, selected cases of disease isolated to the liver after a long disease-free interval raise the possibility of a single site of metastatic disease that could be cured with surgical therapy. Table 6.2 reviews the largest series for hepatic metastasectomy with a variety of histologies.

Breast cancer

Many reviews have been published on hepatic metastasectomy for breast cancer. Due to the high incidence of breast cancer and the frequency of liver metastases for this histology, the first site of metastases is frequently observed to be hepatic. In highly selected patients, favorable results of section of such liver metastases have been reported. Raab et al. reported a 5-year survival of 18.4% in 34 patients after hepatic metastasectomy for breast cancer. 19 Elias et al reported 9% 5-year survival after resection in 21 patients. 20 The relatively few patients in these reports compared to the total number of breast cancer patients in each institution during the study period reflect the degree of patient selection for surgery. The survival rates reported are actuarial survival rates and the actual cure rate is much lower. At most, hepatic metastasectomy for breast cancer should be
considered cytoreductive. It may delay the development of symptoms and prolong survival, but it has very little chance of curing the disease.

**Sarcoma**

Similarly, hepatic resection for sarcoma metastases may be associated with long-term survival in highly selected patients, but it is unlikely to result in cure. In a series of 14 hepatic resections for metastatic sarcoma, recurrence was found in all patients during follow-up, and 11 of 14 failed in the liver. 21 The median survival in that series was 30 months.

**Melanoma**

Metastatic cutaneous melanoma to the liver has been resected with long-term survival,
but these tumors also ultimately recur. The erratic behavior of melanoma makes conclusions regarding the benefit of hepatic metastasectomy difficult. Only in highly selected cases is it appropriate to consider resection of cutaneous melanoma. Ocular melanoma, on the other hand, has a unique natural history. Ocular melanoma preferentially metastasizes to the liver and the majority of patients die of liver failure as a direct result of tumor progression. Anecdotal reports exist of long-term survival after metastasectomy for ocular melanoma, although these tumors are also almost always multifocal and resection of what appears to be a solitary metastasis is most often associated with liver recurrence. These hepatic metastases may show up many years after the treatment of the primary tumor. A long disease-free interval reflects a slow tumor doubling time, and suggests resection may achieve durable palliation. Usually in this disease, however, the appearance of a solitary liver metastasis is merely a precursor of the later appearance of multiple metastases.

**Other gastrointestinal cancers**

In general, hepatic metastasectomy for gastrointestinal primaries other than colorectal is not associated with prolonged survival. For tumors such as esophageal, gastric, small bowel, and pancreatic cancer the pattern of spread includes regional lymph nodes, the peritoneal cavity, and lung metastases in addition to liver metastases. It is unlikely that these patients will die of liver failure as a result of progression of hepatic metastases, but instead, suffer other gastrointestinal sequelae from extrahepatic tumor progression. A major operative procedure can be of significant detriment to these patients with aggressive cancers where survival is expected to be of the order of weeks to months. Nevertheless, even for these tumors selected cases exist where one might consider resection, and the literature contains anecdotal reports of long-term survivors after liver resection.

**Genitourinary tumors**

For non-colorectal, non-neuroendocrine tumors, metastases from genitourinary primaries seem to have the best prognosis following hepatic metastasectomy. In a recent review by Harrison et al., 34 patients underwent hepatic resections for genitourinary primaries (including testicular, adrenal, ovary, renal, uterine, and cervix) with a 5-year actuarial survival of 60%. Other investigators have reported prolonged survival after resection for renal cell cancer and adrenal cancer. While the natural history of genitourinary tumors contributes to these remarkable results, it does suggest a survival benefit to resection in selective cases.

**Do metastases metastasize?**

For small solitary hepatic metastases, where many months of growth would still not preclude resection, the question is whether a waiting period would allow for further spread of the tumor from the metastatic deposit itself. If metastatic tumors were unable to
further metastasize, waiting for the first sign of progression prior to initiating treatment and allowing other metastatic disease to declare itself would seem a reasonable approach. If, however, metastases are able to spread during that waiting period, then the chance of potential cure may be adversely affected by the delay in definitive treatment. Unfortunately, it is clear that metastatic tumors do have the potential to metastasize themselves, and this must be considered when recommending observation alone.

Experimental evidence suggests that cells from spontaneous metastases are more likely to metastasize than cells populating the parent neoplasm. Clinically, the most obvious examples of metastases from metastatic colorectal cancer deposits are in the cases of perihepatic lymph node metastases, and satellite-tumor formation.

Published data would indicate that metastases to periportal lymph nodes occur in 10–20% of cases of hepatic colorectal metastases. The presence of lymph node metastases portends a poor prognosis. Therefore, excision of liver tumors before they spread to regional lymph nodes would be advantageous.

A recent paper examined the incidence of satellite micrometastasis in colorectal liver metastases by careful histologic examination of resection specimens and found that 56% of specimens had micrometastases as far as 3.8 cm away from the tumor being resected. In some cases, these satellites could be traced to the original metastasis by a trail of cells, suggesting spread from the original metastasis. As discussed previously, the presence of satellitosis is an important independent poor prognostic factor. It may be that a delay in resection allows for the development of satellitosis, which negatively impacts on prognosis. On the other hand, the presence of satellitosis may be an indicator of biologic aggressiveness which portends a poor prognosis regardless of when the tumor is resected.

**Patient selection**

**Colorectal metastases**

In order to decide when surgical resection is reasonable for small solitary hepatic metastases, it is important to review prognostic factors which are independent of size and number that may influence the decision regarding management of these tumors. Many studies have examined data on prognostic factors for outcome after hepatic resection for colorectal metastases. The time to development of liver tumor after resection of the primary, pathologic margin, stage of the primary tumor, tumor number, carcinoembryonic antigen levels, satellitosis, extrahepatic disease, and positive surgical margin have all been shown to predict survival after hepatic resection for colorectal metastases independent of size.

Extrahepatic disease is considered a contraindication to hepatic resection. Even the presence of perihepatic lymph nodes portends a poor prognosis and generally is felt to be a contraindication to resection. Particularly in the cases of small solitary hepatic metastases with extrahepatic disease, there would be no advantage to resection or ablation of the liver tumor because systemic disease will likely be the ultimate cause of death regardless of what is done with the liver metastases. Of the other various factors
that are prognostic for outcome, surgical margin, and satellitosis are the least useful in patient selection. No one would subject a patient to surgical resection expecting a positive margin. Satellitosis cannot be easily assessed preoperatively and therefore is a poor selection criterion for surgery.

We analyzed our recent data on factors prognostic for outcome after resection of hepatic metastases from colorectal cancer. In data derived from our last 1001 liver resections for this disease, the seven factors found to be independent predictors of poor long-term outcome were:

(1) node positive outcome,
(2) presentation of liver disease within 12 months of the primary cancer,
(3) CEA >200 ng/dl,
(4) number of liver tumors >1,
(5) size >5 cm,
(6) positive margin, and
(7) extrahepatic disease.

From this we formulated a clinical risk score (CRS) based on the first five of these factors for use in

![Figure 6.1](image)

**Figure 6.1** Prediction of long-term outcome for small (<3 cm) (N=293) metastatic deposits based on clinical risk score (CRS). CRS is based on the following five criteria: (1) node positive primary cancer, (2) disease-free interval <12 months, (3) number of liver tumors >1, (4) size of liver tumor >5 cm and (5) CEA >200 ng/dl. For score=0–2 (N=236) (open box), the median survival was 56 months and the 5-year survival 47%. For score =3–4 (N=57) (filled triangles), the median survival was 32 months and the 5-year survival 24%.

patient selection for surgery and for stratification of patients for clinical studies. Using one point for each criterion, a summed score of 0–2 puts patients in a low risk group and is a strong indication for hepatectomy. In the patients with small tumors, a maximum score of 4 is possible. The 5-year survival of patients with small tumors and 0–2 points on the CRS is 47% and the median survival is 56 months. Patients with a score of 3–4
are in a high risk group, with a median survival of 32 months and 5-year survival of 24% (Fig. 6.1). In these high risk patients, a period of observation with no therapy or systemic chemotherapy allowing for the extent of metastases to declare themselves is reasonable. Improved imaging techniques such as fluorodeoxyglucose positron emission tomography (FDG PET) scanning should be considered and may help discover extrahepatic disease non-invasively in these patients at high risk for additional cancer. Finally, these patients should be considered for clinical studies of aggressive adjuvant chemotherapy after liver resection.

**Neuroendocrine tumors**

Patients with symptomatic neuroendocrine tumors should be considered for resection or ablation. For the small tumor, symptoms are most likely derived from hormonal secretion by the tumors, and such hormone levels will also provide a marker for effectiveness of the ablation or resection. For asymptomatic tumors, a period of observation to allow assessment of the pace and aggressiveness of the tumors is reasonable when the tumors are small. At the first signs of progression, resection or ablation should be considered.

**Non-colorectal, non-neuroendocrine tumors**

Harrison et al. defined prognostic factors involved in the resection of non-colorectal, non-neuroendocrine hepatic metastases. In this study, 96 patients underwent liver resection. The prognostic factors of significance on multivariate analysis included the disease-free interval (>36 months), curative resection (versus palliative incomplete resection) and primary tumor type. Their conclusions would suggest that regardless of histology, with a long disease-free interval patients may benefit from surgical resection.

**Resection techniques**

For small solitary metastases to the liver, the goal of resection is to completely excise the tumor while preserving the maximum normal hepatic parenchyma. Preserving parenchyma facilitates postoperative recovery and also provides flexibility for further resections should intrahepatic recurrences occur. Small surface oriented metastases can be excised using a non-anatomic wedge resection, whereas deeper lesions require formal segmentectomies or sectorectomies. A goal of at least a 1 cm margin is reasonable. The use of intraoperative ultrasound is important to rule out other small hepatic metastases which may not be evident on preoperative scans and in defining the intersegmental planes for designing the approach to segmentectomy. Even for wedge resections, ultrasound is beneficial in defining the vascular anatomy around the lesion, which may help minimize blood loss.

**Wedge resections**

Wedge resections must be performed meticulously to avoid inadvertently leaving a
A positive margin. Large chromic liver sutures can be placed and used for retraction during dissection. The parenchymal dissection should be performed along the lines used for other forms of liver resection. We prefer the Kelly clamp technique where the clamp is used to crush the normal parenchyma, exposing vessels that are then clipped, tied, suture ligated or stapled using a vascular stapling device. The Pringle maneuver is used intermittently for 5 minutes at a time followed by reperfusion of the parenchyma, during which time the argon beam coagulator is used to coagulate small bleeding vessels on the surface. This technique is superior to the simple use of electrocautery for the dissection which is often attempted for what seems to be routine wedge resections. The char effect of the electrocautery prevents adequate visualization of the anatomy, making it quite easy to stray into large vessels or into the tumor.

The most difficult margin in performing a wedge resection is the deep margin of dissection. Using intraoperative ultrasound, the depth of dissection should be measured prior to the initiation of parenchymal dissection, including at least a 1 cm margin deep to the tumor. The dissection should be carried down perpendicular to the liver surface to the predetermined depth. At this point the tumor can be lifted up and dissection can proceed horizontally across the base of the wedge. The tendency to resect with a ‘V-shaped approach’ is more likely to be complicated by a positive deep margin. At the end of the dissection the Pringle maneuver is removed and the argon beam coagulator is used to control bleeding vessels. Careful examination is made for any evidence of a bile leak, which is controlled with suture ligature.

For larger lesions where it is especially difficult to achieve the deep margin safely, a cryoassisted wedge resection can be performed. The cryotherapy probe is inserted into the tumor and freezing is begun with real time ultrasound imaging. When the zone of freezing is confirmed by ultrasound to be at least 1 cm beyond the tumor, wedge resection is performed using the freeze margin as the margin of resection. The cryotherapy probe makes a ready retracting device and the parenchyma is usually easy to dissect at the margin of the ice-ball. Freezing must continue intermittently during dissection to ensure that the ice-ball does not retract and expose the tumor.

**Segmental resections**

For all but the most superficial lesions, we prefer a segmental approach for the resection of tumor. Segmental resections have a significantly lower rate of pathologic positive margins, and this translates into improved long-term survival. Small, deep solitary metastases and surface lesions adjacent to major vascular structures lend themselves particularly well to segmentectomies or sectorectomies. The intersegmental planes can be identified intraoperatively using vascular landmarks with the aid of intraoperative ultrasound. Using these planes for parenchymal dissection will minimize blood loss and help ensure a safe margin.

Inflow occlusion for the segment can almost always be performed first, thereby producing demarcation of the segmental planes to further enhance the dissection. The portal triad to segments II, III and IV can be identified and controlled within the umbilical fissure with little parenchymal dissection. The right posterior sectoral pedicle can be found by dividing the parenchyma along a horizontal cleft (fissure of Gans).
present on the inferior surface of the right lobe of the liver. The pedicle can be traced to its bifurcation to segments VI and VII for control of the individual segmental portal triads. The anterior sectoral pedicle can be dissected from an inferior or anterior approach.

The major hepatic veins lie within the intersegmental planes, and can be a source of significant blood loss during the parenchymal transection phase of a segmentectomy. The use of low central venous pressure (0–5 mmHg) during parenchymal dissection can decrease back bleeding in these veins. Extrahepatic control of the left, middle and right hepatic veins can also be achieved and the vein of concern temporarily clamped at its junction with the vena cava during parenchymal transection to further minimize blood loss.

When the solitary metastases lies near an intersegmental plane, two segments can be removed. This is most easily done as a formal sector such as the left lateral sectorectomy (segments II and III) and right posterior sectorectomy (segments VI and VII). The caudate lobe (segment I) can be resected as an isolated segmentectomy when the tumor is confined to this lobe. This requires a more extensive dissection, including complete division of all the perforating caudate veins draining directly into the vena cava as well as the numerous small portal triads extending off the main left pedicle at the base of the umbilical fissure.

Figure 6.2 demonstrates a case of a small, solitary segment of hepatic metastasis for colorectal cancer which was detected on an MRI scan used for screening because of a rising CEA. Although this was a surface lesion, intraoperative ultrasound revealed the segment VI triad immediately adjacent to the tumor. The segment VI triad was located by ultrasound and ligated at its origin with minimal parenchymal dissection. The intersegmental planes were then marked by electrocautery and a formal segmentectomy was performed with negative margins. While an aggressive resection was indicated and performed, the patient can still undergo a formal left or right hepatic lobectomy in the future if indicated. No dissection of the vena cava or porta hepatis was required.

**Morbidity and mortality**

The mortality rates for major hepatic resection have decreased significantly over time to a common reporting of mortality in the 1–4% range. These values are even lower for wedge resections and segmentectomies. In a recent report of 270 wedge or segmental resections, the operative mortality was 0.5%. This low mortality is not surprising considering that the main cause of death in studies of liver resection is liver failure secondary to inadequate residual normal parenchyma, an unlikely event for resection of small solitary hepatic metastases where minimal normal parenchyma is sacrificed.

While mortality rates are low, the complication rate for major hepatic resection is still relatively high, ranging from 20% to 50%. Bile leaks, perihpatic abscess, hemorrhage, cardiopulmonary complications, pleural effusions, pneumonia, and pulmonary embolism are among the most common complications. Many of these could be expected after segmentectomy and wedge resections as well as major hepatic resections. Even though these complications do not translate into a high mortality rate, they may affect recovery time and quality of life. While this is not a significant issue for patients expected to
undergo a long-term disease-free interval or cure, it may be significant for patients whose survival is expected to be of the order of months. For those patients with aggressive tumors who are likely to fail outside the liver in the near future, less invasive techniques which are associated with a lower complication rate and quicker recovery time are more appealing.

Figure 6.2 An example of a small, solitary colorectal metastasis to segment VI. (A) MRI reveals subtle abnormality not seen on CT scan. (B) Intraoperative ultrasound reveals the tumor and adjacent segment VI portal vein. (C) Intersegmental planes have been marked on the liver capsule with electrocautery and parenchymal dissection begun. (D) Resected segment with tumor (microscopic negative margins). (Special thanks to Dr Peter Choyke for MRI scan.)

Ablative techniques

Other minimally invasive techniques include local ablative therapies such as laparoscopically directed
Figure 6.3 An example of a small, solitary pancreatic cancer metastasis treated with percutaneous radiofrequency ablation. (A) Pretreatment CT scan reveals hypodense 3 cm right lobe liver metastasis. (B) Ultrasound photo with radiofrequency probe inserted into tumor. (C) Post-treatment scan (3 weeks) reveals large zone of necrosis replacing prior tumor. (Special thanks to Dr Thomas Shawker for ultrasound photo.)

cryotherapy \(^{44}\) or radiofrequency ablation. \(^{45}\) These techniques will be discussed further in Chapter 8. They provide ideal alternatives to laparotomy and major liver resection for the treatment of small solitary hepatic metastases, since the small tumor is the most likely to be completely treated by ablation techniques. Furthermore, treatment by ablative techniques does not preclude future resection.

Percutaneous approaches to tumor ablation are even more attractive than laparoscopic procedures. Local injection of toxic agents such as ethanol has been shown to be effective for hepatocellular cancers, however these agents have not been proven for other histologies and are known to be poorly effective for colorectal cancer. \(^2\) Radiofrequency ablation can be performed percutaneously under ultrasound guidance with local anesthesia. Figure 6.3 demonstrates a case of a metastatic pancreatic cancer 2 years after a dramatic primary response to gemcitabine and radiation therapy. Because the patient will likely begin to fail in multiple sites in the near future with limited survival potential, a laparotomy and hepatic resection was not considered reasonable. She was treated with...
percuteaneous radiofrequency ablation, achieving a good zone of necrosis encompassing the mass, and she spent only one day in the hospital with very minimal discomfort. How such procedures, which have low morbidity and which maintain quality of life, will factor in the treatment of patients with small hepatic metastases must be addressed by studies with sufficient follow-up to define the local recurrence rate.

Adjuvant chemotherapy

The role for adjuvant systemic chemotherapy after the removal of small solitary hepatic metastases is not well defined. Even for hepatic colorectal metastases, which are commonly treated with surgery, data on adjuvant chemotherapy after liver resection is sparse. Two retrospective studies have suggested a benefit of adjuvant systemic chemotherapy after metastasectomy, but others have not supported this. 6, 46 – 48 Use of systemic chemotherapy after resection of hepatic colorectal metastases is based mainly on data demonstrating adjuvant 5-fluorouracil (5-FU) and levamisol or 5-FU and leucovorin to decrease recurrence rate and improve survival when used after resection of the primary tumor. 49 It is hoped that a similar benefit will be seen when 5-FU-based chemotherapy is used after metastasectomy. Current practice is to offer adjuvant 5-FU-based chemotherapy after hepatic resection to patients who have had no previous chemotherapy. There are currently no data to support the use of irinotecan and oxaliplatin in an adjuvant setting, although studies are in progress.

For patients with hepatic colorectal metastases, the most common site of tumor recurrence after liver resection is the remnant liver. 50 In the treatment of patients with small hepatic metastases, there is particular concern that even smaller undetected metastases may subsequently present as a liver tumor recurrence. Regional chemotherapy to treat the liver site is therefore a theoretically attractive option for adjuvant care. Data addressing the utility for such hepatic arterial infusional (HAI) chemotherapy had been sparse, consisting only of four small single arm studies 51 – 53 and a single, small, randomized trial consisting of 36 patients. 54 These preliminary studies demonstrated safety of such an approach, but efficacy data were insufficient to support the routine use of adjuvant intra-arterial chemotherapy. Two large randomized trials examining adjuvant HAI have been completed. In the first trial, 55 224 patients from 25 centers were randomized to either no adjuvant therapy, or adjuvant HAI 5-FU+systemic folic acid. Although no difference was found between the groups, technical factors compromised this study such that only 34 of the 114 patients randomized to chemotherapy completed the adjuvant treatments. In another study, Kemeny et al. randomized 156 patients to either systemic 5-FU+ leucovorin or HAI floxuridine (FUDR)+systemic 5-FU after complete resection of tumor. 56 There was a significant survival advantage to HAI that is most likely related to local liver tumor control. We believe HAI chemotherapy is effective and should be considered as an adjuvant to resection of hepatic colorectal metastases.
Figure 6.4 Algorithms for the management of small hepatic metastases. (A) Algorithm for colorectal metastases (CRS, clinical risk score). (B) Algorithm for neuroendocrine metastases. (C) Algorithm for noncolorectal, nonneuroendocrine metastases.

For non-colorectal, non-neuroendocrine histologies metastatic to the liver the most
likely cause of death will be related to the disease outside the liver, regardless of how the liver is managed. For patients who are likely to develop systemic metastases in the near future it may be reasonable to offer chemotherapy prior to resection. If the tumor responds then a resection will be performed with confidence that other micrometastatic disease may be effectively treated with chemotherapy. If the tumor does not respond and the liver remains the only site of metastatic disease, resection is performed with increased confidence conferred by the longer period of observation. If the patient advances systemically during chemotherapy then it is very unlikely that a resection would have been of benefit and the patient will have avoided the potential morbidity, pain, discomfort and recovery time of an hepatic resection. That patient can go on to obtain second-line chemotherapy, investigational chemotherapy, or have no additional treatment.

Conclusions

Algorithms for the management of small solitary hepatic metastases are shown in Figure 6.4. Both patient and tumor characteristics must be considered in making management decisions. The most important tumor related characteristic is histology. For patients with colorectal cancer (Fig. 6.4A), the prognostic factors for tumor recurrence after resection are well defined. Using the clinical risk score (CRS) as selection criterion, patients with CRS=0–2 are ideal candidates for resection. Those with CRS=3–4 should consider observation or chemotherapy prior to a definitive hepatic procedure. Immediate ablation or resection should be performed in the setting of a clinical trial, and most appropriately a trial examining adjuvant therapy.

For neuroendocrine cancers (Fig. 6.4B), symptomatic tumors should be treated with resection and/or ablation when possible. When the cancer is found in an asymptomatic patient, a period of observation is not unreasonable because of the often indolent nature of these tumors. At resection, the principle should be to leave as much normal liver behind in order to minimize the risk of liver failure and in order to allow for repeat anatomic liver resections in the future for recurrent disease. Enucleation with positive margins is acceptable for treatment of this histology because resection is almost never curative, and such cytoreduction can provide significant and durable palliation with minimum risk.

For patients with small, solitary, non-colorectal non-neuroendocrine tumors the most significant factor in terms of prognosis seems to be the diseasefree interval (Fig. 6.4C). For patients with a long disease-free interval from primary resection a curative surgical resection is indicated as the most effective means of therapy. While it may be still unlikely that these patients can be cured, they must be given the benefit of the doubt and the most optimal procedure performed. The definition of ‘long’ has been arbitrarily set at 36 months by Harrison et al., but in reality it must vary according to histology. For gastric cancer, 12–24 months would be considered long, whereas for ocular melanoma, 3–5 years would be more reasonable.

Patients with a short disease-free interval from a tumor with a poor prognosis should undergo a trial of chemotherapy if there is a known effective agent. If no effective agent exists (as is the case for most solid malignancies), then these patients are ideal for an
experimental, minimally invasive, local ablative therapy. This provides an advantage to observation alone, given the low but definite risk of the metastases spreading during the observation period. It will be psychologically more comforting to the patient to know that the lesion has been ablated, and risk, pain and recovery duration are minimal. Observation alone is also quite reasonable, but it is often not accepted by patients. Patient related factors must also be taken into consideration. Patients who have concomitant illnesses which make them poor operative candidates may be better served with a minimally invasive or percutaneous technique, even in the case of potentially curable metastases from colorectal cancer.

Because of improvements in diagnostic techniques and the routine use of serum tumor markers, the detection of small solitary hepatic metastases from various tumors will likely increase in the future. A uniform approach to these patients such as that which is outlined in the treatment algorithm should be considered.

Key points

**Factors that determine management**

- Natural history of tumor type
- Expected cure rate after surgical treatment
- Effectiveness of alternative treatment strategies
- Morbidity of surgical resection.

**Survival rates following hepatic resection**

- Good evidence for long-term survival
  - Colorectal metastases
  - Neuroendocrine metastases.
- Survival possible in highly selected cases
  - Breast cancer
  - Sarcoma (especially gastrointestinal stromal tumors)
  - Melanoma.

**Patient selection factors in colorectal metastases**

- Contraindications
  - Extrahepatic disease (except solitary pulmonary metastases)
  - Positive hilar lymph nodes.
- Relative contraindications
  - Presentation within 12 months of resection of primary tumor
  - CEA >200 ng/dl
  - >1 liver tumor
  - Tumor >5 cm in size
  - Positive resection margin.
REFERENCES

5. Fong Y, Blumgart LH, Cohen AM. Surgical treatment of colorectal metastases to the liver. CA Cancer J Clin 1995; 45:50–62
At present, in the West, the main indication for hepatic resection is the treatment of colorectal liver metastases. Among these patients, those with bilobar metastatic disease represent the biggest challenge for the surgeon. In the multicentric retrospective study of the French Association of Surgery, the largest series of liver resections for colorectal metastases to date, of the 1818 patients treated with a curative resection 20% of the cases were bilobar. (Figure 7.1). We shall try to answer the following questions:

(1) Is it therefore justifiable to resect bilobar colorectal liver metastases?
(2) How should diagnostic procedures and the preoperative evaluation be managed? (With special reference to the hepatic functional reserve.)
(3) How should bilobar metastases be resected? (Intraoperative evaluation, contraindications and various types of resections.)

Is it justifiable to resect bilobar colorectal liver metastases?

Surgical resection is currently accepted as a safe, and also the only potentially curative treatment available for patients with colorectal liver metastases, offering a chance of long-term survival with rates ranging from 25% to 50% at 5 years. During the last decade, significative technical advances have been accomplished in liver surgery. They allow bilobar resections with very low mortality (around 1%) and low morbidity. However, it has been estimated that a curative resection (RO resection), i.e. with complete excision of the metastatic deposits, can only be achieved in about 10% to 15% of all patients who develop colorectal liver metastases. Furthermore, there is still a lack of enthusiasm among many physicians regarding surgical resection of liver metastases when they are multiple; many of them are clearly reluctant in the case of bilobar disease.
(4) Which other local treatments can be used?
(5) What results can be expected after surgery?
(6) What strategies are available in certain conditions, especially with a small left lobe?
(7) Is there a place for adjuvant or neo-adjuvant chemotherapy?
(8) The follow-up: is repeat hepatectomy worthwhile?

Nevertheless, most studies in the literature show clearly that there is no difference in 5-year survival rate between patients with solitary or fewer than four metastases, whether the location is unilobar or bilobar. The multicentric retrospective study that we performed with the French Association of Surgery collected 1818 patients in whom the resection was considered to be curative. The data showed, on multivariate analysis, that the following factors were associated with a significantly better prognosis: presence of fewer than four metastases, diameter of less than 5 cm (Tables 7.1 and 7.2), no extra-hepatic disease, carcinoembryonic antigen (CEA) level below 30 ng/1 and detection 2 years or more after resection of a primary tumor which had not involved the serosa or the periolic lymph nodes. In contrast, unilobar versus bilobar location had no influence on survival in this group (Figure 7.1) of candidates for resection, provided that the deposits could be completely removed (RO resection) with a free resection margin of at least 1 cm. Similar results were reported by Elias and Minagawa. Giving one point to each factor, including the age of the patient, the population could be divided into three risk groups with different 2-year survival rates.
Table 7.1 **Survival according to the size of the metastases (<5 cm, >5 cm)**
(multicentric retrospective study by the French Association of Surgery \(^1\))

<table>
<thead>
<tr>
<th>Size of metastases</th>
<th>No of patients</th>
<th>Survival (%)*</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm</td>
<td>857</td>
<td></td>
<td>90</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>818</td>
<td></td>
<td>83</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Not available</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001

Table 7.2 **Survival according to the number of the metastases (1–3, 4 or more)**
(multicentric retrospective study by the French Association of Surgery \(^1\))

<table>
<thead>
<tr>
<th>Size of metastases</th>
<th>No of patients</th>
<th>Survival (%)*</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>1510</td>
<td></td>
<td>88</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>4 or more</td>
<td>214</td>
<td></td>
<td>79</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Not available</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001

Table 7.3 **Prognostic scoring system\(^{11}\)**

<table>
<thead>
<tr>
<th>Number of risk factors a</th>
<th>2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>79</td>
</tr>
<tr>
<td>3–4</td>
<td>60</td>
</tr>
<tr>
<td>5–7</td>
<td>43</td>
</tr>
</tbody>
</table>

\(^a\) Risk factors:
• age (>60 years)
• size of largest metastases (>5 cm)
• CEA (>30 ng/ml)
• stage of primary tumor extension to serosa lymphatic spread
• disease-free interval <2 years
• number of liver nodules (5≥4)
• resection margin (<1 cm).
survival rates: 0–2 (79%), (3–4 (60%) and 5–7 (43%) (Table 7.3). In contrast to some reports where bilobar liver involvement was found to be associated with lower survival and higher postoperative mortality and morbidity rates, our study confirmed that the prognosis is not influenced by the location of the tumor deposits on one or both lobes of the liver or by the extent of the liver resection, provided the tumor was totally removed. Moreover, the postoperative complication rate is similar in subjects with unilobar or bilobar involvement. This means that surgical excision of two or three metastases, for example, should be undertaken if technically feasible, whether they are located on one half of the liver and require a lobectomy or in both lobes and demand two separate resections. It also means that if complete resection of the secondary tumors can be achieved with a wedge resection there is no need to perform a larger hepatectomy, provided a 1 cm clearance of normal parenchyma is resected with the tumor.

Several studies have evaluated the prognostic impact of the surgical margin when, under certain circumstances, it has to be less than 1 cm (for example in the case of metastases located near a main vessel: vena cava, porta hepatis). It was concluded that if complete resection of the tumor is mandatory, a margin less than 1 cm should not be considered as an absolute contraindication to surgery. In these situations, cryotherapy has been recommended to improve the proportion of negative resection margins; however, the proximity of a metastasis to a large blood vessel compromises an adequate freezing margin.

Finally, there is a strong argument in favor of segmentectomies or minor resections rather than extended resections if they can be undertaken safely. This approach contributes to preservation of the residual liver. Indeed, recurrences will unfortunately occur in the majority of patients after the first liver resection. A clinical score predicting recurrences after hepatic resection for metastatic colorectal cancer has been established by Fong et al. We demonstrated in our multicentric series that there is a clear survival benefit for repeat liver resections in some selected patients with long-term survival rates.
after the second resection similar to that obtained after the first resection. These findings have been confirmed by others, and they emphasize the need not only for a careful follow-up after hepatectomy in order to detect resectable recurrences, but also for a policy of economical but complete resections of the liver metastases rather than routine major hepatic resections when the size and/or the number of the tumors do not require it. Other studies tried to identify parameters that could help to select subpopulations of patients with recurrent liver metastases who have a better prognosis after repeat resections. Bozzetti showed that patients with a disease-free interval greater than 1 year between the first and second liver resections had a greater disease-free survival after the second resection. However, in the largest series no parameter significantly related to outcome could be identified, even for bilobar liver involvement. Several authors recommended an aggressive approach for patients with recurrent or multiple bilobar liver metastases from colorectal primaries.

Figure 7.3 CT scan and MRI imaging of bilobar metastases. (A) CT scan with intravenous contrast. (B-D) MRI imaging with gadolinium enhancement: T1 (B) and T2 (C) weighted images; coronal view (D).
Pathophysiology of bilobar distribution

Many studies have attempted to explain (1) the ability of some primary tumors to develop metastases, and (2) the lobar distribution of these metastases in the liver. Several factors are involved, linked to the biology of the tumor and of the target organ. It has been suggested that right-sided colon cancers involve the right hepatic lobe more selectively while left-sided tumors involve the entire liver, according to streaming of flow in the portal vein. These hypotheses need further investigations but should not influence the specific therapeutic strategy. Obviously, metastatic potential of the primary tumor correlates with several factors, including angio genesis, or genetically coded disorders which will have a strong effect on the prognosis of the disease. Other prognostic factors have been studied including the macroscopic morphology of the metastases: simple nodular or confluent nodular, according to the characteristics of the cut surface of the tumor. The presence of satellite nodules around the metastases predicts a poorer prognosis; in this situation an extended hepatectomy seems to be a better option in order to reduce the risk of local recurrence (Fig. 7.2).

How should diagnostic procedures and the preoperative evaluation be managed?

Diagnostic procedures

Preoperative liver imaging and also intraoperative ultrasound are routinely used to detect hepatic metastases. The two main difficulties are distinguishing metastases from incidental benign focal liver lesions (particularly hemangioma) and being able to detect small metastases less than 2 cm in diameter. At the preoperative stage, some cases of bilobar invasion may not be recognized if the deposits on one side are too small.

Percutaneous ultrasound (US) is the most widely used imaging technique. For lesions greater than 2 cm the sensitivity exceeds 94%, but this falls to less than 56% for lesions below this size. Ultrasound should always employ color Doppler, which may show more clearly displacement, interruption or thrombosis of the hepatic and portal vein or of the IVC.

The use of CT scanning with intravenous contrast (enhanced CT scanning), bolus dynamic CT, delayed scanning, and dynamic CT scanning during arterial portography has led to increased sensitivity in detection of liver metastases (68% of the nodules less than 1 cm diameter were detected and 99% of those larger than 1 cm) (Fig. 7.3A). The portoscanner (dynamic CT during arterial portography CTAP) involves selective catheterization of the superior mesenteric artery followed by bolus contrast injection and CT scanning during the portal phase. This method is particularly helpful to detect lesions less than 5 mm in diameter; it has been proven to be significantly better than US, contrast CT or hepatic angiography in detecting metastases less than 10 mm in diameter. However, this investigation is invasive and the second major limitation is the number of false positive findings caused by perfusion defects from flow artefacts. Moreover, all focal intrahepatic abnormalities (biliary cyst, angiomas, benign tumors) appear as lucent areas with this imaging technique; if smaller than 5 mm they cannot be compared to other
preoperative examinations and possible guided needle biopsy.

Figure 7.4 (A-C) Image reconstruction techniques in three dimensions showing connections between the vessels and the tumors.

The development of MRI, including the use of gadolinium ferumoxide (Endorem), and other enhancement methods, raised the possibility that this technique could be even better and more efficient in detecting small lesions (Fig. 7.3B,C). The T1-weighted MRI appears to have the lowest false positive rate (11%). Staging laparoscopy with laparoscopic ultrasonography has also been reported. This method allows accurate preoperative hepatic staging, needle biopsy and also assessment of peritoneal involvement. However, it is an invasive procedure which carries a potential risk for metastatic seeding of the port sites. In the near future, the PET (positron emission tomography) scan might be more sensitive and specific for detection of metastatic deposits in the liver, as well as for detection of local recurrences, carcinomatosis and metastatic lymph nodes. Finally, a chest CT scan is used routinely to establish the presence or absence of pulmonary metastases. CT of the brain and isotope bone scans are usually only performed in the presence of clinical symptoms.
Figure 7.5 Preoperative measurement of the respective volumes of (A) hepatic resection (1310 ml) and (B) remnant liver (750 ml) according to simulation of central hepatectomy.

**Evaluation of hepatic functional reserve and measurement of liver volume**

The development of image reconstruction techniques in three dimensions is very helpful to evaluate the total volume of the tumors and the volume of healthy liver. It also shows very clearly the relationship between vessels and the tumors (Fig. 7.4). It enables the surgeon to determine an exact strategy of resection and to draw it on the computer screen.

Patients with bilobar metastases often require either extended hepatectomies or multiple resections and are therefore at risk of developing liver failure after hepatectomy. Although the normal liver is reported to tolerate removal of up to 70% of its volume, the extent to which the liver parenchyma may be resected in patients with steatosis (after chemotherapy) or with chronic liver disease has not yet been completely elucidated. The hepatic functional reserve may be evaluated by measurement of the respective volumes of hepatic tumors together with the resection margin and of the remnant liver, or by evaluation of preoperative liver function as a guide before making decisions with regard to the extent of liver resection.

**Measurement of liver volume**

This has been performed by several imaging techniques (Fig. 7.5). However, CT has been shown to be the most adequate procedure both in liver resection and liver transplantation, especially in assessing graft sizes for living-related liver transplantation. It is currently accepted that in patients with normal hepatic function, resection of up to 60% of the noncancerous parenchyma is well tolerated. After excluding the tumor volume, the ratio of the non-cancerous parenchymal volume of the resected liver to that of the whole liver is the crucial value to estimate. Actually, when the volume of the future remnant liver estimated by CT-scan volumetry is less than 40%, right portal vein embolization has been recommended in order to improve the safety of the right hepatic lobectomy. This procedure efficiently reduces the size of the liver volume to be resected (right lobe) and induces hypertrophy of the contralateral liver (left lobe).
Evaluation of preoperative liver function

Standard liver biochemistry tests have not been shown to be of any predictive value. Other methods have included measurement of uptake of organic anions (such as bromsulphalein, rose bengal and indocyanine green (ICG), the arterial ketone body ratio, redox tolerance test, aminopyralene breath test and the amino acid clearance test. The ICG clearance test appears to be the best discriminating investigation. Before a decision is made to undertake a major hepatectomy, ICG retention should be less than 20% at 15 minutes. Hepatectomy involving resection of up to 60% of the non-tumorous parenchyma can be justified in patients with normal liver function and with ICG 15 values >20%. Minor hepatectomies can be accomplished even if ICG retention at 15 minutes reaches 23 to 25%. The lidocaine test (MEGX) can also be used to evaluate the hepatic function. Lidocaine is metabolized almost exclusively (97%) in hepatocytes by the P-450 cytochrome. Fifteen minutes after an IV bolus injection of 1mg/kg of lidocaine, a venous blood sample is taken and the MEGX rate is assessed: values over 50 ng/ml are considered as normal, between 25 and 50 ng/ml intermediately reduced and below 25 ng/ml greatly reduced.

How should bilobar metastases be resected? (Intraoperative evaluation and contraindications and various types of resections)

Surgical resection should only be undertaken if all the liver metastases can be removed (RO resection). In the case of associated extrahepatic disease, resection is not justified except in cases where all the tumoral tissue—intrahepatic and extrahepatic—can be completely removed. The surgical strategy has to achieve two contradictory goals: (1) perform an oncological resection with clear free resection margins, and (2) save most of the non-cancerous parenchyma in order to avoid liver failure and to allow further repeat resection in case of possible recurrence.

Involvement of lymph nodes in the hepatic pedicle

Extensive lymph node dissection of the hepatic pedicle was undertaken prospectively in 100 consecutive patients undergoing curative hepatectomy for colorectal liver metastases in whom lymph node involvement of the hepatic pedicle was not macroscopically detectable. Microscopic lymph node involvement was found in 14 patients, and the presence of microscopic disease related to the number of metastases, extent of liver involvement and CEA level. Colorectal tumors that spread to the lymph nodes of the hepatic pedicle or coeliac region are generally considered to be metastases derived from liver metastases. The incidence of macroscopic involvement of these lymph nodes varied from 1 to 10% in a major series of liver resections for colorectal metastases. One series showed up to 28% tumor infiltration of the hepatoduodenal ligament lymph nodes. Low 5-year survival rates have been reported for these patients, despite complete resection of the macroscopically involved lymph nodes. However, the 5-year survival rate of this group of patients was up to 12% in the study by the French
Association of Surgery,\(^1\) compared to the expected 0 to 2% without resection.\(^{65}\) Therefore, our recommendation would be to perform

![Image](image_url)

**Figure 7.6** Operative view of extensive lymphadenectomy of the hepatic pedicle.

...hepatectomy even in the case of hepatic pedicle lymph node involvement, but to complete the procedure with an extensive lymphadenectomy from the liver hilum (Fig. 7.6) to the origin of the hepatic artery (coeliac axis). The prognostic and therapeutic value of such a lymphadenectomy is currently unknown;\(^{66}\) the answer could only be found by a prospective randomized study comparing groups with and without lymphadenectomy.

**Other extrahepatic involvement**

Liver resection should only be undertaken when curative resection is possible, which clearly means complete resection of intrahepatic and extrahepatic deposits.\(^{60}\) In the case of extrahepatic involvement, the probability for curative resectability is less: 5.9% compared to 27.1% without extrahepatic involvement in synchronous metastases and 5.4% compared to 37.4% in metachronous metastases.\(^5\)

**Intraoperative ultrasound (IOUS)**

The importance of detecting all metastatic nodules present in the liver and also the need for a negative margin with adequate liver function after resection emphasize the role of intraoperative ultrasonography combined with Doppler examination. Assessment of the hepatic vasculature and the localization of the tumors with regard to any adjacent vessels is essential in order to provide an overall assessment of the extent of the lesions and also to determine the limits of the resection. The information obtained at the beginning of the operation will avoid unnecessary tissue dissection or traumatic surgical maneuvers. Small linear probes are most commonly used for hepatic surgery. Ultrasound frequency ranges from 5 to 10 MHz. The 5 MHz probe offers a reasonable compromise between optimal resolution and maximum depth of exploration.\(^{67}\) The examination may be repeated during the operation, for instance in assessing the resection margins or in identifying the...
relations between the tumor and the main intrahepatic vessels. The concept of ultrasound-guided segment-orientated procedures has been developed and is particularly useful in resection of multiple metastases. 68 – 72 IOUS is able to detect lesions as small as 4 or 5 mm and to find metastases which were not diagnosed preoperatively: detection of 5–10% of unsuspected liver lesions has been reported by employing this technique. 73 , 74 One prospective study designed to compare diagnostic accuracy of preoperative ultrasonography, surgical examination and IOUS showed a higher sensitivity and specificity for IOUS. 67 During liver resection, IOUS is repeated to ensure a sufficient safety margin and to follow an adequate plane of parenchymal division with respect to the limit of the tumor.

How to choose the type and the number of hepatic resections in bilobar metastases

Complete knowledge of the segmental structure of the liver is essential for the performance of this type of surgery. The description by Couinaud 75 , 76 was originally adopted in France and then throughout the world (see Chapter 1). It divides the liver into eight segments (or even nine), 77 , 78 based on the portal and hepatic veins distribution (Fig. 7.7). A new terminology, accepted by the scientific committee of the International Hepato-Pancreato-Biliary Association (IHPBA), has also been reported. 79

In the case of bilobar metastases it seems convenient and realistic to consider schematically five types of situations (Fig. 7.8A-E):

(1) Major deposit in the right liver and small deposit in the left liver (Fig. 7.8A). This situation can be treated:

• either by an extended right hepatectomy (Starzl’s right trisegmentectomy) removing segments V, VI, VII, VIII and IV (8A1);
• or by a right hepatectomy combined with a wedge resection in the left lobe (8A2);
• or by one or more segmentectomies in the right liver combined with a wedge

Figure 7.7 Couinaud’s segmentation of the liver.
resection in the left lobe (8A3).

(2) Major deposit in the left liver and small deposit in the right liver (Fig. 7.8B). This situation can be treated by a left lobectomy (8B1) or a left hepatectomy (8B2+3) combined with a wedge resection in the right lobe. If the left liver is involved and also segments V and VIII, an extended left hepatectomy can be performed (8B4) removing segments II, III, IV, V and VIII.

(3) Major deposit located in the central part of the liver and involving both lobes (Fig. 7.8C). This presentation can be treated by a central hepatectomy removing segment IV (either totally (8C1) or only the anterior portion (8C2) if the posterior portion is not involved) and both segments V and VIII.

(4) Both lobes present, each with a major deposit (>5 cm) (Fig. 7.8D). This presentation can be treated by a left lobectomy combined with a bisegmentectomy in the right liver (segments VI and VII) (8D1), segments V and VI (8D2) or segments VII and VIII (8D3). In this last situation, venous drainage from segments V and VI

<table>
<thead>
<tr>
<th>Type of bilobar hepatic resection a</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>6</td>
</tr>
<tr>
<td>A2</td>
<td>8</td>
</tr>
<tr>
<td>A3</td>
<td>20</td>
</tr>
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<td>B1</td>
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</tr>
<tr>
<td>E1</td>
<td>14</td>
</tr>
<tr>
<td>E2</td>
<td>4</td>
</tr>
</tbody>
</table>

| Total                            | 92              |

a As shown in Fig. 7.8
Figure 7.8 Five types of schematic presentation of bilobar metastases and various types of adequate bilobar resections. (A) Major deposit in the right liver and small deposit in the left liver. Five types of schematic presentation of bilobar metastases and various types of adequate bilobar resections. (B) Major deposit in the left liver and small deposit in the right liver. Five types of schematic presentation of bilobar metastases and various types of adequate bilobar resections. (C) Major deposit located in the central part of the liver, involving both lobes. Five types of schematic presentation of bilobar metastases and various types of adequate bilobar resections. (D) Both lobes present, each with a major deposit (>5 cm). Five types of schematic presentation of bilobar metastases and various types of adequate bilobar resections. (E) Both lobes present, each with several minor deposits.
is maintained by one or more right inferior hepatic veins, if they are large enough. (This can be assessed by ultrasound, Doppler and visual exploration along the inferior vena cava.) If not, reconstruction of the right hepatic vein can be performed.

(5) Both lobes present, each with several minor deposits (Fig. 7.8E). This presentation can be treated by several minor resections (segmentectomies or wedge resection) according to the location of the deposit (8EI, 8E2).

The various types of hepatectomies (Fig. 7.9A-D), following this classification, that we performed in 92 cases of resection of bilobar colorectal metastases are summarized in Table 7.4.

The possible involvement of the caudate lobe (segment I) must be systematically assessed. Located behind the hilum of the liver and in front of the inferior vena cava, this lobe is an independent functional and anatomical unit consisting of two parts. One is situated to the left of the vena cava which corresponds to the Spieghel lobe or Couinaud’s segment I (Fig. 7.10). The second part, or right caudate lobe, is located in front and to the right of the vena cava, with an elevation situated between the right end of the hilum and the anterior aspect of the inferior vena cava called the caudate process or also Couinaud’s segment IX. 77 , 78 In the case of large metastases located in the left liver and in the caudate lobe, left hepatectomy extended to the caudate lobe is necessary. At the opposite end of the scale in the case of small deposits in the caudate lobe, isolated resection of segment I is feasible after complete mobilization of the liver on both sides. 81 – 83 The inferior vena cava must be controlled for total vascular exclusion in the event of hemorrhage. In the case of infiltration of the caudate lobe by a large tumor which has developed in the posterior part of the right liver, a right hepatectomy extended to the caudate lobe is necessary.

A large variety of resections can be undertaken, following the distribution of the metastases. Usually true segmentectomies are suitable for the vast majority of situations and are technically easier. The liver parenchyma is separated along the lines of ischemic demarcations produced by selective clamping of the various glissonian pedicles. This procedure has been made much easier by the use of an ultrasonic dissector, which facilitates a quick separation of the parenchyma with elective control of vessels and bile ducts.

Clamping

The control and prevention of intraoperative hemorrhage is obtained by the use of pedicle clamping (Pringle maneuver). This procedure reduces the need for blood transfusion, which represents one of the main factors associated with postoperative morbidity 84 , 85 and also tumor recurrence rates. However, the relationship between pressure within the inferior vena cava and blood loss during liver resection has now been established, suggesting one should maintain low venous pressure (<5 mmHg) in the inferior vena cava. 86 There are several types of clamping:
(1) Non-selective clamping, whereby the hepatic pedicle is clamped in order to limit bleeding as much as possible. A number of authors have shown that the liver has a good tolerance to normothermic ischemia, even for periods of more than 1 hour. 87 – 90 Intermittent clamping for periods of up to 15 minutes has been proposed in order to reduce the ischemic damage to the hepatocytes. 91 , 92

(2) Hemihepatic vascular occlusion with selective clamping of the right or left glissonian pedicle, depending on the site of the parenchymal resection, has been advocated to increase the safety of the clamping maneuvers. 93 This policy can be followed in segmentectomies. However, before the type of clamping is chosen, several criteria have to be considered, such as the number and extent of resections, the quality of liver function
Figure 7.9 Different types of bilobar resections. (A) Central hepatectomy removing segments IV, V and VIII (A1). Perioperative (A2) view and postoperative CT scan at 3 months (A3). Different types of bilobar resections. (B) Bisegmentectomy VII-VIII combined with either wedge resections or left segmentectomy (B1,2,3). Right inferior hepatic vein(s) (B4) may achieve (if caliber large enough) the venous drainage of segments V and VI when right
superior hepatic vein has to be resected. Different types of bilobar resections. (C) Right hepatectomy combined with partial resection of segment IV. Different types of bilobar resections. (D) Various types of bilobar segmentectomies preserving a maximum of healthy liver: D1: segmentectomy VI+left lobectomy; D2: segmentectomy VIII+left lobectomy; D3: segmentectomy V+VI+VII+segmentectomy II.

(sometimes impaired by previous chemotherapy or associated chronic liver disease) and also the general condition of the patient (associated cardiovascular disease). Research is ongoing to evaluate a number of therapeutic substances able to reduce the ischemic reperfusion injury to the liver. 94
(3) Total vascular exclusion is particularly useful in cases of tumor infiltration of the vena cava or of the caval-hepatic vein confluence. If this maneuver is not well tolerated then the use of a veno-venous bypass is indicated. However, in many other cases, total vascular exclusion of the liver with preservation of caval flow can be obtained by selectively controlling the hepatic veins by taping the right hepatic vein on one side and the middle and the left hepatic vein on the other side. \(^{95, 96}\) (Fig. 7.11).

(4) Innovative techniques for major liver resections with hypothermic perfusion. These

**Figure 7.10** (A) Anatomical view of the Spieghel lobe. (B) Metastatic involvement of the Spieghel lobe (MRI imaging).
techniques

Figure 7.11 Selective control of the hepatic veins without clamping of the inferior vena cava.

were developed together with orthotopic liver transplantation and may be associated with vascular reconstruction, for instance in the case of invasion of the vena cava. Liver perfusion with a 4°C preservation solution has been used in three different approaches in major liver resections: ex vivo (bench procedure) (see Chapter 10), in vivo in situ or in vivo ex situ.

• In the ex vivo technique, the liver is completely removed from the abdominal cavity by transection of afferent and efferent vessels, as well as the common bile duct; liver resections and vascular reconstruction are performed on the bench and the remnant liver is reimplanted as it would be done for a liver graft. Veno-venous bypass is used during the anhepatic phase (see Chapter 10).

• In the in situ procedure, after vascular exclusion, the liver is perfused in situ, and a draining cavotomy is performed on the infrahepatic IVC. When resection is complete, the preservative solution is flushed out of the remnant parenchyma by perfusing 4°C Ringer lactate or albumin solution. To avoid cardiac arrhythmias the potassium level must be carefully controlled in the blood before reperfusion.

• The ex situ in vivo procedure has been proposed for very selected cases in which a long ischemia time is necessary (3–5 hours). Compared to the ex vivo technique, the significant advantage is to avoid the need to perform portal, arterial and biliary anastomoses. The application of these techniques may open a different strategy in very selected cases for the treatment of multiple or huge tumors with extrahepatic vascular involvement. However, it is too early to evaluate the results of these procedures. It is very likely that, in most cases, low morbidity and low mortality can best be achieved with less sophisticated techniques avoiding too complex surgical
Liver parenchyma resection

The easiest way to carry out parenchymal division is to crush small portions of the liver tissue with a Kelly forceps. The smaller vessels are coagulated with unipolar or bipolar coagulation. The bigger ones as well as the biliary structures are either ligated with absorbable sutures or sutured or clipped. Use of the ultrasound dissector, in our experience, makes the exposure of the vascular and biliary intrahepatic pedicles easier and appears of particular help in segmentectomies. The waterjet dissection has been recently introduced and needs further evaluation.

Hemostasis and biliostasis must be achieved very cautiously to avoid any source of hemorrhage or bile leak. The Argon beam coagulator represents a significant advantage in performing coagulation without necrosis on small surface hemorrhage. In order to achieve biliostasis, the use of a dilute solution of methylene blue injected via the cystic duct facilitates detection of small bile leaks on the resected surface of the liver. In our experience, in accidental lesion of a main bile duct or in complex surgery with extended resected surface, external biliary drainage through a transcystic catheter in patients with dilated bile ducts can be quite useful.

Which other local treatments can be used?

Liver resection is the best treatment for liver colorectal metastases and the only therapy giving a chance of cure. However, it may be achieved in only 10 to 20% of patients. If curative liver resections cannot be performed, palliative resection shows no significant benefit. Other local treatments have been evaluated in the treatment of these unresectable hepatic metastases which, in fact, represent the majority of secondary liver tumors.

Cryosurgery

Cryosurgery has been used with some interesting results. This method is less limited than resection techniques by the anatomic distribution of liver metastases. Therefore, the addition of cryosurgery to surgical ablation could increase the number of patients rendered disease-free. The cryosurgical probes are placed into each lesion, which is frozen using liquid nitrogen to a temperature of −196°C for about 10–15 minutes. This is followed by a 10 minute thaw period and then a second 10–15 minute freeze. Usually, the size of the ice-ball achieved by the cryoprobe is visible as a hypoechoic area with the intraoperative ultrasonography and exceeds by 1 cm the diameter of the lesion. In the case of bilobar metastases this procedure can be used to avoid extensive loss of parenchyma in combining resection of the lobe predominantly involved and freezing of lesion(s) in the remaining part. Unfortunately, the recurrence rate seems to be high, around 50%, which suggests that cryosurgery does not achieve total destruction of the tumoral tissue in all cases. The effect on overall survival will require further
evaluation. Rather than an alternative to resection, cryosurgery appears to offer a complementary strategy in achieving tumor eradication when total excision cannot be performed. Hewitt et al. have reported the use of cryotherapy to destroy residual metastases following liver resection in patients with multiple bilobar liver metastases, with promising results (2-year survival 60% and median survival 32 months). \(^\text{107}\)

### Other forms of local treatments
Other techniques which produce controlled hepatic destruction include thermotherapy, interstitial radiotherapy and ethanol injection.

#### Thermotherapy
The concept of heat destruction of tumors dates from antiquity. However, this approach requires extremely accurate localization to avoid injury of healthy tissue and of adjacent major vascular and biliary trunks, which are very heat sensitive. Thermotherapy may be achieved by saline-enhanced radiofrequency, by electromagnetic or microwave radiation or finally by laser.

During radiofrequency ablation (RFA)—or radiofrequency ‘destruction’—a high frequency alternating current flows from the uninsulated tip of an electrode into the tissue. Several preliminary clinical and experimental reports suggest that this may be a safe and efficacious treatment for some liver tumors. \(^\text{108} – 112\) The debate whether RFA probes should be used percutaneously or at laparotomy or laparoscopy is only beginning. It has been suggested that RFA is more efficient when the blood flow through the liver is reduced by a Pringle maneuver. The use of electromagnetic or microwave radiation has been advocated in the treatment of liver tumors. \(^\text{113}\) The heat produced has to cross normal tissue before reaching the tumor and, again, the proximity of main vessels or biliary ducts may contraindicate the use of this method for a deeply located tumor.

Laser hyperthermia can be used intraoperatively or percutaneously under ultrasound control. The magnetic-resonance-guided laparoscopic approach has been studied experimentally for interstitial laser therapy of the liver. \(^\text{114}\) At present, only a few reports are available concerning the results of laser-induced thermotherapy: they show partial and transitory benefit. \(^\text{115} , 116\) It is too early to draw conclusions from these series. Nonetheless, this method may be effective for the treatment of small superficial hepatic metastases; it does not seem applicable to large, deeply located tumors in the neighborhood of the main vascular and biliary trunks.

#### Interstitial radiotherapy
Radioactive implants have been used to treat gross residual disease or to sterilize positive margins following hepatic resection of colorectal metastases. The observed results were poor, with early as well as distant recurrence. \(^\text{117}\) Intestinal radiotherapy has no advantage over other local treatments and its cost and inherent problems limit its usefulness.

#### Ethanol injection
Percutaneous alcohol injection has been used to treat unresectable colorectal liver metastases. Results are far from satisfactory as early recurrence and partial responses are commonly observed. Morphologically the opposite of hepatocellular carcinoma, colorectal liver metastases present with dense stroma into which it is difficult to inject alcohol. Pain following the injection is common and the technique seems ineffective, as the alcohol spreads out into the normal parenchyma.

What results can be expected after surgery?

The mortality associated with elective liver resections for colorectal metastases is less than 5% in most recent series, even for bilobar liver involvement. In the French Association of Surgery survey there was a 2.4% postoperative death rate; these deaths were more frequent after a major resection (3%) than after a minor one (1–2%). An increased risk was also observed in older patients (median age of patients who survived was 60 years compared to 68 years for the group of patients who died during the postoperative period). The postoperative mortality rate was also higher in patients with the largest metastases (>5 cm) than in patients with smaller metastases (3.2% vs 1.3%; \( P=0.01 \)). The postoperative risk of major liver resections was greater when primary tumor resection and liver resection were performed at the same operation than when liver resection was postponed for more than one month (6.9% vs 2.3%; \( P=0.01 \)). Conversely, more recently, in our own experience in selected cases, we did not notice a higher mortality in the group of patients undergoing simultaneous resection; we believe it is a safe strategy, especially for patients presenting with a primary tumor of the right colon with liver metastases resectable by means of a minor hepatectomy and through the same abdominal incision.

Reversible complications occurred in 23% of the patients and were more frequent after major than after minor resections (26% vs 17%; \( P=0.001 \)). Among these complications
observed with decreasing frequency: sepsis, biliary leaks, liver failure and bleeding. Most postoperative complications after liver resection can be managed without reoperation; percutaneous drainage of perihepatic collections and endoscopic stenting of biliary leaks are now used routinely. 5 If bleeding can be avoided during hepatic resection, this results in lower mortality. Excessive bleeding during hepatic resection is a major complication, associated with a perioperative mortality as high as 17%. 1 Hepatic failure occasionally occurs after liver resection for colorectal metastases and is often a lethal complication. 120 It is especially related to the extent of hepatic resection; its occurrence is related to the quantity and quality of the remnant parenchyma. After prolonged chemotherapy the liver parenchyma is often more fragile and steatotic and the risk of bleeding is higher, which requires the use of the Pringle maneuver. The use of intermittent rather than continuous clamping, and also limiting the period of vascular occlusion, are safer procedures for these patients. Factors leading to higher morbidity after hepatic resection have been identified. 121 Among them are longer operation time, major hepatic resection, preoperative cardiovascular disease and the presence of chronic liver disease. When the liver is diseased, either due to chronic disease or to previous chemotherapy, serum total bilirubin level and plasma retention rate of indocyanine green at 15 minutes may be good predictors when deciding the volume of a safe hepatic resection 121 (Fig. 7.12).

The reported overall 5-year survival rates range from 25% to 50%.1–6,10,31,51 Analysis of the various prognostic factors which were studied in the survey of the French Association of Surgery is shown in Table 7.5. 1, 11 The survival for patients who were treated for bilobar metastases is summarized in Table 7.1. There is no difference from survival of patients with unilobar disease. The predictors of survival were also predictors of disease-free survival. Extension into serosa and lymphatic spread of the primary tumor were strong predictors. Other factors include a period of more or less than 2 years between treatment of the primary tumor and discovery of metastases, the size of the largest deposit (≥5 cm) and the number of metastases (≥4), which all correlated with survival as well as preoperative CEA level. On the other hand, distribution of resectable metastases on one or both liver lobes was not correlated with survival. Neither was extent of liver resection correlated with survival. However, clearance of normal parenchyma resected with the tumor was strongly correlated with prognosis. This means that surgical excision of two or three metastases, for example, should be undertaken, if technically feasible, whether they are located on one liver lobe and require one lobectomy or in two lobes and demand two separate resections. It also means that if complete resection of the tumors can be performed with wedge resections there is no need to perform larger hepatectomies, provided a 1 cm clearance of normal parenchyma is resected with the tumor.

What strategies are available in certain conditions, especially with a small left lobe?

One of the prerequisites for hepatectomy, particularly in case of bilobar metastatic disease, is the presence of enough remaining liver parenchyma to avoid life-threatening postoperative liver failure. 69 This concern may occur when there is a small left lobe and
an extended right hepatectomy is mandatory or when major liver resection is necessary in patients with impaired liver function due, for instance, to previous prolonged chemotherapy. To render hepatectomy feasible and safe in such cases, preoperative portal vein embolization (PE) represents a very helpful method which is able to redistribute portal blood flow rich in hepatotrophic substances toward the future remnant liver. At the same time it induces a slight shrinkage in the volume of the embolized liver for which

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk of mortality</th>
<th>Relative risk of mortality or disease recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>RR 95% CI P value</td>
<td>RR 95% CI P value</td>
</tr>
<tr>
<td>Patient</td>
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<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.1 0.9–1.3 0.25</td>
<td>1.0 0.9–1.2 0.66</td>
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<tr>
<td>Age (3≥60 years)</td>
<td>1.2 1.0–1.3 0.06</td>
<td>1.0 0.8–1.1 0.46</td>
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<td>Primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of primary tumor (rectum)</td>
<td>1.1 0.9–1.3 0.25</td>
<td>1.2 1.0–1.3 0.03</td>
</tr>
<tr>
<td>Extension into serosa</td>
<td>1.4 1.2–1.6 &lt;0.001</td>
<td>1.4 1.2–1.6 &lt;0.001</td>
</tr>
<tr>
<td>Lymphatic spread</td>
<td>1.5 1.3–1.8 &lt;0.001</td>
<td>1.4 1.2–1.6 &lt;0.001</td>
</tr>
<tr>
<td>Hepatic metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay from primary tumor (&lt;3 months)</td>
<td>1.1 0.9–1.3 0.29</td>
<td>1.1 0.9–1.2 0.25</td>
</tr>
<tr>
<td>Delay from primary tumor (&lt;2 years)</td>
<td>1.4 1.1–1.7 0.001</td>
<td>1.3 1.1–1.5 0.01</td>
</tr>
<tr>
<td>No of metastases resected (≥4)</td>
<td>1.6 1.3–2.0 &lt;0.001</td>
<td>1.3 1.1–1.6 0.004</td>
</tr>
<tr>
<td>Size of the largest lesion (≥5 cm)</td>
<td>13 1.1–1.5 0.002</td>
<td>1.3 1.1–1.4 0.001</td>
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<tr>
<td>Location on liver (bilateral)</td>
<td>1.1 0.9–1.3 0.58</td>
<td>1.2 1.0–1.4 0.08</td>
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<tr>
<td>Type of resection (major)</td>
<td>1.1 0.9–1.3 0.36</td>
<td>1.0 0.9–1.1 0.95</td>
</tr>
<tr>
<td>Clearance of normal parenchyma (edge or &lt;1 cm)</td>
<td>1.4 1.1–1.6 &lt;0.001</td>
<td>1.3 1.1–1.6 &lt;0.001</td>
</tr>
<tr>
<td>Adjuvant chemotherapy (No)</td>
<td>1.2 1.0–1.4 0.05</td>
<td>1.1 1.0–1.3 0.09</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: relative risk.
Figure 7.13 Case of a bilobar metastatic (A) sigmoid cancer in a 59-year-old man. The right portal vein was embolized (B before, C after embolization). Before embolization, the volume of the left lobe was estimated at 210 ml. Six weeks later the volume of the left lobe reached 470 ml (D). Volumetric CT scan shows clearly the increase of the left lobe (E, F). (G) Three months after right hepatectomy was
extended to segment IV and combined wedge resection of deposit in the left lobe, CT scan shows the left lobe remnant.

resection is planned 48, 52, 53, 122 (Fig. 7.13). In 1920, it was shown that portal branch ligation in the rabbit resulted in shrinkage of the affected lobe; 123 and the origin, nature and action of hepatotrophic substances in portal venous blood were largely investigated. 124 Hepatocyte growth factor has also been isolated and reported to increase after hepatectomy. 125 Portal embolization induces a decrease in hepatocyte growth factor clearance and reroutes hepatotrophic hormones to the unembolized liver. For these reasons, in patients with multiple bilobar colorectal liver involvement, metastases in the future remnant liver (non-embolized) should be resected before portal vein embolization, since growth rate of metastatic nodules in the remnant liver can be more rapid than that of non-tumoral liver parenchyma after portal vein embolization; 126 otherwise, progression of metastases in the remnant liver may result in non-resectable disease. A major hepatic resection (embolized liver) can then be performed after the period of liver regeneration. Our preliminary experience of this two-stage hepatectomy procedure combined with portal vein embolization has been recently reported 127, showing that surgical outcome and 3-year survival were similar to those of initially resectable patients (Figs. 7.14 and 7.15). However, occlusion of the portal branches has to be complete and durable. Therefore, at present, cyanoacrylate appears to be the most suitable agent for PE. Some necrotic reactions have been described after PE, but less severe than after hepatic arterial embolization, which could explain the good clinical tolerance of this procedure. Injection is performed under a percutaneous transhepatic approach with a Blue Histoacryl® and Lipiodol Ultrafluide® mixture. Liver volumetric measurements are obtained with threedimensional, color-encoded CT, before portal embolization and before surgery. Expected hypertrophy of the future remnant liver is usually around 80 ± 50% after a 4–5 week interval between PE and surgery. Fewer than 20% of the patients develop insufficient hypertrophy of the future remnant liver and cannot undergo hepatic resection. 52, 53 Clear criteria for the use of PE have not been established; however, it has been suggested that PE is indicated when the volume of the future remnant liver estimated by CT-scan volumetry is less than 40% in patients with normal liver tissue (ICG 15 between 10 and 20%). 51, 52 Preoperative portal vein embolization widens the possibility of curative hepatectomies, particularly when extensive surgery is needed. It also appears effective for increasing the safety of hepatectomy for patients with multiple small metastases who require major right-sided resection combined with wedge resection of the left lobe 128 (Fig. 7.16).

Is there a place for adjuvant or neo-adjuvant chemotherapy?

After resection of hepatic metastases no study has shown that systemic chemotherapy prevents recurrence; however, controlled trials are currently ongoing to further answer this question.

Intra-arterial chemotherapy has a proven benefit on survival, but this is modest and the technique has important drawbacks (chemical hepatitis, sclerosing cholangitis, arterial
thrombosis). \(^{129} - ^{131}\)

Neo-adjuvant chemotherapy seems more promising. It has been shown that initially unresectable colorectal metastases could be debulked by chronomodulated chemotherapy, \(^{132}\) using an association of 5-fluorouracil, folinic acid and oxaliplatin. Hepatic resection could then be performed using either major hepatectomy or minor

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**Figure 7.14** Two-stage hepatectomy procedure combined with portal vein embolization. (A) first stage: resection of left liver nodules (day 0). (B) percutaneous right portal vein embolization (day 20–30). (C) second stage: right hepatectomy (day 60–80).
Figure 7.15 Case of bilobar metastases treated by two-stage hepatectomy procedure. (A,B) distribution of nodules before resection (arrows show nodules located in segment II and IV). (C,D) first stage hepatectomy: resection of the two left liver nodules. (E,F) right portal vein embolization. (E) portogram after embolization. (F) CT-scan five weeks after embolization shows lipiodol deposits in the right embolized atrophic liver and hypertrophy of the left liver. (G) second stage hepatectomy with right hepatectomy (day 72). (H) postoperative cholangiogram. (I) CT-scan 6 months after right
hepatectomy showing hypertrophy of the left liver without nodule. (J,K)
alternative to first stage hepatectomy: radiofrequency ablation is used
as an alternative to left liver nodule resection or combined with left
liver nodule resection.

resections. There was no operative mortality in this group of 53 patients and the
cumulative 3- and 5-year survival rates were 54% and 40%, respectively. Two-staged
hepatectomies were performed in some patients with large bilateral lesions in which one-
stage resection of all involved segments would have led to liver failure (e.g. segments V–
VIII at the first operation and segments II–III thereafter). All the patients who underwent
curative hepatic resection were treated by the same regimen of chronomodulated
intravenous chemotherapy for at least 6 months. It must be emphasized that this now
offers hope in treatment of patients who were initially considered unsuitable for radical
surgery. The combined approach of neo-adjuvant systemic \textsuperscript{132} , \textsuperscript{133} or intra-arterial \textsuperscript{134}
chemotherapy followed by curative resection is a concept which may provide reasonable
hope for long-term survival in some patients.
Figure 7.16 (A-E) Schematic representation of tumor location and type of liver resection in five patients with bilateral multiple liver metastases from colorectal cancer.

The follow-up: is repeat hepatectomy worthwhile?

After resection of colorectal liver metastases, it is estimated that unfortunately in about 60 to 70% of the patients, the disease will recur.\(^1\), \(^2\), \(^{22\text{–}24}\), \(^{65}\), \(^{135\text{–}137}\) In approximately 30% of these cases, the disease will present as isolated liver metastases.\(^{137\text{,}138}\) If metastases recur soon after surgery it is likely that, although not detected, they were already present during liver surgery.\(^{139}\) In most cases they are diffuse and clearly unresectable. However, in a limited number of cases, recurrent metastases appear either solitary or localized and resectable. The results of the retrospective study of the French Association of Surgery are based on the data from 130 patients who received 143 repeat liver resections for recurrent liver metastases.\(^{22}\) The operative mortality and morbidity rates were 0.9% and 24.7%, respectively. The 2- and 3-year survival rates were 57% and 33%, respectively, which were very similar to those obtained after first resections (57% and 38%, respectively). Twelve patients underwent more than two successive liver resections with some benefit. Other series have been reported with similar results,\(^{23\text{,}24}\),\(^{140}\) encouraging an aggressive approach for selected patients. Combined extrahepatic surgery may sometimes be required to achieve tumor eradication.

The results of these studies suggest that very careful follow-up is recommended after resection of colorectal liver metastases with regular monitoring of CEA levels, liver ultrasound and CT imaging in order to detect recurrent disease.\(^{141\text{,}142}\) In selected cases, repeat hepatectomy seems to be worthwhile.
Conclusions

The widest experience of hepatic surgery for metastatic disease has been gained with colorectal secondaries. Indeed, hepatic resection is currently the only form of treatment that offers both a chance of long-term survival, with rates ranging from 25 to 50% at 5 years and also a chance for cure: bilobar metastatic disease represents a clinical challenge that hepatic surgeons have to face up to more and more frequently. Without surgery the prognosis is so poor that patients have nearly no chance of long-term survival. The tremendous development of liver surgery techniques, assisted by the development of new strategies (portal vein embolization, two-stage hepatectomies, repeat hepatectomies, neoadjuvant chemotherapy), has brought great enthusiasm in the treatment of patients with hepatic metastases from colorectal cancer. These new strategies have proven to be safe and postoperative mortality is now very low (around 1%). However, only a minority of patients (about 20%) can be considered for surgery and the first crucial point for the future is to increase the number of patients who will benefit from surgery. The second point is to develop efficient adjuvant treatments which will be able to reduce significantly the risk of recurrence after surgery. Progress will only be made through a multidisciplinary approach.

Acknowledgements

The authors thank Professor Francis Veillon and Dr Bernard Woerly for their help in selecting X-ray illustrations. They express their gratitude to Mrs Véronique Rohfritsch for editing the manuscript and to Mrs Caroline Gstalter for processing the slides.

Key points

- Better prognostic factors:
  1–3 metastases
  <5 cm diameter
  No extrahepatic disease
  CEA <30 ng/l
  Detection >2 years after resection of primary tumor.
- French Association of Surgery Study of 1818 patients showed no difference in survival following resection of uni- versus bi-lobar disease.
- Preoperative assessment
  Spiral CT (dual phase) or MRI
  CT angio-portography Experimental: PET scanning.
- Evaluate residual hepatic reserve before considering resection.
- Consider:
  Two-stage procedure
  Combination of resection with residual tumor destruction.
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Non-resectional treatment of colorectal cancer metastases

David L Morris, Ian Finlay, Sivakumar Gananadha and Winston Liauw

Introduction

Between 25 and 35% of colorectal cancer patients will develop hepatic metastases. However, only 25% of these patients will be suitable for potentially curative hepatic resection. Patients may be considered unsuitable for hepatic resection for a variety of reasons:

- The presence of extrahepatic disease.
- Bilobar distribution of disease (relative).
- Unilobar disease in an awkward location, e.g. hepatic vein/IVC confluence.
- A large number of metastases (most centres resect a maximum of four metastases).
- The remaining liver volume would be inadequate.
- The patient is unfit for major surgery.

Fifty per cent of patients who undergo hepatic resection will develop hepatic recurrence. For these patients one should consider other treatment options, i.e. non-resectional treatment. Non-resectional treatments can be categorized into two groups: imaging controlled tumour destructive techniques and those employing chemotherapy.

Imaging controlled tumour destructive techniques

The purpose of these methods is to destroy metastatic disease leaving the surrounding normal hepatic parenchyma unaffected. Three techniques have been used widely: cryotherapy, which freezes tissue, and radiofrequency ablation and interstitial laser hyperthermia, which heat tissue. These methods are indicated only for relatively limited, well-defined disease and have no place in the treatment of patients with additional extrahepatic metastases.

Percutaneous ethanol injection is a further method of producing localized tissue destruction which has produced good results in the treatment of small (less than 2 cm diameter) hepatocellular tumours. However, the technique has been shown to be relatively ineffective in treating colorectal hepatic metastases.

Chemotherapy techniques

Two methods of delivering chemotherapy are currently employed in the treatment of
colorectal hepatic metastases: regional delivery via the hepatic artery and systemic intravenous infusion. Both techniques are associated with particular complications and results differ between the techniques.

Regional chemotherapy treats only hepatic disease and has no role in the treatment of patients with extrahepatic disease. In such patients systemic intravenous chemotherapy is the only treatment option.

This chapter will review these various methods of non-resectional treatment for colorectal hepatic metastases, concentrating upon their relative results and complications. Figure 8.1 provides a brief overview of the indications for each of the treatment modalities later expanded upon in this chapter.

**Figure 8.1** Selection of the appropriate non-resectional treatment for hepatic colorectal metastases.
Hepatic cryotherapy

Introduction

Cryotherapy is the most developed technique of imaging controlled tumour destruction. The currently used system of liquid nitrogen and trocar probes was first used in 1961, and has since been employed in the treatment of lesions in various organs in addition to the liver. Figure 8.2 details the basic design of modern cryotherapy probes.

The mechanism of action of cryotherapy upon tumours is multifactorial. Rapid freezing results in the formation of intracellular ice crystals, which damage intracellular structures and cell membranes, resulting in cell death. Slower freezing to higher temperatures results in the formation of extracellular ice crystals, producing an osmolar gradient between the intra- and extracellular fluid compartments, and results in cellular dehydration. Extracellular ice crystals also expand and distort tissue architecture, particularly the microvasculature, which is also damaged by thrombus formation. Histologically cryolesions are very similar to areas of ischaemic necrosis.

Indications

Current indications for hepatic cryotherapy include liver metastases of colorectal origin, neuroendocrine tumours and hepatoma. Patients should be free of extrahepatic disease, with liver disease judged to be unresectable due to multiple tumours of bilobar distribution. Cryotherapy may also be employed in patients with anatomically resectable disease in whom resection is not possible due to poor liver reserve (cirrhosis).

Figure 8.2 Cross-section of a cryoprobe. Liquid nitrogen is delivered through the inner tube (A) to the tip of the probe where it vaporizes, and travels back along the outer tube of the probe.

The number of lesions which can usefully be treated by cryotherapy depends on the tumour type, but in colorectal cancer is probably limited to six lesions. There is no proven role for the debulking of colorectal liver metastases by cryotherapy, whereas in neuroendocrine cancers the destruction of most, but not all, disease can be of symptomatic and possibly survival benefit.

There are currently few data to support the use of cryotherapy as an alternative to liver resection. Liver resection is associated with a perioperative mortality of below 2% and
the long-term results are well established.\textsuperscript{15, 16} While the safety of cryotherapy is established, with a perioperative mortality less than 5%,\textsuperscript{12} the long-term results are not established as being equivalent to liver resection.

Cryotherapy might be of use as an adjuvant to liver surgery. It can be used to treat an inadequate or involved resection margin\textsuperscript{17} or synchronous lesions in the residual liver at the time of resection.\textsuperscript{18} This approach is potentially capable of increasing the proportion of patients to whom resection can be offered.

The use of hepatic cryotherapy at the time of colonic resection of the primary tumour is dangerous, the combination of an area of necrosis (the cryolesion) and a contaminated peritoneum may cause liver abscess formation.

\textbf{Technique}

Cryotherapy is often a prolonged procedure, therefore careful attention should be paid to the positioning of the patient, and antithromboembolic measures (subcutaneous heparin, graded pressure stockings and calf compression) should be employed together with antibiotic prophylaxis. To prevent the development of hypothermia, warming devices such as the Bair Hugger should be used.

The liver is fully mobilized and a plan for probe placement is made. Probe positioning is sometimes easily achieved but may require the use of needle localization under ultrasound control, particularly if a lesion is impalpable. The use of a Seldinger technique with a dilator and sheath being passed over the localizing needle followed by insertion of the probe through the sheath is optimal. Ultrasound assessment is essential to confirm correct probe placement and it is important to examine placement in both longitudinal and transverse sections.

The diameter of the lesions to be treated is of principal importance, and the capability of the particular cryoprobe must be appreciated. In brief, a 5 mm liquid nitrogen cryoprobe might be expected to produce a 5 cm cryolesion. If a 1 cm cryomargin is required then one perfectly sited probe might adequately treat a 3 cm lesion.

The time of freezing is determined by the time taken to achieve an ice ball of adequate size. The proximity of the lesion to major vascular structures is of importance because of the heat sink effect. It may be necessary to position a probe eccentrically and closer to such a heat sink. When multiple probes are used to treat large lesions, this should be performed synchronously rather than serially. Portal inflow occlusion reduces the time required to achieve large ice ball diameters and probably increases efficacy. We limit inflow occlusion to a total of 60 minutes.

Careful intraoperative assessment using ultrasound is necessary to ensure that each boundary of a tumour is well enveloped by a margin of at least 1 cm.

We advise passive thawing of a 1 cm rim followed by refreezing. The destructive effects of a twin freeze thaw cycle appear to be greater than single cycle freeze. We are, however, concerned that double freeze thaw cycles are involved in the pathogenesis of the cryoshock phenomenon. The thaw and refreeze of the edge of the ice ball is intended to re-treat the least effectively treated part of the lesion—the peripheral rim. We do not know the critical temperature for the destruction of colorectal cancer metastases in the liver, but the edge of a large ice ball may only be exposed to a degree or two below zero
because of the almost exponential fall of temperature around an ice ball.

![Image of hepatic cryotherapy in progress.](image)

**Figure 8.3** Hepatic cryotherapy in progress.

After thawing, a gelfoam plug is placed in the cryoprobe track to arrest any bleeding. Large parenchymal cracks can develop during freezing and, upon thawing, can cause significant bleeding which may require compressive sutures or packing until haemostasis is achieved. Such bleeding might not appear until the lesions have completely thawed, therefore the wound should not be closed until thawing is complete. We routinely place a catheter for hepatic artery chemotherapy following cryotherapy.

Care must be taken to avoid freezing the gut or any other extrahepatic structure. Injury to bile ducts within the liver seldom seems to be a problem, but one must avoid injury to the extrahepatic biliary tree.

Laparoscopic and percutaneous approaches to hepatic cryotherapy are currently under clinical evaluation, with encouraging results.

Figure 8.3 depicts cryotherapy in progress, with two probes being used to treat two individual lesions synchronously.

**Complications**

While serious complications are rare, good postoperative monitoring is important.

- **Postoperative haemorrhage** is a very rare event if the ice ball has fully thawed and any parenchymal cracks have been dealt with before closure of the abdomen.
- **Cryoshock** is perhaps the most important specific complication. This is very rare, but in a recent world questionnaire of surgeons employing cryotherapy 1% of hepatic cryotherapy patients had developed this syndrome and it was responsible for six out of 33 perioperative deaths in 2173 patients. Cryoshock is seen only in patients subjected to at least two freeze thaw cycles. The syndrome consists of renal impairment, ARDS-like pulmonary injury and coagulopathy and requires active supportive treatment with ventilation and replacement of coagulation factors. We have not seen this complete syndrome in our experience of almost 200 patients.
- **Thrombocytopenia** is common following large volume cryotherapy and may require platelet transfusion.
• **Abscess:** subphrenic or hepatic abscesses are a rare complication of cryotherapy, except when it is performed at the time of colectomy.

• **Biloma** is a specific complication of the use of hepatic arterial 5-fluoro-2’-deoxyuridine (FUDR) chemotherapy following cryotherapy, perhaps as a result of chemical biliary sclerosis causing increased biliary pressure.

• **Pyrexia:** postoperative pyrexia is common and perhaps due to tissue necrosis. Septic screening in such cases is negative.

• **Deranged liver function tests:** there is often a striking but self limiting rise in serum hepatic transaminase levels, present by the first postoperative day and resolving within 7 days.

**Imaging**

**CT portography**

Hepatic cryotherapy is dependent upon accurate imaging. CT portography scanning is useful in the preoperative assessment of hepatic metastases necessary to plan treatment. CT scanning of the rest of the abdomen and the chest together with a bone scan is desirable to exclude extrahepatic disease.

**Intraoperative ultrasound**

Intraoperative ultrasound is indispensable at laparotomy. It can detect additional small tumours in 30% of patients compared to other imaging techniques. Cryotherapy trocars are inserted under two-dimensional ultrasound guidance, and once successfully placed the development and extent of the ice ball are monitored by ultrasound.

Colorectal malignancies are variable in their ultrasonic appearance between patients, being hyperechoic, hypoechoic or isoechoic compared to the surrounding normal liver. However, in any one patient all lesions should have a similar echogenic appearance. The

![Figure 8.4 CT scan showing the ‘golf ball in the sand’ appearance of a cryolesion.](image-url)
position of the lesion in respect to hepatic veins can be distinguished from portal structures as the veins lack a hyperechoic sheath.

As freezing develops, the ice ball appears as a hypoechoic (black) area surrounded by a hyperechoic rim, and can be monitored in real time. When thawed the cytoplasm appears hypoechoic compared to the normal liver, and the extent of the treated area is readily assessed.

On postoperative CT the cryolesion initially appears as a large avascular lesion with gas in the probe track. This gradually involutes to leave a smaller fibrous retracted spherical lesion—the so-called ‘golf ball in the sand’ appearance, as illustrated in Fig. 8.4. 23

**Postoperative follow-up**

Postoperatively we routinely use serial 3-monthly carcinoembryonic antigen (CEA) levels to monitor patients with CEA secreting tumours. CEA levels fall rather more slowly following cryotherapy than after hepatic resection, taking several weeks to decrease. 24 The percentage fall in CEA levels pre- and postoperatively may be prognostic for survival, 25, 26 with some 60% of patients’ CEA levels returning to the normal range. 13 CT scanning of the liver and abdomen is used only in the follow-up of non-secretors, or to assess patients with a CEA rise.

**Results**

A recent review of published clinical series found 14 postoperative deaths in 869 patients treated with cryotherapy, a 1.6% mortality rate. Reported rates of postoperative complications ranged from 0 to 45%, chest infection being the most common complication. 12

**Survival**

The most striking survival results published are those of the Boston group. 27 They reported 5-year survival and disease-free survival rates of 78 and 39%, respectively. However, there were only 18 patients in this series, and only one to three lesions were treated in each patient. Our own 5-year survival data are more modest at 13%, but constitute a group of inoperable patients with a median of 3.9 lesions, 83% having bilobar disease. Other series tend to have short median follow-up times but report median survival times of 13.5–16 months, again with some patients surviving longer than 5 years. 12 These results certainly compare well with those of hepatic artery chemotherapy, but it is not yet clear whether cryotherapy is able to achieve results comparable to liver resection.
Interstitial laser hyperthermia (ILH)

Introduction and theoretical considerations
Lasers are particularly suitable to generate localized hyperthermia within the liver. They produce a highly collimated, coherent beam of light of a set wavelength and can be transmitted down thin, flexible optical fibres and directed towards a target area with great accuracy. Neodymium yttrium aluminium garnet (Nd YAG) laser is the most suitable for ILH, as it produces light with a wavelength of around 1064 nm which is capable of penetrating tissue to a far greater depth than that produced by either CO₂ or argon lasers.

Nd YAG laser light can be delivered down thin (0.2–0.6 mm diameter), flexible, optical quartz fibres, and is emitted only at the tip of the fibre. This allows treatment to be performed percutaneously, the fibre being introduced via a 19 gauge needle under local anaesthetic with little chance of damage to major blood vessels or biliary structures, making it suitable for percutaneous application.

Mechanism of tissue destruction and techniques
When light from an Nd YAG laser at low (<2 W) power settings is emitted from the end of a single optical fibre embedded in tissue, it is scattered in multiple directions by the surrounding tissue. This results in an almost spherical distribution of the light around the fibre tip. Light is absorbed and heating results; when the temperature exceeds 45°C coagulation of cellular proteins occurs and well-defined areas of necrosis ensue.

Early investigators employed modified tips on the fibres in an attempt to enhance diffusion of the light and maximize effects. However, these tips had no significant advantage over plain fibre tips, they were too large in diameter to be safely used percutaneously and required gas coolant, which was responsible for a fatal gas embolus. When plain fibre tips are employed, light is transmitted throughout the tissue for around 20–30 seconds but then blood coagulation and charring occur around the tip. The charred area then strongly absorbs light and acts as a point heat source, diffusing heat into the surrounding tissue.

Using plain fibres and low (<2 W) power laser energy for up to 2400 seconds a highly reproducible, near spherical area of necrosis is produced with a maximum diameter of 1.6 cm. In order to increase the area of necrosis produced and treat larger diameter lesions, beam splitters have been employed to allow one laser to illuminate four optical fibres. These fibres can be placed no more than 1.5 cm apart around a lesion to allow the area of necrosis to overlap, and treat tumours of up to 3 cm. Larger lesions have been treated by repeated treatments with repositioning of the fibres within or around the tumours.

More recently, investigators have returned to using diffuser tipped fibres; these diffusers are smaller than those used initially and can be placed percutaneously. In contrast to bare fibre tips, diffusers do not produce charring, which absorbs light, and therefore allow deeper light penetration and more extensive and homogeneous heat distribution. Using this method tumours of diameter 2.4 cm can be ablated simply by
placing the tip in the centre of the tumour, and larger lesions by using a beam splitter and/or fibre repositioning. This is a modest size compared with that achieved by modern RFA units.

**Imaging**

Accurate imaging is required at three stages: (a) placement of the fibres within the lesions, (b) real time monitoring of the treatment to ensure the whole lesion is treated and (c) follow-up assessment of the lesion to assess response to treatment.

Once lesions have been diagnosed on CT scanning, most studies of ILH have used ultrasound scanning to guide the placement of fibres within lesions. Unfortunately, the resolution capability of percutaneous ultrasound scanning makes the detection and subsequent targeting of small (<2 cm) lesions difficult. Intraoperative ultrasound is capable of detecting additional liver tumours in 30% of patients compared to other imaging techniques, and laparoscopic ultrasound scanning has been proposed as an alternative technique to guide the placement of fibres.

During ILH of previously hypoechoic, mixed or isoechoic metastases a central bright hyperechoic region appears around the fibre tip. A hyperechoic ring then develops around this point, its radius expanding with the duration of treatment. This is thought to be due to the development of echogenic microbubbles. These well-defined areas correlate well with the extent of necrosis produced. The lesion changes in ultrasonic appearance within 24 hours, becoming a central hyperechoic point of charring surrounded by a hypoechoic ring. The margin of the treated area and normal liver becomes progressively less sharp in the months after treatment, making detection of recurrence difficult by ultrasound scanning.

Dynamic CT scanning with intravenous contrast has been shown to be capable of distinguishing nonenhancing necrosis from enhancing viable tumour tissue, allowing assessment of the effectiveness in tumour destruction to be made post procedure.

More recently, magnetic resonance imaging (MRI) scanning has been employed in an attempt to overcome the limitations of ultrasound scanning. Vogl et al., have used MRI scanning to guide fibre insertion, and by using a novel MRI protocol were able to perform real time thermometry to assess the extent of the treated area. Gadolinium enhanced MRI allowed early and late follow-up of treated lesions. The clinical application of MRI guidance for ILH appears to overcome most of the problems associated with percutaneous ultrasound guidance and results are promising.

**Results**

**Tumour response**

The potential of ILH in the ablation of liver tumours was first investigated by Hashimoto et al., who demonstrated that ILH was capable of reducing the alpha feto protein levels of two hepatoma patients to the normal range, and produced similar dramatic falls in the carcinoembryonic antigen levels of patients with colorectal hepatic metastases. Masters et al. subsequently demonstrated that, by using the four bare fibre tip technique,
radiologically confirmed necrosis of tumours less than 3 cm diameter could be achieved, with 50% of these treated tumours remaining the same size or involuting over the ensuing 6 months. Others have evaluated the use of bare fibre tips by contrast enhanced CT scanning and found 100% necrosis could be produced in 38% of lesions, and greater than 50% necrosis in 82% of lesions, with metastases smaller than 4 cm being treated most effectively. 43

When a diffuser tip was used 12 of 16 metastases were found on ultrasound scanning and guided fine needle aspiration biopsy to be completely destroyed. The successfully treated lesions ranged in diameter from 1 to 3.7 cm. 37 Vogl et al. 45 used MRI scanning both to position and monitor the progress of ILH with a diffuser fibre tip, and found that in 69% of lesions 2 cm or smaller 100% necrosis could be produced, and 44% of these did not progress within 12 months. However, in lesions over 2 cm complete necrosis was achieved in only 41%, with 27% of these remaining static at 12 months.

Survival

Amin et al. 43 reported basic survival data for a series of 21 patients treated by bare fibre tip ILH for metastases from colorectal and other cancers. Survival of the 15 colorectal cancer patients ranged from 4 to 40 months, with a median of 9 months. Subsequently, Vogl et al. 47 reported comprehensive survival data for a series of 99 patients with 282 hepatic colorectal metastases treated by diffuser tip ILH under MRI guidance and monitoring. Survival rates were 88% at 12 months, 70% at 24 months and 42% at 36 months, with a predicted median of 36.4 months. In both of these studies all patients were unsuitable for hepatic resection, and the survival data compare well with that of other treatments in similar patients. 48

Complications and limitations

As ILH can be performed percutaneously under local anaesthetic the complications of laparotomy and general anaesthesia are avoided. Only one death has been reported and this was from a gas embolus from a gas-cooled system no longer employed. 32

Mild abdominal discomfort is common both during and for 24–48 hours post-treatment. It is more common when treating peripheral lesions, presumably due to irritation of visceral or parietal peritoneum, but is easily controlled with simple analgesics. Bradycardia has been described during the procedure, presumably due to vagal stimulation. Asymptomatic sub- and extracapsular haemorrhage and small pleural effusions have also been seen to occur. No major biliary or vascular damage has been reported and most patients are able to leave hospital within 24 hours. 37 , 43 , 47

The percutaneous approach does render a small number of lesions inaccessible to this method, in particular 9 deep right lobe lesions. 49 The limited resolution of percutaneous ultrasound makes localization and fibre insertion into small (<2 cm) lesions difficult, but the recent development of MRI guidance and monitoring may overcome this. However, interventional MRI is currently prohibitively expensive. For most centres the purchase cost of the laser is prohibitive, but can be justified to some extent as it can also be used for other applications, particularly endoscopic procedures.
Radiofrequency ablation

Introduction
Radiofrequency waves are of lower energy and longer wavelength than conventional diathermy and result in the heat dissipating into the area that is close to the electrode-tissue interface. In the radiofrequency ablation of tissue, the frequency range used is between 400 and 500 kHz. At this frequency, stimulation of muscles and nerves does not occur. 50

Mechanism of radiofrequency ablation
Radiofrequency ablation is produced by alternate current in the frequency range of 400–500 kHz delivered through an electrode tip. This current causes agitation of the particles of the surrounding tissues, which attempt to follow the alternate current, so generating frictional heat. 51 The heat generated is dependent on:

- **Current density**: this is the current divided by the area. As current density is highest at the tissue adjoining the electrode, the heat generated is the maximum at this plane.
- **Current intensity**: the heat generated is proportional to the square of the current.

Therefore the more current delivered, the higher the heat generated. However, current that is too high or applied too rapidly results in overheating and charring of the tissue adjacent to the electrode, thus resulting in a rise of impedance and loss of efficacy.
- **Distance from the electrode**: as the distance increases the heat generated drops to the fourth power of the radius.

Indications
The current indications include patients with primary liver cancer and those with liver metastases from colorectal and neuroendocrine tumours. 52

The size of these lesions has an important impact on the local recurrence rate, as larger lesions are more likely to develop local recurrence. 53 This is due to the fact that larger lesions require multiple overlapping electrode placements. The development of newer probe designs means that a 7 cm ablation is now possible in 20 minutes with a single probe placement.

In one reported series, patients with severe coagulation disorder and portal vein thrombosis were excluded from RFA. 52 Patients with tumours close to the hepatic hilum risk damage to the biliary structures and tumours adjacent to blood vessels may be inadequately heated due to the heat sink effect. 54
Equipment

Probes

Early designs of probe had a single electrode but the size of the ablation was small (approximately 2 cm). Multiple arrays of conventional electrodes resulted in larger ablations. Expandable needle electrodes (4–10 electrodes) arranged as lateral hooks at 90° to each other are now used. Figure 8.5 shows a RITA 5 cm probe. The geometry of these electrodes is such that the separate elliptical lesions overlap to produce a spherical lesion. 55

Internally cooled electrodes using chilled perfusate through the hollow electrode can be used to produce a larger ablation. The cooled electrode prevents overheating of the tissue adjacent to the electrode, thus preventing charring and a rise in impedance. 56

Saline infusion through the hollow electrode has also resulted in larger ablation size. The proposed mechanism includes increased surface area and conductivity of the electrodes, reduced tissue vaporization and diffusion of the boiling saline into the tissue. 57

Generator

The generator is used to deliver the radiofrequency energy in the range of 460–480 kHz. Figure 8.6 shows one of the commercially available generators and the computer used for data collection and display. There are currently three commercially available radiofrequency ablation devices. The RITA medical system (Mountain View, CA) uses a temperature thermocouple on the electrodes to monitor the temperature of the ablation. The electrodes are deployed partially until the target temperature is reached, then deployed fully until the target temperature is again reached, then maintained for a fixed duration of time.

The Radiotherapeutics (Mountain View, CA) device uses impedance to monitor the lesion size. After electrode deployment, the initial power is applied at 50 W and then the power increased at increments of 10 W at intervals of 1, 2, 3 and 4 minutes to 90 W. The treatment is continued until power roll-off occurs. After a 20 second pause the power is reapplied at 75% of maximum until power roll-off occurs again. 52

![Figure 8.5 RITA radiofrequency probe when fully deployed.](image)
The Radionics (Burlington, CA) system uses the cooled electrode tip to produce thermal ablation. A peristaltic pump is used to infuse saline at 0°C into the lumen of the electrode to maintain the electrode tip temperature at 20–25°C.  

**Bipolar/monopolar mode**

Radiofrequency energy can be delivered in either monopolar or bipolar mode. In the monopolar mode the current is delivered through the electrode and the return current is through a larger, dispersive, patient grounding pad. In the bipolar mode the current passes between two electrodes, separated by a distance of 1–4 cm, both of which are placed in the lesion. The bipolar mode results in larger ablation and the effect is greater than twice the size obtained by a single electrode as the entire energy is delivered to the tissue instead of a distant larger grounding pad.  

![Figure 8.6](image)

**Figure 8.6** One of the commercially available generators for radiofrequency ablation. A laptop computer is used for data collection and display.

**Technique**

The main advantage of radiofrequency ablation is the ability to create thermal ablation by the percutaneous or laparoscopic approach. Patients having percutaneous RFA can be admitted as day surgery and the procedure can be performed under local anaesthetic, conscious sedation or a general anaesthetic. The patient is positioned either supine or in the left lateral position, depending on the site of the lesion. The patient grounding dispersive pads are applied if the monopolar mode is used. After preparation of the skin and draping, a small skin incision is made and the probe is inserted under ultrasound or CT guidance. Radiofrequency ablation is then performed.

Radiofrequency ablation can also be performed by the laparoscopic approach. The main advantage is easier probe placement in visible lesions, the ability to perform
laparoscopy before the ablation to look for evidence of extrahepatic metastases and the ability to separate the liver from the diaphragm, stomach or bowel to prevent RF injury to these structures when the tumour is close to or involving the surface of the liver. Laparoscopic intraoperative ultrasound facilitates intraparenchymal views of probe placement and monitoring of the ablation.

The advantage of using RFA during open surgery is that the Pringle manoeuvre (hepatic inflow occlusion) can be performed, which has been shown to increase the lesion size as well as the speed of the procedure. Figure 8.7 shows radiofrequency ablation in progress via the open approach.

Imaging

Imaging is essential for the correct placement of the probe, monitoring of the ablation and follow-up of

Figure 8.7 Radiofrequency ablation in progress.

the patient. Imaging of the RF lesion can be by either ultrasound, CT scan or MRI. Ultrasound is the only method for laparoscopic as well as for open operation. Ultrasound shows a slowly enlarging speckled hyperechoic area. It is considerably harder to judge the edge of the lesion during RFA than during cryotherapy, where the ice ball can be clearly seen.

The use of CT for monitoring the ablation gives better correlation as the RF lesion and liver-lesion interface is better demonstrated when compared to ultrasound.

Both CT scan and MRI have been used in the followup and assessment of treatment efficacy. Contrast enhanced CT shows well-demarcated non-enhancing areas that correspond to the RF induced necrosis. A CT scan performed 1–3 days after treatment shows sharper margins between the RF treated and untreated regions of the lesion than scans performed immediately after the ablation.

MRI images show a hypointense and unenhancing area representing the area of RF ablation. PET scan has also been used in the evaluation and follow-up of patients treated with RFA. It was found to be useful for distinguishing the inactive (RF treated) from the
recurrent disease which CT was unable to do. 64

Results
The use of radiofrequency ablation has now been reported in more than 500 patients with unresectable liver malignancies for both primary and metastatic tumours. RFA has been used in the treatment of hepatocellular carcinoma (HCC) in patients with cirrhosis and has been found to be safe with results that are comparable to those of cryotherapy. 65 In patients with colorectal metastases treated with RFA, the results are comparable to those of cryotherapy, with local recurrence rates of 1–30%. There are as yet no reports on 5-year survival and disease-free survival in these patients. RFA was found to be safer with fewer complications than cryoablation in a retrospective analysis of patients with HCC. 66 Comparison of alcohol injection to RFA showed a significantly lower local recurrence rate as well as higher 1- and 2-year disease-free survival rates in the RFA group after a median follow-up of 2 years. 67

Local recurrence rates
Local recurrence is due either to inadequate heating of the tumour or to inadequate coverage of the tumour. As imaging of the radiofrequency ablation is not optimal, lesions requiring multiple electrode placements are associated with higher local recurrence rates. 56 Probes that are capable of producing larger lesions are likely to decrease the local recurrence rates. Inadequate heating is another cause of local recurrence. Tumours that are situated near blood vessels are inadequately heated due to the heat sink effect as heat is conducted away by blood flow. 54

Survival
There are few reports of the long-term follow-up of these patients. The median follow-up of patients in the reported series has been between 10 and 18 months. In 50 patients with HCC treated with RFA, the overall survival was 94% at 1 year, 86% at 2 years, 68% at 3 years and 40% at 4 and 5 years. 68 As yet, there are no randomised controlled trial data to show the benefit of RFA treatment.

Complications
Radiofrequency ablation has been found to be safe with few major complications. There have been only two reported deaths in over 500 patients who underwent RFA. 66 , 69 Major complications have been rare, with haemorrhage, haematoma and abscess formation accounting for the most of these complications. 52 , 65 , 66 , 69 Minor complications including fever, mild to moderate pain and pleural effusion were more common, but did not require any intervention in the majority of these patients.
Conclusions

Radiofrequency ablation is emerging as a new minimally invasive treatment modality for unresectable liver malignancies with low complication rates. The results appear to be better in patients with small lesions, but larger lesions are associated with higher local recurrence.

The main advantage is the facility to perform the procedure via the percutaneous or the laparoscopic route. The major disadvantages are the expense of the disposable probes and the need to treat multiple lesions concurrently.

Hepatic artery chemotherapy

Introduction

The regional delivery of cytotoxic drugs into the artery supplying malignant tumours was first described in 1950. The infusion of chemotherapy to the liver via the hepatic artery was first reported by Sullivan et al. in 1964. In the following 30 years hepatic artery chemotherapy evolved, with improved delivery technology and pharmacological understanding.

The aim of any cancer chemotherapy regimen is to maximize its cytotoxic effect against tumour cells while minimizing the effects upon normal cells which result in side effects, in order to prolong survival and maintain quality of life. Two theoretical principles suggest that hepatic colorectal cancer metastases may be particularly suited to this method of cytotoxic administration.

1) Drug targeting

Most cytotoxic agents have a steep dose response curve, therefore the cytotoxic effect is enhanced by higher local drug concentrations. By targeting the administered drug to the diseased area, higher local levels can be achieved.

Widder et al. described three distinct stages in the intravascular targeting of drugs:

- First order targeting—selective distribution of the drug into the capillary bed of the affected organ
- Second order targeting—the selective direction of the drug to tumour cells rather than normal cells
- Third order targeting—delivery of the drug into intracellular sites in tumour cells.

Hepatic colorectal metastases are particularly susceptible to such drug targeting. The arterial supply to the liver is well defined and easily accessed, allowing first order targeting. Both primary and metastatic hepatic neoplasms are supplied via the hepatic artery, unlike normal liver tissue which receives its blood supply predominantly from the portal vein, allowing second order targeting. Hepatic arterial administration of chemotherapeutic agents can potentially expose the tumour to higher concentrations than could be achieved by systemic administration.
(2) Hepatic extraction

The fluoropyrimidines have been extensively used systemically in colorectal cancer and both 5-fluoro2’-deoxyuridine (FUDR) and 5 fluorouracil (5 FU) are catabolized in vitro by hepatic enzymes. In 1978 Ensminger et al. demonstrated that when administered as an infusion via the hepatic artery (even at very high doses), FUDR is efficiently extracted by the liver (92% of the administered dose being extracted on the first pass through the liver). 5 Fluorouracil was shown to be less efficiently extracted, but this is improved with longer duration infusions. This high hepatic extraction of FUDR results in lower systemic drug levels—60% of that seen with systemic administration. Lower systemic levels are associated with less systemic toxicity.

Results

Many studies have been published on the results of hepatic artery chemotherapy. Initial publications reported only patients given hepatic arterial chemotherapy and comparison of these results with those of patients in trials of systemic chemotherapy was difficult as hepatic artery patients tended to have liver only disease, compared to a more systemic distribution in the patients given intravenous therapy, and there was considerable variation between the treatment protocols used.

Later, randomized controlled trials allowed direct comparisons to be made between the two delivery techniques, their merits being assessed in terms of tumour response rates, which are easy and quick to quantify, patient survival and the equally important effects upon patients’ quality of life.

Tumour response rates

Early trials of hepatic artery chemotherapy reported response rates of 39 to 75%, which compare well with response rates seen in trials of systemic single agent chemotherapy of 9.5 to 44%, although such comparisons are tenuous.

Later, randomized controlled trials were able to compare response rates directly for patients with liver only disease. Hepatic artery chemotherapy produced partial or complete responses in 43–62%, compared to 17–21% response rates with systemic chemotherapy. In each trial the differences in response rates were statistically significant.

Survival

The clear differences in response rates between regional and systemic chemotherapy were not shown to translate into a significant survival advantage in early controlled trials. These trials compared relatively small numbers of patients and were therefore of low power, and the largest allowed patients to cross over from the systemic to hepatic artery arms if their disease progressed—potentially masking any survival advantage. Two later European trials did demonstrate clear survival advantages of hepatic artery chemotherapy over controls. However, the control groups were given systemic chemotherapy using regimens at the discretion of each patient’s physician.
In a meta analysis of all controlled trials, a significant survival advantage was seen when all trials were considered but not when restricted to trials in which the control arm received systemic chemotherapy. However, a later meta analysis using different statistical methods and incorporating the data of Hohn et al. reported a small but statistically significant survival advantage for hepatic arterial over systemic chemotherapy. Further trials specifically designed to clarify the issue of survival are nearing completion.

Quality of life

When treating hepatic metastases from colorectal cancer, in addition to improving crude survival time one must aim to improve the length of survival with a normal quality of life. Only one study has addressed this issue. This trial found not only a significant improvement in crude survival over controls, but also improved survival with normal quality of life.

Adjuvant hepatic artery infusion chemotherapy

Adjuvant hepatic artery chemotherapy has been shown to decrease the incidence of liver recurrence after liver resection. Comparison of the outcome of patients undergoing liver resection with adjuvant hepatic artery chemotherapy and systemic chemotherapy has shown a significant improvement in the recurrence-free survival. Two-year recurrencefree survivals of 90% and 60% in the combined hepatic artery and intravenous group and the systemic group, respectively, have been reported.

Surgical procedure and techniques

Preoperative work-up

The advantages of hepatic artery chemotherapy are proven only in patients with liver metastases from colorectal cancer. Patients must be screened to exclude extrahepatic disease. Locoregional recurrence or metachronous tumour should be excluded by colonoscopy or barium enema, and a computed tomographic (CT) scan of the abdomen performed to exclude intra-abdominal extrahepatic disease. In a patient with a histologically confirmed primary colorectal adenocarcinoma, an elevated carcinoembryonic antigen (CEA) level and characteristic lesions on a good quality CT scan, we do not biopsy the liver lesions.

As aberrant hepatic arterial anatomy is seen in about 33–40% of patients, some authors advocate that a preoperative angiogram should always be performed in order to define the anatomy. However, this is unnecessary for surgeons experienced in this technique and familiar with the anatomical variations, which are easily defined at operation.

Catheter placement

The success of hepatic artery chemotherapy is dependent upon achieving uniform
perfusion of the liver and avoiding perfusion of the gut. In addition, cholecystectomy should be performed in all patients to avoid chemical cholecystitis.

In patients with conventional anatomy (demonstrated in Fig. 8.8) the gastroduodenal artery is the ideal site for the insertion of a hepatic artery catheter. The common hepatic, gastroduodenal, hepatic and its division into right and left hepatic arteries are easily exposed and displayed by dividing the gastrohepatic ligament and mobilizing the duodenum. The right gastric artery and any other branches to the stomach or duodenum should be ligated and divided to avoid malperfusion of the gut. The gastroduodenal artery should be ligated 3–4 cm distally with a nonabsorbable tie and controlled proximally. A longitudinal arteriotomy allow a specially designed, beaded, silastic catheter to be advanced retrogradely into and along the artery up to its junction with the hepatic artery. The catheter is secured in place with nonabsorbable ties—one each side of the catheter bead (Fig. 8.9). Care should be taken not to occlude the catheter by excessively tight securing ties.

By injecting 5–10 ml of methylene blue 1% down the catheter parenchymal hepatic perfusion can be assessed, and any malperfusion of the stomach or duodenum detected. Fluorescein and a UV lamp can be used instead of methylene blue; anaphylaxis has been reported with both compounds, but is rare. If the liver does not stain uniformly blue an aberrant accessory hepatic artery must be suspected, as demonstrated in Fig. 8.10. Failure of the right lobe of the liver to perfuse suggests the presence of an accessory right hepatic artery, which invariably arises from the superior mesenteric artery and lies behind the common bile duct on the right side of the portal vein anterior to the foramen of Winslow, as depicted in Figs 8.11 and 8.12. A failure of the left lobe to perfuse suggests an accessory left hepatic artery arising from the left gastric artery or a proximal origin of the left artery from the common hepatic artery before the gastroduodenal branch containing the catheter (Fig. 8.13). In most cases, ligation of the smaller aberrant vessel allows cross perfusion to occur from the contralateral lobe of the liver. This can be confirmed prior to ligation of the vessel by occluding it with a vascular clamp and repeating the methylene blue test. It is rarely necessary to insert a second catheter into a dominant aberrant vessel to achieve uniform perfusion.

Other anatomical variations are encountered in addition to aberrant right or left hepatic
arteries. The most common of these is described as a trifurcation,

**Figure 8.9** Insertion of a hepatic artery catheter into the gastroduodenal artery in a patient with conventional anatomy.

**Figure 8.10** Methylene blue infused via a hepatic artery catheter demonstrating inadequate perfusion of the right liver, indicating an accessory right hepatic artery.
when the gastroduodenal artery arises from the common hepatic artery very close to its division into right and left hepatic arteries. Insertion of the catheter here would result in streaming of chemotherapy into one or other lobes of the liver. This can be overcome by inserting the catheter through a side arm of saphenous vein or prosthetic graft to the side of the proximal common hepatic artery. Coeliac stenosis can be a difficult problem for hepatic artery catheter placement because the whole foregut may derive its blood supply via retrograde flow in the gastroduodenal artery. This should be suspected when one encounters an abnormally large calibre gastroduodenal artery, and can be confirmed by clamping the proximal (hepatic) end of the gastroduodenal artery and palpating distally for a pulse. Placing the catheter in the left hepatic
Figure 8.13 An accessory left hepatic artery arising from the left gastric artery.

artery and tying off the artery around the catheter, or putting a side arm on to the common or right hepatic artery distal to the gastroduodenal, may be required.

For aberrant anatomical variations, an appropriate catheter placement technique can result in the same response rate to chemotherapy as patients with normal anatomy. 98 Variant anatomy has been found to be associated with higher rates of complications, but this was much less of a factor than the experience of the operating surgeon. 90

**Delivery devices**

Once inserted, hepatic artery catheters must be connected to a pump for chemotherapy delivery.

Several implantable systems are available: implantable refillable pumps such as the Infusaid 400 pump (Fig. 8.14) and implantable ports such as the Portacath port used with a connecting needle and external pump (Fig. 8.15). Both of these devices are inserted into subcutaneous pockets, the ports placed over the lower costal margin and pumps over the abdominal wall, and must be sutured in place to prevent them rotating in the pocket.

Ports must be accessed using special non-coring needles each time an infusion is given, the needle being connected to an external pump to deliver the infusion. In order to prevent thrombosis and occlusion of the catheter, it is essential to flush these systems with heparinized saline once every 2 weeks when they are not in use and to ensure that a positive pressure is always applied whenever the port is accessed.

Pumps are easier to manage and are associated with a lower occlusion rate than ports, 94 but are substantially more expensive. Pumps can be loaded with chemotherapy and run at a predetermined set rate, being refilled either with chemotherapy or heparinized normal saline to ensure that they never run dry.
Complications

Drug toxicity

Systemic and hepatic regional cytotoxic chemotherapy are both associated with toxicity. However, the patterns of toxic effects are different with the two methods. While systemic chemotherapy is associated with effects such as diarrhoea, mucositis and leucopenia, hepatic arterial chemotherapy results in more regional toxicity, namely hepatobiliary and upper GI toxicity.

When administered via the hepatic artery, FUDR can result in significant sclerosing cholangitis in 5–29% of patients, 93 which may require biliary stenting or external drainage. This serious complication should be suspected in any patient with a rise in serum hepatic transaminase, bilirubin or alkaline phosphatase levels, and may be averted by immediate cessation of treatment for a period. We would stop treatment if there were a doubling of any of these levels. Serious non-resolving cases are best investigated by endoscopic retrograde cholangiopancreatography (ERCP) as the ducts are sclerotic and undilated, making ultrasound diagnosis difficult.

Several techniques have been advocated to reduce the incidence of this complication. The first is dose reduction, either by using a lower dose from the onset of treatment, 0.2 mg/kg/day as opposed to the more usual 0.3 mg/kg, 86 or upon the development of biochemical changes. Using 5 FU instead of FUDR has been advocated, and may be more efficacious. Some centres use 5 FU alone in preference to FUDR, 99, 100 and others advocate alternating infusions of FUDR with 5 FU infusions. 101 Recently, co-administration of dexamethasone with FUDR has been shown to reduce the incidence of sclerosing cholangitis. 102

![Figure 8.14 An Infusaid 400 implantable infusion pump.](image-url)
The preparations of 5 FU administered via the hepatic artery have a very alkaline pH and can result in arteritis of the hepatic artery in a minority of patients, as depicted in Fig. 8.16. This arteritis may be severe enough to occlude the vessel and is probably responsible for the pseudoaneurysms which can cause major gastrointestinal bleeding. 5 FU has been reported to result in impaired left ventricular function when given systemically, and the possibility should be considered when treating patients with known cardiac disease.

Upper gastrointestinal complications encompass gastritis, ulceration and pain, but are best considered to be technical complications rather than toxic reactions.

**Technical complications**

The rate of technical complications is higher with inexperienced surgeons. It is essential to be aware of the possible complications as they present in innocuous and non-specific ways, yet may be fatal.
1. Gastrointestinal mucosal damage
This encompasses the spectrum of peptic ulcer disease from gastritis to bleeding or perforation of duodenal ulcers. It is usually due to malperfusion of the lesser curve of the stomach or duodenum with chemotherapy via missed branches of the hepatic arterial tree. It typically presents as epigastric pain developing at or shortly after the start of a chemotherapy infusion, and can occur some months after the initiation of treatment. Pain may be absent altogether, upper gastrointestinal haemorrhage being the presenting feature, and can be life threatening. When malperfusion is demonstrated the responsible vessel can usually be embolized at angiography. Treatment can continue following repeated endoscopy with methylene blue perfusion to exclude malperfusion, as demonstrated in Fig. 8.17.

2. Hepatic artery aneurysm formation
This is an uncommon but potentially life threatening complication illustrated in Fig. 8.18, which usually presents with rupture into the duodenum and haematemesis. It is seen more commonly with 5 FU infusions and requires either urgent operation to remove the catheter and ligate the vessel, or radiological embolization using permanent metal coils.

3. Catheter leakage and extravasation
This is usually secondary to occlusion of the catheter or artery further upstream, and is easily diagnosed by a portocathogram (Fig. 8.19). It necessitates cessation

Figure 8.17 Endoscopic picture demonstration of malperfusion of the duodenum from a hepatic artery infusion; methylene blue has been injected via the hepatic artery catheter.
of the treatment and, if appropriate, replacement of the catheter, which may require an end to side anastomosis of vein or prosthetic vascular graft material onto the hepatic artery.
Investigation of the patient with abdominal pain.

4. Inadequate perfusion of one hepatic lobe

This occurs when an accessory vessel supplies an area of liver, and should be suspected when the response of metastases to treatment demonstrated by CT changes appears heterogeneous throughout the liver. Radionuclotide scanning via the port can confirm any perfusion defect, and responsible vessels may be identified and embolized at angiography.

5. Pump or port complications

Both are associated with similar complications, namely development of seromas, pocket infections and extrusion. Seromas are quite common and may require repeated aspiration. Infection is usually obvious and necessitates removal of the device, although we do have some experience of replacing infected ports. Pump malfunction is rare, but the septum is susceptible to damage if ordinary needles or high injection pressures are used when refilling.

Investigation of abdominal pain

As the more serious complications often present as vague epigastric pains, it is essential that all patients presenting with such pain are thoroughly investigated. Three investigations are indicated in all cases of pain in such patients as each investigation provides different information. The investigations are described in Fig. 8.20.
Chemotherapy: agents and regimens

Choice of agent

The theoretical advantages of FUDR over 5 FU in terms of hepatic extraction have been outlined previously. Consequently the majority of the early work and all of the randomized trials investigating hepatic artery chemotherapy used FUDR. More recently, the high rates of sclerosing cholangitis seen with FUDR use have prompted researchers to reconsider the use of regionally delivered 5 FU.

Studies using hepatic arterial 5 FU at various dosages and treatment schedules have produced response rates of 27.3 to 56%, and median survivals of 11–19 months. These results are comparable to those seen with FUDR, with the advantage that sclerosing cholangitis is avoided. As a larger infusion volume is required to deliver an adequate dose of 5 FU, faster running implantable pumps or external pumps must be used.

The biomodulation of fluoropyrimidines by the addition of leucovorin-folinic acid increases the binding of their active metabolite to the target enzyme thymidylate synthase, resulting in enhanced cytotoxicity. When this was combined with systemic 5 FU chemotherapy it produced dramatically improved response rates and enhanced survival in some studies.

<table>
<thead>
<tr>
<th>Hepatic arterial 5 FU via a subcutaneous port and external pump</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>5 FU</td>
</tr>
<tr>
<td>Heparin</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Folinic acid</td>
</tr>
<tr>
<td>Treatment administered every 2 weeks, may be reduced to every 4 weeks based on response</td>
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<tr>
<th>Hepatic arterial FUDR via a subcutaneous port and external pump</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>5 FU</td>
</tr>
<tr>
<td>Heparin</td>
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<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Cycle repeats every 14 days</td>
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<tr>
<th>Hepatic arterial 5 FU via Infusaid implantable pump</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>5 FU</td>
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results prompted investigators to look at the addition of folinic acid to hepatic arterial chemotherapy regimens. The intra-arterial administration of low dose leucovorin with FUDR resulted in an improved response rate of 75%, but the risk of cholangitis was higher than with FUDR alone and others have demonstrated an increased risk of arterial thrombosis with intra-arterial leucovorin. The combination of intravenous leucovorin and intra-arterial 5 FU has been shown to produce good tumour response rates of 48%. 103

The hepatic arterial chemotherapy protocols in use at our institution are reproduced in Fig. 8.21.

Systemic chemotherapy

**Introduction**

The majority of patients presenting with colorectal liver metastases will be unsuitable for resection, guided cytodestructive therapy or hepatic artery chemotherapy due to extensive liver involvement or the presence of extrahepatic disease. In addition, many of these patients may ultimately progress locally or systemically. For these patients palliative systemic therapy can be offered with the intent of prolonging survival and improving or maintaining quality of life.

The use of adjuvant systemic therapy following resection of primary colorectal tumours is well established for Dukes C patients, and is outside the scope of this chapter. Trials evaluating systemic chemotherapy for liver only disease have not been conducted. All trials have involved the entire spectrum of metastatic disease.

Progress in the development of systemic chemotherapy has been slow. 5 Fluorouracil has been the mainstay of chemotherapy for colorectal cancer since its synthesis in 1958. 109 More recently, the benchmarks for systemic therapy have changed with the
introduction of several new agents including irinotecan, oxaliplatin, raltitrexed, trimetrexate and MTA. In addition, the need for intravenous treatment has been challenged by various strategies that enable the oral administration of fluorinated pyrimidines such as capecitabine, UFTx S-l and eniluracil.

**Indications**

Evidence from randomized controlled trials and meta analysis of those trials support the use of systemic chemotherapy for the palliation of inoperable colorectal cancer. The meta analysis conducted by the Colorectal Cancer Collaborative Group reviewed 13 randomized trials involving 1365 patients. These trials were reported prior to July 1998. Individual patient data for 866 patients were associated with a 35% reduction in risk of death (95% confidence interval 24 to 44%). This was equivalent to an absolute improvement in survival of 16% at 6 and 12 months and a median survival improvement of 3.7 months. There appeared to be no difference in benefit between age groups, but fewer than 2.5% of the patients were older than 75 years of age.

Despite small numbers, Scheithauer et al. and Beretta et al. were able to demonstrate in separate trials a survival advantage for chemotherapy over best supportive care. The Scheithauer study found 5 FU, folinic acid and methotrexate to produce a median survival of 11 months for the supportive care group \( (p=0.006) \). Quality of life scores were no different between the groups overall, but patients with abnormal scores pretreatment fared better in the chemotherapy arm.

Cunningham et al. have demonstrated that after failure of 5 FU there is evidence to support second-line therapy with irinotecan. This trial compared 3 weekly irinotecan to best supportive care and found a survival benefit (9.2 versus 6.5 months, \( p=0.0001 \)). Irinotecan appeared to delay time to deterioration in performance status, weight loss, pain control and global quality of life. These advantages were seen despite toxicity related to irinotecan.

The timing and duration of systemic chemotherapy are important considerations. The Nordic gastrointestinal tumour adjuvant therapy group compared early versus delayed introduction of chemotherapy for asymptomatic patients. This study demonstrated a significant improvement in symptom-free survival (10 versus 2 months, \( p=0.001 \)) and a nonsignificant prolongation of survival (14 versus 9 months). An Australian and Canadian meta analysis has failed to confirm a survival benefit for early versus delayed chemotherapy. The MRC Colorectal Cancer Group has investigated whether intermittent or continuous chemotherapy is preferable for responding or stable patients. No survival difference was found between the groups but a quality of life disadvantage was seen in the continuous treatment arm.

One problem in interpreting the literature with respect to both intra-arterial and systemic chemotherapy is that although survival benefits have been demonstrated the principal determinants of enhanced survival are poorly understood. Buyse et al. have conducted a meta analysis to examine the relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer. Survival was found to be associated with response, but the benefit in proportional terms was small. A treatment that lowered the odds of failure to respond by 50% would decrease the odds of death by
6%. The example offered by Buyse et al. is that a treatment that doubles the response rate of an agent from 20 to 40% would only increase median survival from 14 to 16 months. It is possible that delay in progression rather than objective response is a better surrogate marker for survival.

**Agents, regimens and results**

**5 Fluorouracil**

This has been the principal agent used to treat colorectal carcinoma for the past 40 years. 5 FU is a fluorinated pyrimidine antimetabolite prodrug that is converted intracellularly to 5-fluorouracil triphosphate (5 FUTP), 5-fluorodeoxyuridine triphosphate (5 FdUTP) and the principal cytotoxic agent 5-fluorodeoxyuridine monophosphate (5 FdUMP). 5 FdUMP inhibits thymidylate synthase (TS), so producing thymidine depletion, impaired DNA synthesis and apoptosis. 5 FUTP interferes with the nuclear processing of RNA and 5 FdUTP interferes with the nuclear processing of RNA and produces DNA strand breaks.

As a single agent 5 FU has antitumour activity of the order of 10–15%. This low activity is attributable to a number of factors including the pharmacokinetic profile, variable metabolism of 5 FU and intrinsic resistance to 5 FU. 5 FU has an extremely short halflife of 8–20 minutes. Assuming that its principal activity is as an inhibitor of thymidylate synthase, then 5 FU functions as an S phase specific agent. Therefore, at the time of any given bolus only a fraction of the tumour cells will be susceptible to 5 FU. 5 FU is metabolized by dihydropyrimidine dehydrogenase (DPD). This may be expressed variably between patients and between tumours. Approximately 2% of the population are DPD deficient and may experience severe toxicity with 5 FU administration. Tumours may overexpress both DPD and TS or have reduced intracellular folate pools leading to resistance to 5 FU.

A number of strategies have been used to overcome resistance to 5 FU and optimize response to treatment. Folinic acid (calcium folinate or leucovorin) increases intracellular levels of 5-10-methylene tetrahydrofolate. This is a co-factor necessary for the stabilization of FdUMP with thymidylate synthase. The results of nine clinical trials and a confirmatory meta analysis demonstrated that co-administration of folinic acid potentiates the cytotoxic activity of 5 FU, with tumour response rates of 23% compared to 11% for 5 FU alone. This effect was seen in trials involving schedules of high dose folinic acid (Machover regimen: >200 mg/m²/day) and low dose folinic acid (Mayo regimen: <25 mg/m²/day), but each schedule had a different toxicity profile.

Methotrexate is an antifolate agent that blocks dihydrofolate reductase. Inhibition of purine metabolism leads to accumulation of 5-pyrophosphate (PRPP) and enhanced conversion of 5 FU to 5 FUTP and 5 FdUMP. A meta analysis has found that modulation of 5 FU by methotrexate almost doubled the response rate compared to 5 FU alone (19% versus 10%) and yielded a small but significant improvement in survival with median survival times of 10.7 versus 9.1 months.

An alternative strategy to biomodulation of 5 FU has been to alter the schedule of administration of 5 FU in order to overcome the short half-life and relative S phase
selectivity of 5 FU. Delivery of 5 FU as a continuous infusion rather than a bolus injection has resulted in improved response (22%) and survival (12.1 months). The Mayo regimen of bolus 5 FU 425 mg/m2 daily for 5 days every 4 weeks has been regarded as the reference regimen for use as the control arm in randomized trials of new treatments for colorectal cancer. De Gramont et al. compared the Mayo regimen with a protocol of folinic acid 200 mg/m2 as a 2 hour infusion followed by bolus 5 FU 400 mg/m2 and 22 hour infusion of 5 FU 600 mg/m2 for 2 consecutive days every 2 weeks. The trial found in favour of the de Gramont regimen in terms of response rate (36.6% versus 14.4%, \( p = 0.0004 \)) and progression-free survival (27.6 versus 22 weeks, \( p = 0.012 \)); survival times were comparable (62 versus 56.8 weeks, \( p = 0.067 \)). More grade 3–4 toxicity was experienced in the Mayo arm (23.9% versus 11.1%, \( p = 0.0004 \)), in particular granulocytopenia, diarrhoea and mucositis. Infusion schedules tend to be associated with higher rates of cutaneous toxicity including plantarpalmar erythema (hand-foot syndrome).

Other groups have investigated chronomodulation of infusional chemotherapy in order to overcome circadian fluctuation in DPD activity. These studies have found increased response, decreased toxicity but no survival benefit for this strategy. A further strategy has been pharmacokinetically guided dosage. In a trial of the use of therapeutic drug monitoring in 117 patients, Gamelin et al. were able to produce 18 complete responses, 48 partial responses, 35 minor responses or stable disease and only 16 cases where progressive disease was the best response. The median survival time was 19 months, comparable to the best multiagent therapy.

**Irinotecan**

Irinotecan (CPT-11) is a semi-synthetic derivative of the naturally occurring alkaloid camptothecin. Irinotecan is converted by carboxylesterases to SN-38, its principal active metabolite. Irinotecan and SN-38 inhibit the nuclear enzyme topoisomerase I. During the process of replication and transcription topoisomerase I relieves the torsional stress associated with the unwinding of DNA. It does this by creating a single strand break through which the intact strand can pass, and then by resealing the strand break. Topoisomerase I inhibitors block the reannealing of the strand break such that DNA fragmentation and cell death occur when the replication fork encounters the single-stranded break.

Irinotecan has been demonstrated to enhance survival compared with supportive care (9.2 versus 6.5 months, \( p = 0.0001 \)) or infusional 5 FU (10.8 versus 8.5 months, \( p = 0.35 \)) in patients with 5 FU refractory colorectal cancer. In North America, Saltz et al. compared irinotecan 125 mg/m2, 5 FU 500 mg/m2 and folinic acid 20 mg/m2 given weekly for 4 out of 6 weeks to single agent irinotecan and the Mayo regimen. In Europe Douillard et al. compared irinotecan combined with infusional 5 FU to infusional 5 FU alone. The physician could use either the weekly AIO regimen with 80 mg/m2 irinotecan or the fortnightly de Gramont regimen with 180 mg/m2 irinotecan. Both trials found statistically significant advantages for irinotecan in overall survival (\( p = 0.05 \)), tumour response and progression-free survival. Whilst there was a tendency for increased toxicity with the irinotecan/5 FU combinations, at least with
respect to diarrhoea, quality of life was not compromised in either of the trials. Douillard et al. demonstrated a delay to deterioration in performance status for the irinotecan recipients (11.2 versus 9.9 months, \( p=0.046 \)). The Mayo regimen exhibited increased mucositis and febrile neutropenia compared with the other treatments. Although not strictly comparable, these studies consistently demonstrate survival times that are two to three times greater than the 5-month survival observed in the supportive care arms of the Scheithauer and Beretta studies (Table 8.1).

**Oxaliplatin**

This is a novel platinum compound in which the platinum atom is associated with 1,2-diaminocyclohexane (DACH). Oxaliplatin forms inter- and intrastrand DNA adducts between adjacent guanines (GG or GNG) or between adjacent guanine adenine (GA) base pairs, so impairing DNA replication and inducing cell death. The chemistry of Oxaliplatin may confer better DNA replication inhibition and cytotoxicity than cisplatin and may be responsible for the non-cross resistance seen when compared with cisplatin. Importantly, DNA mismatch repair complexes do not recognize DACH-Pt adducts, a major pathway of chemoresistance for colorectal cancer.

Oxaliplatin has low intrinsic activity against colorectal cancer, with response rates as a single agent of approximately 10%. Substantial synergy is seen when Oxaliplatin is administered with 5 FU. De Gramont et al. studied the de Gramont regimen with and without Oxaliplatin 85 mg/m\(^2\) on day 1 in 420 patients. An improved response rate (50.7% versus 22.3%, \( p=0.0001 \)) and progression-free survival (9.0 versus 6.2 months, \( p=0.0003 \)) were observed, but the median survival difference did not reach significance (16.2 versus 14.7 months). There were significantly increased rates of neutropenia, diarrhoea and the typical cold-exacerbated neuropathy of oxaliplatin, but there was no overall difference in quality of life.

Recent studies from both France and the United States have demonstrated that between 10 and possibly 33% of patients with colorectal liver metastases, previously deemed inoperable by experienced liver surgeons, can be resected after chemotherapy using oxaliplatin. Long-term survival for these patients following hepatectomy is virtually identical to those patients who were deemed resectable at the outset. These observations have formed the basis of an ongoing EORTC trial of neoadjuvant and adjuvant oxaliplatin combined with 5 FU around surgery versus surgery alone. In early 2002 the UK National Institute of Clinical Excellence advised that oxaliplatin-based treatment should be considered as first line chemotherapy for patients with non-resectable liver metastases who, in the opinion of an experienced liver surgeon, might be suitable for resection after successful treatment. If these data are correct, resectability rates for patients with colorectal liver metastases might rise from the current rate of 10% of all patients with disease confined to the liver to possibly over 30%.
Raltitrexed

This is a quinazoline folate analogue that specifically inhibits thymidylate synthase. A 3-weekly schedule is possible with this agent due to uptake and retention within cells by the reduced folate carrier system and subsequent polyglutamation by folyl polyglutamate synthetase. The development and acceptance of raltitrexed has been hampered by the determination in separate phase I studies of differing maximum tolerated doses. The North American phase III study compared raltitrexed at doses of 3 and 4 mg/m² every 21 days with the Mayo regimen. The higher dose arm was closed due to excessive toxicity. The final results of this trial showed a survival benefit for the 5 FU arm. Two other phase III studies have been completed that have demonstrated comparable response and survival data to 5 FU. Early toxicity appears greater with 5 FU due to the difficulty in dose selection mediated by variable DPD expression. Overall, raltitrexed is thought to be a useful substitute to 5 FU with comparable efficacy and toxicity and potential improvements in convenience and cost-effectiveness.

Table 8.1 Result of irinotecan and 5 FU as first-line therapy for metastatic colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>Salt regimen, weekly irinotecan, 5 FU and folinic acid</th>
<th>Mayo regimen</th>
<th>Single agent weekly irinotecan</th>
<th>Irinotecan and infusional 5 FU</th>
<th>Infusional 5 FU AIO or de Gramont</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>39%</td>
<td>21%</td>
<td>18%</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>7 months</td>
<td>4.3 months</td>
<td>4.2 months</td>
<td>6.7 months</td>
<td>4.4 months</td>
</tr>
<tr>
<td>Overall survival</td>
<td>14.8 months</td>
<td>12.6 months</td>
<td>12.0 months</td>
<td>17.4 months</td>
<td>14.1 months</td>
</tr>
<tr>
<td>Mucositis grade 3–4</td>
<td>2%</td>
<td>17%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Emesis grade 3–4</td>
<td>10%</td>
<td>4%</td>
<td>12%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhoea grade 3</td>
<td>15%</td>
<td>6%</td>
<td>18%</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhoea grade 4</td>
<td>8%</td>
<td>7%</td>
<td>13%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutropenia grade 4</td>
<td>24%</td>
<td>43%</td>
<td>12%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7%</td>
<td>15%</td>
<td>6%</td>
<td>5%</td>
<td>1%</td>
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Non-resectional treatment of colorectal cancer  221
**Oral fluoropyrimidines**

These have increasingly been investigated given the convenience of administration that would be achieved when compared with the cost and morbidity of infusional regimens that require placement of temporary or permanent venous access devices. While this has been demonstrated, the compounds developed to date have not demonstrated any survival advantage over conventionally administered 5 FU and, unexpectedly, severe gastrointestinal and haematologic toxicity has been observed with some agents.

The best established of these agents is capecitabine, a fluoropyrimidine carbamate prodrug. Capecitabine is converted by hepatic carboxylase to 5′-deoxy-5-fluorocytidine (5′ DFCR). 5′ DFCR is converted to 5′-deoxy-5-fluorouridine (5′ DFUR) by cytidine deaminase and then 5′ DFUR is converted to 5 FU by thymidine phosphorylase within the tumour cell. Hoff et al. have reported the phase III trial comparing the twice daily for 14 to 21 days schedule to the Mayo regimen. The overall response rate was higher (24.8% versus 15.5%, \( p=0.005 \)), but no difference was observed for time to progression and overall survival, which was in the order of 12 to 13 months. The principal adverse effect of capecitabine is hand-foot syndrome.

UFT is a combination oral preparation of uracil and tegafur (florafur) in a molar ratio of 4:1. Tegafur is metabolized by CYP2A6 to 5 FU while uracil inhibits DPD, resulting in higher intratumoral exposure to 5 FU. Folinic acid is also administered to biomodulate the preparation further. In the phase II setting the response rate was 42.2%. Diarrhoea is the main adverse effect.

Eniluracil is a DPD inhibitor that modifies the bioavailability of 5 FU to allow oral administration. The largest of the phase II trials demonstrated a 13% response rate and severe gastrointestinal and haematologic toxicity, including one treatment related death. Further development will require an alternative schedule.

S-1 is an oral combination drug comprising tegafur, 5-chloro-2,4-dihydroxypyrimidine (CDHP) and potassium oxonate in a 1:0.4:1 molar ratio. Tegafur is metabolized to 5 FU, CDHP blocks DPD and potassium oxonate inhibits the phosphorylation of 5 FU by orotate phosphoribosyl transferase in the normal gastrointestinal mucosa. In the phase II setting S-1 has demonstrated a 35% partial response rate and median survival of 12 months.

**Antifolate agents**

Such agents under development include trimetrexate and MTA (multitargeted antifolate). Trimetrexate enters cells by passive diffusion and inhibits dihydrofolate reductase. In the phase II setting the overall response rate to trimetrexate combined with 5 FU and folinic acid is 42% in untreated patients. Phase III studies are in progress. MTA is transported by the reduced folate carrier and is retained within cells by polyglutamation via folypoly-γ-glutamate synthetase. It inhibits multiple enzymes including thymidylate synthase, dihydrofolate reductase, glycaminide ribonucleotide formyltransferase (GARFT) and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT). The phase II response rate for MAT given as 500 mg/m² every 3 weeks is
Myelosuppression is common and a maculopapular rash can be treated or prevented with the co-administration of corticosteroids.

**Which combination to use**

Currently there is no consensus as to which of the available agents or combinations appears to confer a substantial advantage. The prescription for any given patient may depend on ease of administration, age and performance status. Tournigard et al. have conducted a trial that is likely to answer the number of questions related to the sequence of chemotherapy for patients with advanced colorectal cancer and good performance status. 151 This group has compared the sequence of irinotecan and infusional 5 FU (FOLFIRI) followed by oxaliplatin and infusional 5 FU (FOLFOX) at time of progression to the same schedules given in reverse sequence.

<table>
<thead>
<tr>
<th>Weekly 5 FU/folinic acid adjuvant or palliative—weekly bolus</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>5 Fluorouracil</td>
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<td>Folinic acid</td>
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<td>Capecitabine</td>
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<td>Ralitrexed</td>
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Cycle repeats every week, folinic acid administered before 5 FU

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<th>FOLFOX4 regimen</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>Oxaliplatin</td>
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<td>Folinic acid</td>
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<td>5 fluorouracil</td>
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<td>5 fluorouracil</td>
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<tr>
<th>Weekly 5 FU/folinic acid for palliative patients with disease progression on weekly bolus treatment</th>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>5 Fluorouracil</td>
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<td>Folinic acid</td>
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Continuous infusion administered via external portable pump

<table>
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<tr>
<th>Irinotecan/De Gramont regimen</th>
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Figure 8.22 Examples of systemic chemotherapy protocols.

Response rates were 57.5% for first-line FOLFIRI and 21% for second-line versus 56% for FOLFOX first-line and 7% for FOLFIRI second-line. Resection of inoperable hepatic metastases was possible in 15% after FOLFOX and 4% after FOLFIRI. Median survivals were 21.5 months for FOLFIRI first-line and 20.4 months for FOLFOX first-line. While no difference was seen in the survival the trial suggests that oxaliplatin may remain active after irinotecan failure, rather than vice versa.

A number of general conclusions can be drawn: irinotecan and oxaliplatin are best used in combination with 5 FU providing the toxicity observed is acceptable, infusional regimens of 5 FU confer an advantage over bolus 5 FU, folinic acid is an essential biomodulator of 5 FU and oral fluoropyrimidines are likely to be equivalent to, and substituted for, intravenous 5 FU. The systemic chemotherapy protocols used in our institution are detailed in Fig. 8.22.

Key points

- Cryotherapy and other imaging-controlled ablative techniques can be associated with longterm survival in patients with unresectable disease.
- Ablative techniques can be used as an adjunct to liver resection.
- Hepatic artery chemotherapy is associated with high response rates and significantly better survival, but has serious complications.
- Systemic chemotherapy for colorectal cancer has changed; several new active agents are reviewed here.
- Adjuvant hepatic artery chemotherapy after liver resection improves disease-free survival.

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Neuroendocrine gastrointestinal tumours are derived from the neuroendocrine cell system. These tumours have widely differing clinical presentations that reflect both their organ of origin and syndromes related to excess hormone production. The neuroendocrine gastrointestinal tumours are divided into two main groups, carcinoid tumours and endocrine pancreatic tumours. Carcinoid tumours are now described according to their organ of origin, whereas pancreatic endocrine tumours are described according to their main hormone production and related clinical syndrome (insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas and nonfunctioning endocrine pancreatic tumours). The first part of this chapter considers the clinical presentation and metastatic potential of primary neuroendocrine tumours. Given the rarity of these tumours, the experience of treatment of liver metastases from individual tumours is limited. Most studies combine carcinoid tumours derived from various organs of origin together with pancreatic endocrine tumours. The second part of this chapter is therefore devoted in general to the diagnosis and management of neuroendocrine hepatic metastases, albeit from a wide variety of primary tumours.

Neuroendocrine tumours: historical perspective

The diffuse neuroendocrine system was first described by Feyrter in 1938 (diffuse endokrine epithelial organe). The term ‘carcinoid’ was first introduced by Oberndorfer in 1907 to describe a morphologically distinct class of intestinal tumours that behave less aggressively than the more common intestinal adenocarcinomas. Lubarsh originally described this tumour in 1888. Multiple small tumours were observed at autopsy in the distal ileum of two patients. Microscopic examination revealed the absence of glandular structures, suggesting development of these tumours from epithelial cells within the glands of Leiberkuhn. The first case of metastatic disease, and indeed the carcinoid syndrome, was described by Ranson in 1890 who reported a patient with ileal carcinoma and multiple liver metastases who experienced diarrhoea and dyspnoea after eating. ¹ In 1914, Gosset and Masson, using silver impregnation techniques, demonstrated that carcinoid tumours arose from the enterochromaffin cells of the glands of Leiberkuhn, thereby establishing their endocrine origin. In 1953, Lembeck demonstrated the presence of serotonin in carcinoid tumours and in 1954 Waldenstrom described the carcinoid syndrome, reporting a series of patients with small intestinal carcinoids and liver metastases with symptoms of diarrhoea, flushing, asthma, cyanosis and right-sided valvular heart disease. ² In 1955, Page et al. demonstrated increased urinary 5-
hydroxyindoleacetic acid (5-HIAA) in patients with carcinoid syndrome, thereby defining a relationship between carcinoid syndrome and tumour serotonin secretion. Finally, in 1969, Pearse showed that similar cells could be found in organs outside the gastrointestinal tract with the common capacity for amine precursor uptake and decarboxylation (APUD system). As described today, the diffuse neuroendocrine system includes all neuronal and endocrine cells that share a common phenotype characterized by simultaneous expression of general neuroendocrine markers and cell type specific regulatory peptides. It is now recognized that neuroendocrine cells are involved in a wide variety of tumours. The majority occur as primary tumours of the gastrointestinal tract; however, they can also be found in locations such as the lung, ovary, thymus and kidney. Tumours are found to have different hormonal profiles depending on their site of origin (Fig. 9.1). In addition, neuroendocrine tumours show great heterogeneity with respect to both histological and endocrinological features and also clinical presentation and metastatic potential.

**Gastrointestinal neuroendocrine (carcinoid) tumours**

**Stomach**

In early studies, gastric neuroendocrine tumours accounted for only 3% of neuroendocrine tumours of the gut. However, according to later series their incidence ranges from 11% to 41%. In part, this is due to an increased use of endoscopy, though many tumours are now seen in association with hypergastrinaemia. Three types of gastric neuroendocrine tumours are now recognized. Type I tumours (80%) are associated with
chronic atrophic gastritis. These tumours are usually multiple and arise against a background of gastrin-induced enterochromaffin-like (ECL) cell hyperplasia. They are generally small (<1 cm) and rarely metastasize. Type II tumours (6%) are associated with hypertrophic gastropathy due to multiple endocrine neoplasia (MEN) type 1 and Zollinger-Ellison syndrome (ZES). These tumours again are usually small, but are more aggressive than type I tumours and are somewhat more likely to metastasize. In general though, type I and type II tumours are considered to be benign. Endoscopic removal is recommended for tumours less than 1 cm, whereas surgical excision is recommended for lesions greater than 1 cm. Type III tumours (14%) are sporadic lesions that are not associated with hypergastrinaemia. These tumours are considered malignant (Fig. 9.2). Regional lymph node metastases have been described in 20 to 50% of patients and liver metastases have ultimately developed in as many as two-thirds of patients. Rindi et al. described 32 sporadic gastric neuroendocrine tumours, with liver metastases present in 52%. Patients with type III disease will usually require formal gastrectomy and lymph node clearance.

**Duodenum**

Neuroendocrine tumours of the duodenum represent 1–2% of neuroendocrine gastrointestinal tumours. Five main types of tumour are recognized in the duodenum: gastrin producing tumours, somatostatin producing tumours, gangliocytic paragangliomas, serotonin/calcitonin/PP producing tumours and poorly differentiated carcinomas. Gastrin producing tumours are the most frequent (60%) and these are...
found as small, sessile submucosal nodules in the first or second parts of the duodenum (Fig. 9.3). They may be associated with a sporadic ZES or as part of MEN-1 syndrome. Somatostatin producing tumours (20%) generally present as bulky lesions in the ampulla of Vater. These tumours are considered of low grade malignancy and although metastasis to regional lymph nodes may occur, liver metastases are rare. Gangliocytic paraganglionomas occur in the ampullary region and are considered to be benign. The serotonin, calcitonin or PP producing tumours that occur outside the ampullary region are benign. However, about half of these tumours found in the ampulla are considered to be of low grade malignancy.

**Small bowel**

Neuroendocrine tumours of the jejunum and ileum account for 20 to 30% of neuroendocrine tumours of the gut. The majority of tumours are found in the terminal ileum and these are generally of the classic argentaffin carcinoid type. Most tumours are associated with the production of serotonin and substance P. Small bowel carcinoids are rarely diagnosed prior to surgery, and patients are frequently treated conservatively for an extended period of time. Patients usually present with bowel obstruction or ischaemia due either to the mechanical effects of tumour or due to a marked desmoplastic reaction involving the mesentery (Figs 9.4 and 9.5). Optimal treatment involves small bowel resection, together with resection of draining lymph nodes. However, this might not be easily achieved in the presence of extensive mesenteric desmoplastic reaction and in this situation a surgical bypass of the obstructing tumour may be the only possible palliative procedure. A careful laparotomy should be performed. Small bowel carcinoids
are frequently multiple and are often also associated with a second primary gastrointestinal malignancy.\textsuperscript{10} As with other gastrointestinal neuroendocrine tumours, there is a positive correlation between tumour size and the

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{image1}
\caption{Macroscopic view of a surgically resected small bowel (terminal ileum) carcinoid tumour. The patient presented with the carcinoid syndrome due to liver metastases.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{image2}
\caption{H&E stained micrograph of the same small bowel carcinoid demonstrated in Figure 9.4.}
\end{figure}

risk of metastases. Tumours less than 1 cm have a 20 to 30\% incidence of nodal and hepatic metastases. Tumours between 1 and 2 cm have a 60–80\% incidence of nodal metastases and a 20\% incidence of hepatic metastases. Tumours greater than 2 cm have an 80\% incidence of nodal metastases and a 40–50\% incidence of hepatic metastases.\textsuperscript{8 , 11 , 12} Overall 5-year survival rates are 75\% for node negative patients, 59\% in patients with positive lymph nodes and 20 to 30\% if liver metastases are present.\textsuperscript{12 , 13} However, Thompson et al. have reported a 53\% 5-year survival rate when hepatic metastases are present.\textsuperscript{8}
Appendix

Approximately 40 to 50% of gut neuroendocrine tumours (Figs 9.6 and 9.7) are found in the appendix. These tumours have a good prognosis and the

Figure 9.6 Macroscopic view of an appendix carcinoid removed because of acute appendicitis.

Figure 9.7 H&E stained micrograph of the same appendix carcinoid demonstrated in Figure 9.6.

risk of metastases is between 1.4 and 8.8%. $^{10, 14-18}$ Tumours that metastasize are usually greater than 2 cm. Tumours between 1 and 2 cm rarely metastasize, but lymph node metastases have been shown in some cases. $^{8, 16}$ Tumours less than 1 cm were said never to metastasize. Size of tumour is clearly related to risk of malignancy. However, mesoappendix invasion has also been shown to be predictive of an increased risk of metastases for tumours less than 2 cm. $^{19}$ Thus tumours greater than 2 cm should be treated by right hemicolectomy, whereas appendicectomy is usually adequate for tumours less than 1 cm. For tumours between 1 cm and 2 cm, treatment should be determined by tumour site, the patient’s age and health and the presence of mesoappendix invasion or
vascular and lymphatic invasion.

Colon

Colonic neuroendocrine tumours represent 2.8% of all of all gastrointestinal neuroendocrine tumours. Tumours are found predominantly in the right colon and usually present with abdominal pain and weight loss. Colon neuroendocrine tumours should be treated by standard colonic resection, as would be performed for adenocarcinomas of the colon. Overall 5-year survival rates for colonic neuroendocrine tumours are approximately 37%.

Rectum

Rectal neuroendocrine tumours share similarities with neuroendocrine carcinomas of the appendix in that they are often found incidentally and usually have a good prognosis. Rectal neuroendocrine tumours may present with rectal bleeding, constipation, tenesmus or proctitis. Mayo Clinic experience suggests that one tumour will be found for every 2500 sigmoidoscopies performed. Again, there is a correlation between tumour size and the risk of metastases. For tumours less than 1 cm, metastases only occur in 3% of cases. For tumours between 1 and 2 cm, metastases occur in 11% of cases. However, for tumours greater than 2 cm, metastases are found to occur in 74% of cases. Invasion of the muscularis propria has also been identified as an additional risk factor. Small tumours, less than 1 cm, are usually treated by local excision. Tumours between 1 and 2 cm may be treated by local excision, but muscular invasion should be considered a further indication for radical surgery (Figs 9.8 and 9.9). Tumours greater than 2 cm should generally be treated by anterior or abdominoperineal resection. Five-year survival rates are 92% in the absence of metastases, 44% when lymph node metastases are present and 7% when distant metastases are present.

Figure 9.8 H&E stained low power micrograph of a rectal carcinoid tumour.
Gastrinoma is the most common malignant endocrine tumour of the pancreas, with an incidence of 0.1–3 per million. 26 Although the majority of gastrinomas arise within the pancreas (Fig. 9.10), it is now recognized that up to 40% of gastrinomas may arise in the duodenum (Table 9.1). Gastrin overproduction results in ZES. 27 Approximately 20% of patients with ZES will also have MEN-1. 28 Patients present with peptic ulceration, gastritis, diarrhoea and malabsorption (Table 9.2). Severe peptic ulceration is now seen less commonly due to the widespread use of H2 receptor blockers and proton pump inhibitors. With improved medical treatment, the development of liver metastases has become an important determinant of long-term survival (Table 9.3). The overall 5-year survival rate for patients with liver metastases is 20–38%. 29 In a series published in 1994, hepatic metastases developed in 3 of 98
Figure 9.10 H&E stained micrograph of a primary pancreatic gastrinoma.

Table 9.1 **Gastrinoma syndrome (Zollinger-Ellison 1955)**

<table>
<thead>
<tr>
<th>Fulminating ulcer diathesis</th>
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<tbody>
<tr>
<td>Recurrent ulceration despite therapy</td>
</tr>
<tr>
<td>Non-beta cell pancreatic islet tumour</td>
</tr>
<tr>
<td>Incidence 1:1 000 000</td>
</tr>
<tr>
<td>60% Malignant</td>
</tr>
<tr>
<td>30% MEN-1</td>
</tr>
<tr>
<td>20–40% Duodenal microgastrinomas</td>
</tr>
</tbody>
</table>

Table 9.2 **Gastrinoma syndrome: clinical features**

- Peptic ulceration
- Multiple
- Atypical sites: oesophagus, jejunum
- Complications: perforation, haemorrhage, obstruction
- Diarrhoea/steatorrhoea
- Enzyme inactivation
- Mucosal damage

Table 9.3 **Gastrinoma syndrome: diagnosis**

- Gastrin >40 pmol/l
- Fasted sample
- Off antisectory medication
- Other causes of elevated gastrin:
  - Achlorhydria
  - Hypercalcaemia
  - Chronic renal failure
  - G-cell hyperplasia
- Basal acid output >10 mmol/hour
- Secretin test
- Equivocal cases
- Not able to stop antisectory medication
patients (3%) treated by gastrinoma excision compared to 6 of 26 patients (23%) managed medically. The goals of surgery have therefore now shifted from the control of gastric acid hypersecretion to resection of the primary tumour and any involved lymph nodes. Surgery is also the most effective treatment for patients with liver metastases. Aggressive resection of metastases results in a 5-year survival of 79%, compared to 28% in patients with inoperable metastases (Fig. 9.11). 29, 31

**Insulinoma**

The incidence of insulinoma is approximately one per million. 28 In contrast to gastrinomas, only approximately 5–10% of insulinomas are malignant (Figs 9.12 and 9.13) (Table 9.4). 32 Patients present with symptoms of acute hypoglycaemia with anxiety, dizziness, confusion, loss of consciousness and seizures (Tables 9.5 and 9.6). Treatment is surgical and the majority of tumours exist as small solitary benign tumours distributed uniformly within the pancreas. Dranoth et al. have reviewed 62 cases of
malignant insulinoma. Tumours are usually larger and approximately 6 cm in size. The median disease-free survival after resection of malignant tumours was approximately 5 years. Recurrence was observed in 63% of cases at a median interval of 2.8 years, followed by a median survival of only 19 months. Re-resection resulted in a median survival of 4 years, compared to 11 months for biopsy alone. Hepatic resection has rarely been reported for malignant insulinomas, however, surgery remains the optimal treatment for recurrent disease.

Other endocrine tumours of the pancreas

Other endocrine tumours of the pancreas (Table 9.7) include vasoactive intestinal peptide (VIP)-oma,

**Table 9.4 Insulinoma syndrome**

| • Incidence 1:1 000 000 |
| • 90% Benign |
| 10% Multiple—microadenomas |
| 10% MEN-1 |
| Pancreatic |
| • Nesidioblastosis |
| Neonatal hypoglycaemia |

**Table 9.5 Insulinoma syndrome: clinical features**

| • Neuroglycopenic symptoms |
| ‘Funny turns’/faints, especially after fasting |
| Altered mood, behaviour, personality |
| Neurological disturbance |
| • Autonomic symptoms |
| Palpitations, tremors, sweating |

**Table 9.6 Insulinoma syndrome: biochemical diagnosis**

| • 3×1 5-hour fast or single 72-hour fast |
| Hypoglycaemia: glucose <2.5 mmol/l |
| Suppressed ketones (hydroxybutyrate) |
| Elevated insulin and C-peptide ± proinsulin |
| • Negative sulphonylurea screen |
### Table 9.7 Other functioning tumour syndromes

- **Glucagonoma**
  Incidence 1:20,000,000 invariably pancreatic
  75% Malignant
- **VIP-oma (Verner-Morrison syndrome)**
  Incidence 1:100,000,000
  10% Extrapancreatic—neural crest tissue (usually children)
  50% Malignant
- **Somatostatirtoma**
  Incidence 1:40,000,000
  50% Pancreatic—90% malignant
  50% Duodenal—50% malignant (NF 1)

### Table 9.8 VIP-oma syndrome

- Secretory diarrhoea
  Usually >3 l/day
  Severe dehydration and weakness
- Hypokalaemic acidosis
  Stool loss—may also cause hypomagnesaemia
- Hypochlorhydria 50%
- Inhibition of gastric acid
- Hypercalcaemia 50%
  ? PTHrP
- Glucose intolerance 50%
  Glucagon-like action
- Flushing 20%

### Table 9.9 VIP-oma syndrome: diagnosis

- Elevated VIP
  Usually 60 pmol/l
- Associated increase in circulating PHM
NB Other causes of elevated VIP
  Bowel ischaemia
  Hepatic cirrhosis
  Renal impairment
Table 9.10 Glucagonoma syndrome

- Necrolytic migratory erythema
- Mucous membrane involvement
- Impaired glucose tolerance 90%
- Weight loss 90%
- Normochromic normocytic anaemia
- Depression (5%) and mental slowness
- Severe venous thrombosis 1 5%
- Bowel disturbance

Table 9.11 Glucagonoma syndrome: diagnosis

- Elevated glucagon (usually 10–20-fold)
- Decreased amino acid levels
- Impaired glucose tolerance
- Coagulation abnormalities
- NB Other causes of elevated glucagon
- Hepatic or renal failure
- Oral contraceptive pill, danazol
- Stress
- Prolonged fast
- Familial

Table 9.12 Somatostatinoma syndrome

- Impaired carbohydrate metabolism
- Hyperglycaemia—90% pancreatic tumours
- Hypoglycaemia—rare
- Steatorrhoea (90%)
- Gallbladder disease (90% pancreatic, 40% duodenal)
- Duodenal tumours
- Local symptoms: obstruction, haemorrhage

Glucagonoma, somatostatinoma and non-functioning islet cell tumour or pancreatic polypeptide (PP)oma. Other hormones produced by functional pancreatic endocrine tumours include growth hormone releasing factor (GRF), adrenocorticotropic hormone (ACTH), parathyroid hormone (PTH) and neurotensin. These tumours have a combined incidence of less than 0.2 per million. They behave in a similar fashion to gastrinoma and they are usually malignant.26 VIP-omas are associated with watery diarrhoea, hypokalaemia, hypochlorhydria and acidosis (WDHHA syndrome or VernalMorrison
syndrome (Table 9.8). Tumours are usually confined to the pancreas, but may be found in the lung or sympathetic ganglia (Table 9.9). Glucagonomas may present with a characteristic rash (necrolytic migratory erythema), diabetes, weight loss and venous thrombosis (Tables 9.10 and 9.11). Somatostatinomas may present with diarrhoea, malabsorption, gallstones and diabetes (Table 9.12). Somatostatinomas may also occur in the duodenum and present with symptoms related to location such as jaundice, pancreatitis or bleeding. Pancreatic polypeptide has no known biological function and so symptoms are usually due to mass effect and include abdominal pain, biliary obstruction and gastrointestinal bleeding. Tumours should be managed by surgical resection.

Hepatic metastases

**Diagnosis**

**Clinical features**

Neuroendocrine hepatic metastases may be diagnosed preoperatively following investigation and diagnosis of a specific neuroendocrine hormonal syndrome. Patients may also be diagnosed following the incidental finding of hepatomegaly or an abdominal mass. Liver metastases may be discovered at laparotomy following the acute presentation of carcinoid disease. Up to 45% of patients with abdominal carcinoid will present with bowel obstruction and between 50 and 65% of patients are found to have liver metastases at the time of diagnosis (Fig. 9.13; Table 9.13).35

![Figure 9.13 Photomicrograph of a pancreatic insulinoma stained using antibodies for insulin.](image)
Carcinoid syndrome occurs when 5-hydroxytryptamine and other hormonal products are secreted directly into the systemic circulation. The carcinoid syndrome is therefore usually only seen in patients with liver metastases. Common symptoms and signs typically include cutaneous flushing (80%) (Fig. 9.14), diarrhoea (76%), hepatomegaly (71%), carcinoid heart disease (41–70%) and asthma (25%); the cause of the different features of the carcinoid syndrome is not fully understood (Table 9.14). Serotonin may be responsible for the diarrhoea whereas tachykinins such as neuropeptide K may be involved in the symptoms of flushing. Carcinoid heart disease with pulmonary stenosis and tricuspid regurgitation may also be due to excess hormone production.

![Macroscopic view of a post-mortem specimen of liver from a patient who died from the carcinoid syndrome.](image)

Table 9.13 **Carcinoid tumours**

- Incidence 1:150 000
- Derived from embryonic gut
  - Foregut: 5-hydroxytryptamine-producing, argentophilic
  - Midgut: serotonin-producing, argentaffin-positive
  - Hindgut: non-secreting, non-staining
- Carcinoid syndrome
  - 10% of cases
  - Almost invariably metastasized
  - Usually small bowel
- Aetiology: serotonin, histamine, bradykinin, substance P

Carcinoid syndrome occurs when 5-hydroxytryptamine and other hormonal products are secreted directly into the systemic circulation. The carcinoid syndrome is therefore usually only seen in patients with liver metastases. Common symptoms and signs typically include cutaneous flushing (80%) (Fig. 9.14), diarrhoea (76%), hepatomegaly (71%), carcinoid heart disease (41–70%) and asthma (25%); the cause of the different features of the carcinoid syndrome is not fully understood (Table 9.14). Serotonin may be responsible for the diarrhoea whereas tachykinins such as neuropeptide K may be involved in the symptoms of flushing. Carcinoid heart disease with pulmonary stenosis and tricuspid regurgitation may also be due to excess hormone production.
Levels of both 5-hydroxyindoleactic acid (5-HIAA) and neuropeptide K are higher in patients with carcinoid heart disease and the increased fibrosis seen in the heart is thought to be due to increased expression of transforming growth factor (TGF)-B.39

The features of this syndrome are well known; however, a diagnosis of carcinoid disease is rarely made preoperatively. Typically, the development of flushing and diarrhoea is preceded by a long history of vague abdominal pain.40 Many patients have been diagnosed as having irritable bowel syndrome, peptic ulcer disease or Crohn’s disease. Flushing attacks are usually confined to the face and chest. They may occur spontaneously or may follow a specific stimulus such as drinking alcohol or eating a particular food. Eventually patients may develop a permanent flush across the face which may vary from mild telangectasia to a deep cyanotic discoloration. Cardiac manifestations of carcinoid syndrome may be detected by echocardiography in 60 to 70% of patients.39 The three most common abnormalities are pulmonary stenosis, tricuspid regurgitation and tricuspid stenosis.

The carcinoid syndrome may occur in up to onethird of patients with gastric carcinoid, although this is generally of an atypical type with a bright red severe flush, cutaneous oedema, lacrimation and bronchoconstriction. Diarrhoea is episodic and may be associated with abdominal pain and urgency; nocturnal diarrhoea is unusual. This syndrome is related to histamine secretion and urinary estimates of the histamine metabolite MelMAA may serve as a useful tumour marker. 5-HIAA is also often excreted, although this is less so than for midgut carcinoids.

Carcinoid crisis may be precipitated by anaesthesia or by surgical procedures in patients with carcinoid tumours. This occurs when large amounts of hormonal products are suddenly released into the systemic circulation. Clinical features include hypotension, tachyarrhythmias, bronchospasm and CNS abnormalities. Carcinoid crisis is treated by the intravenous administration of somatostatin (50–100 µg). Further boluses may be given or a somatostatin infusion set up as required.

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<thead>
<tr>
<th>Table 9.13 Carcinoid syndrome</th>
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<tr>
<td>• Flushing 95%</td>
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<tr>
<td>Site-specific flush—? different mediators</td>
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<tr>
<td>Carcinoid crises</td>
</tr>
<tr>
<td>• GI manifestations</td>
</tr>
<tr>
<td>Secretory diarrhoea</td>
</tr>
<tr>
<td>Cachexia</td>
</tr>
<tr>
<td>• Endocardial fibrosis 50%</td>
</tr>
<tr>
<td>Tricuspid incompetence 50%</td>
</tr>
<tr>
<td>Pulmonary valve lesions 50%</td>
</tr>
<tr>
<td>• Respiratory complications</td>
</tr>
<tr>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Pleural fibrosis</td>
</tr>
<tr>
<td>• Pellagra 10%</td>
</tr>
<tr>
<td>• Arthropathy, myopathy</td>
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</table>

Levels of both 5-hydroxyindoleactic acid (5-HIAA) and neuropeptide K are higher in patients with carcinoid heart disease and the increased fibrosis seen in the heart is thought to be due to increased expression of transforming growth factor (TGF)-B.39

The features of this syndrome are well known; however, a diagnosis of carcinoid disease is rarely made preoperatively. Typically, the development of flushing and diarrhoea is preceded by a long history of vague abdominal pain.40 Many patients have been diagnosed as having irritable bowel syndrome, peptic ulcer disease or Crohn’s disease. Flushing attacks are usually confined to the face and chest. They may occur spontaneously or may follow a specific stimulus such as drinking alcohol or eating a particular food. Eventually patients may develop a permanent flush across the face which may vary from mild telangectasia to a deep cyanotic discoloration. Cardiac manifestations of carcinoid syndrome may be detected by echocardiography in 60 to 70% of patients.39 The three most common abnormalities are pulmonary stenosis, tricuspid regurgitation and tricuspid stenosis.

The carcinoid syndrome may occur in up to onethird of patients with gastric carcinoid, although this is generally of an atypical type with a bright red severe flush, cutaneous oedema, lacrimation and bronchoconstriction. Diarrhoea is episodic and may be associated with abdominal pain and urgency; nocturnal diarrhoea is unusual. This syndrome is related to histamine secretion and urinary estimates of the histamine metabolite MelMAA may serve as a useful tumour marker. 5-HIAA is also often excreted, although this is less so than for midgut carcinoids.

Carcinoid crisis may be precipitated by anaesthesia or by surgical procedures in patients with carcinoid tumours. This occurs when large amounts of hormonal products are suddenly released into the systemic circulation. Clinical features include hypotension, tachyarrhythmias, bronchospasm and CNS abnormalities. Carcinoid crisis is treated by the intravenous administration of somatostatin (50–100 µg). Further boluses may be given or a somatostatin infusion set up as required.
Laboratory investigations

Blood

Following a suspected diagnosis of neuroendocrine liver metastases, radioimmunoassays may be performed in order to search for the products of specific pancreatic endocrine tumours. Otherwise, there are no blood tests diagnostic of hepatic metastases, although plasma alkaline phosphatase and gamma glutamyl transferase may be elevated in the presence of advanced disease. The plasma concentration of chromogranin A is a non-specific marker for neuroendocrine tumours, but this test is not in widespread clinical use.41,42

Urine

The 24-hour urinary excretion of the serotonin metabolite 5-HIAA is the most valuable biochemical screening test for the presence of metastatic carcinoid tumours. The level is usually calculated as the mean value of two 24-hour urine collections. Elevated levels are typical of metastases of small bowel origin. Gastric carcinoid tumours may have relatively small amounts of 5-HIAA in the urine but a marked excess of 5-HTP. This is thought to be due to a lack of aromatic amino acid decarboxylase. In addition, urinary estimates of the histamine metabolite MelMAA may serve as a useful marker for metastases secondary to gastric carcinoid tumours.

Pathology

Neuroendocrine tumours are characterized by uniform round cell nuclei and regular growth patterns (Fig. 9.15). A number of distinct histological growth patterns have been described (insular, trabecular, glandular, mixed and undifferentiated) and it has been suggested that morphology may influence survival.43–45 Tumours are further classified on the basis of silver staining. Neoplasms that can directly deposit soluble silver salts are termed argentaffin positive. Tumours requiring an exogenous reducing agent for silver salt deposition are classified as argyrophil positive. Argyrophil staining by the Grimelius method is a general marker for neuroendocrine differentiation. Carcinoids of midgut origin also show an argentaffin reaction, reflecting the presence of serotonin.

Immunohistochemistry is now commonly used for the diagnosis of neuroendocrine tumours. Tumours are classified according to their expression of neuroendocrine markers. These markers are divided into cytosolic markers (neurone specific enolase), small vesicle associated markers (synaptophysin) and secretory granule associated markers (chromogranins). Cell specific or secretory neuroendocrine products are peptides or amines that normally act as hormones or neurotransmitters. However, elevated levels are usually responsible for the systemic symptoms or syndromes associated with neuroendocrine tumours.

Historically, gastrointestinal carcinoid tumours were classified according to their embryonic origin into foregut, midgut and hindgut tumours, the embryological foregut
including respiratory tract and thymus. Foregut carcinoids were described as producing low levels of serotonin and sometimes secreting 5-hydroxytryptophan (5-HTP) or adrenocorticotropic hormone (ACTH). Midgut carcinoids were described as having high serotonin production, whereas hindgut carcinoids were hardly ever found to secrete serotonin, 5-HT or ACTH. Later, a new classification of neuroendocrine tumours was proposed whereby tumours are distinguished according to their site of origin. Thus tumours of the stomach, duodenum, jejunum-ileum, appendix, colon and rectum are considered separately. The second principle is to subdivide neoplasms into (I) tumours with benign behaviour, (II) tumours with uncertain behaviour, (III) tumours with low-grade malignant behaviour and (IV) high-grade malignant tumours exhibiting angioinvasion, invasion of neighbouring structures or the presence of metastases. Tumour size has also been established as a reliable prognostic indicator for a number of tumours. The third principle is to incorporate hormonal function. Tumours causing an endocrine syndrome are designated as ‘functioning’, whereas those without a hormonal syndrome are called ‘nonfunctioning’. The classic endocrine tumours of the pancreas are not included in this classification of neuroendocrine tumours. Insulinomas and glucagonomas arise from the islets of Langerhans. From an embryological point of view, the pancreatic islets are not part of the diffuse neuroendocrine system. They first occur as a separate islet organ and are later included in the pancreas as disseminated, minute endocrine glands. In contrast, gastrinomas and somatostatinomas, which may occur in the duodenal wall, are included.

Figure 9.15 H&E stained micrograph of a surgically resected hepatic carcinoid metastasis.

Diagnostic imaging

Radiology

Ultrasound, CT and MRI are all used in the diagnosis of neuroendocrine hepatic metastases. Relatively few studies have compared the sensitivity of these techniques. In one study from Sweden, 84 patients with neuroendocrine tumours were identified. Seven patients had single liver metastases, 44 patients had multiple metastases. Ultrasound and
CT showed similar sensitivities of 57% and 53%, respectively. A study by the National Institutes of Health (NIH) prospectively evaluated 80 consecutive patients with ZES. In 24 patients with histologically proven liver metastases, the sensitivities for the detection of metastatic liver lesions were 46% for US, 42% for CT and 71% for MRI (Fig. 9.16).

There has been some controversy regarding the optimal CT technique for the evaluation of neuroendocrine hepatic metastases. In contrast to colonic carcinoma metastases, neuroendocrine metastases are often hypervascular relative to the background hepatic parenchyma (see Fig. 9.5). It has been suggested that the administration of intravenous contrast may render metastases isoattenuating or hyperattenuating when compared to the background liver. This may obscure metastases and complicate the assessment of tumour size. Some authors have therefore recommended the use of non-contrast enhanced CT for the evaluation of patients with suspected neuroendocrine metastases. With the development of spiral CT, it is now possible to image the liver twice following the administration of intravenous contrast, once during the early hepatic arterial dominant phase (HAP) and again during the portal venous dominant phase (PVP) of enhancement. Paulson et al. have evaluated triple phase spiral CT in 31 patients with proven neuroendocrine liver metastases. In this study, each phase identified metastatic lesions that were not seen in the other images. The HAP images showed more lesions than either the non-contrast or PVP images and in two patients lesions were only seen on the HAP images. The authors therefore recommend triple phase spiral CT for the evaluation of patients with suspected neuroendocrine hepatic metastases. Visceral angiography may also be useful in the localization of

**Figure 9.16** CT scan of the liver of a patient with carcinoid syndrome showing widespread multiple bilobar tumours clearly not suitable for any surgical intervention.
pancreatic tumours (Fig. 9.17).

**Figure 9.17** Visceral angiogram (splenic artery injection) showing a tumour ‘blush’ in the pancreas at the site of a primary insulinoma.

**Radionuclear investigations**

**Somatostatin receptor scintography**

Neuroendocrine tumours have a high density of somatostatin receptors. Somatostatin is a 14 amino acid peptide that acts as both a hormone and a neurotransmitter. Its main physiological role is to inhibit the release of growth hormone. Somatostatin was first isolated from hypothalamic extracts and shown to inhibit the release of growth hormone. However, somatostatin has also been shown to inhibit the release of other anterior pituitary hormones, including adrenocorticotropic hormone (ACTH), prolactin and thyroid stimulating hormone (TSH). Somatostatin also inhibits the release of a number of gastrointestinal peptides including insulin, glucagon, gastrin motilin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), secretin, cholecystokinin and gastrin releasing peptide (GRP). GRP stimulates proliferation of normal and malignant intestinal epithelium. Somatostatin may also inhibit epidermal growth factor (EGF) induced cell proliferation. Somatostatin analogues have been used in the treatment of neuroendocrine tumours. Antiproliferative effects may be mediated by a number of different mechanisms including the inhibition of regulatory peptide release and the direct antagonism of growth factor effects on tumour cells. Somatostatin has an extremely short half-life and this has limited its therapeutic applications. Octreotide is a somatostatin analogue with a much longer half-life, now used for the treatment of patients with metastatic neuroendocrine tumours. Radiolabelling of octreotide has allowed the development of somatostatin receptor scintography (SRS). Initially octreotide was labelled with $^{123}$I and the first localization of a neuroendocrine tumour by this technique was reported by Krenning et al. in 1989. Although initial results were encouraging, there were a number of problems with $^{123}$I-labelled octreotide including cost and inefficient labelling. However, the main problem was the fact that this compound is rapidly cleared by the liver and excreted into the biliary system and intestines, thereby interfering with images of the abdomen and pelvis. These problems
have been overcome by the introduction of $^{111}$In-DTPA labelled octreotide, which has a longer half-life and is excreted by the kidneys. This Dutch group have subsequently published their experience of SRS in over 1000 patients.\textsuperscript{54}

A number of groups have now reported their experience of SRS for the imaging of primary and metastatic neuroendocrine tumours (Fig. 9.18). Kwekkeboom et al.\textsuperscript{55} have studied a group of 52 patients diagnosed as, or suspected of having carcinoid tumours. Accumulation of labelled octreotide was found in 86\% of patients with histologically proven carcinoid tumours. However, in 27 patients (52\%) accumulation of radioactivity was found at previously unsuspected sites not identified by conventional imaging techniques (Fig. 9.19). Joseph et al.\textsuperscript{56} have reported positive findings in 81\% of patients with carcinoid tumours, with additional tumour deposits identified in one-third of patients. Westlin et al.\textsuperscript{57} detected tumour sites in 78\% of patients with carcinoid tumours,
with additional tumour localizations in 32% of patients. In a study from the National Institute of Health, SRS was used to evaluate 80 consecutive patients presenting with ZES. Primary tumours were detected in 9% of patients by ultrasound, in 31% of patients by CT, in 30% of patients by MRI and in 28% of patients by angiography. However, the sensitivity of SRS for the detection of primary tumours was 58%. Metastases were identified by ultrasound in 19% of patients, by CT in 38% of patients, by MRI in 45% of patients, by angiography in 40% of patients and by SRS in 70% of patients. In 24 patients with histologically proven liver metastases, the sensitivity of SRS for the detection of liver metastases was 92%. It seems likely that the widespread introduction of SRS will dramatically influence patient management. Ahlman et al. have reported a sensitivity of 84% for octreotide scintography in 27 patients with carcinoid tumours. Tumour deposits not identified by US or CT were found in 19 patients and 8 patients underwent further surgery. Lebtahi et al. have assessed the clinical impact of SRS in 160 consecutive patients with gastrointestinal neuroendocrine tumours. On the basis of conventional imaging, patients were divided into three groups according to the presence or absence of liver and/or extrahepatic metastases. Group 1 included 90 patients with no detected metastases. Group 2 included 59 patients with liver metastases but no extrahepatic metastases. Group 3 included 11 patients found to have extrahepatic metastases. Patients were then restaged following SRS. In group 1, 17 patients were found to have extrahepatic metastases, one patient was found to have extrahepatic and liver metastases and seven patients were found to have metastases confined to the liver. Six of these seven patients were found to have only one liver metastasis and these patients were considered for liver resection. In group 2, SRS confirmed the presence of liver metastases in 56 patients, but new liver metastases were found in 5 patients and 13 patients (22%) were found to have previously undetected extrahepatic metastases. As a result, two proposed hepatic resections were cancelled and in three patients liver transplantation was cancelled. In group 3, SRS missed tumour deposits in three patients, but discovered new metastatic deposits in a further three patients. Clearly conventional imaging dramatically underestimates tumour burden and

**Figure 9.20** (A-C) Diagnostic hepatic scintography using $^{131}$I-metaiodobenzylguanidine (MIBG) and demonstrating uptake in multiple hepatic carcinoid metastases. This patient suffered from the carcinoid syndrome and went on to be successfully relieved of her symptoms by a therapeutic course of MIBG treatment.
SRS is now frequently recommended as the first line imaging technique for patients with neuroendocrine tumours. However, SRS is dependent on the density and subtype of somatostatin receptors and large tumours are sometimes missed by SRS. Therefore, when patients are considered for curative surgery, SRS and conventional imaging techniques will probably remain complementary.

**Metaiodobenzylguanidine (MIBG) scintography**

Radiolabelled metaiodobenzylguanidine (MIBG) was initially introduced for the localization of phaeochromocytomas. Since then, MIBG has been used to image a variety of endocrine tumours such as neuroblastoma, medullary thyroid cancer and paraganglioma. These tumours all arise from the neural crest and, in common with gastrointestinal neuroendocrine tumours, they share the specific amine precursor uptake and decarboxylase (APUD) pathway. MIBG is taken up by the same pathway and so may be used for imaging. Fisher et al. reported the first case of neuroendocrine hepatic metastases detected using MIBG. A number of other groups have subsequently reported the use of $^{123}$I-labelled MIBG for imaging.

![Figure 9.21 CT scan of a solitary carcinoid hepatic metastasis in a patient with carcinoid syndrome. This is suitable for surgical resection with potentially curative intent.](image)

Few studies have compared the relative sensitivities of MIBG and somatostatin receptor scintography for the detection of neuroendocrine hepatic metastases. In a review of all published series up to 1994, Hoemagel identified a sensitivity of 86% for Octreoscan and 70% for labelled MIBG (Fig. 9.20). One study from King’s College Hospital, London, showed a sensitivity of 94% for Octreoscan and only 30% for MIBG. In this study, no previously occult primary sites were identified by either modality; however, two patients who had previously undergone orthoptic liver transplantation were found to have hepatic recurrence and bony metastases using Octreoscan. It is likely that SRS will supersede imaging with labelled MIBG. However, in some circumstances the techniques may be complementary and imaging with MIBG may be useful in the identification of patients likely to respond to therapy with $^{131}$I MIBG.
Liver resection is now considered potentially curative for selected patients with colorectal liver metastases. In the majority of series, hepatic resection is performed with an operative mortality of less than 5%. Neuroendocrine hepatic metastases are generally slow growing and surgery is therefore an attractive therapeutic option. In addition, palliative resection of hepatic metastases may result in the relief of debilitating symptoms related to hormone overproduction (Fig. 9.21).

Figure 9.22 CT scan of the liver of a patient suffering from the carcinoid syndrome and showing several tumour deposits. These tumours would be suitable for surgical resection with the intention of debulking for relieving symptoms.

A number of early reports described the potential benefits of hepatic resection. Norton et al. reported three patients who underwent curative resection for metastatic gastrinoma. Two of the three patients were alive at 22 and 32 months. Martin et al. reported five patients who had undergone hepatic resection for metastatic carcinoid tumours. Three were alive with no evidence of disease at 12, 39 and 45 months. One patient developed recurrence at 19 months and one died at 31 months. In a collective series of 54 patients with hepatic resection for metastatic neuroendocrine tumours, Hughes and Sugarbaker found an operative mortality of 7% with palliation of symptoms in 33 of 36 of patients available for follow-up. Survival ranged from 2 months to 10 years, with palliation lasting up to 78 months. These findings suggested that hepatic resection should be the first-line treatment for patients with operable hepatic neuroendocrine metastases.

McEntee et al. have published the Mayo Clinic experience of hepatic resection for metastatic neuroendocrine tumours. Between 1970 and 1989, 37 patients underwent hepatic resection. Seventeen resections were considered curative, with no evidence of gross residual disease. In this group, 11 patients were disease-free with a median follow-
up of 19 months. Two patients were alive with recurrence at 59 and 92 months. The remaining 20 resections were considered palliative (Fig. 9.22). In this group, 16 patients had symptomatic endocrinopathies and eight patients had complete relief of symptoms. However, the mean duration of response was only 6 months. The authors recommended that palliative resection should only be performed when at least 90% of the tumour bulk can be safely excised. This group subsequently published a retrospective series of 74 patients with neuroendocrine hepatic metastases undergoing resection between 1984 and 1992.75 Twenty-eight patients underwent curative resection, whereas 46 patients had palliative or incomplete resections. The overall survival at 4 years was 74%. Median survival had not been reached with a mean follow-up of 2.2 years. The overall postoperative symptomatic response rate was 90%, with a mean duration of 19.3 months. This study did not compare survival with unresected patients. However, historical series suggest that the 5-year survival of patients with untreated carcinoid or islet cell hepatic metastases is 30 to 40%.76,77

Carty et al. have prospectively evaluated 42 patients presenting to the National Institute of Health with metastatic pancreatic neuroendocrine tumours.29 Twenty-five patients were found to have inoperable disease with diffuse hepatic and distant metastases. This group had a 60% 2-year survival and a 28% 5-year survival. The remaining 17 patients were thought to have resectable disease on the basis of preoperative imaging studies. Of these, 13 patients underwent potentially curative resection; four patients were found to have unresectable disease at operation. In the 17 patients who underwent surgery, the 2-year survival was 87%, with a 5-year survival of 79%. The majority of patients subsequently developed recurrent disease. However, four patients remained disease free at 51, 39, 22 and 14 months. Thus hepatic resection appeared to offer a potential cure in selected patients and, in addition, long-term survival occurred despite the presence of recurrent disease.

Dousset et al. have published their experience of 34 patients with bilateral neuroendocrine hepatic metastases treated by either surgical resection, liver transplantation or medical management.78 Seventeen patients underwent hepatic resection and in 12 patients resection was considered curative. Overall, the 2-year and 5-year actuarial survival rates were 87% and 46%, with disease-free survival rates of 43% and 36%. However, for patients considered to have undergone curative surgery, the 5-year survival rate was 62%, with a disease-free survival of 52%.

Chen et al. have published a further series suggesting that hepatic resection may prolong survival.79 In this study, between 1984 and 1995, 38 patients with neuroendocrine metastases confined to the liver were assessed for hepatic resection. The survival of a group of patients with localized disease, treated by complete resection, was compared to that of a group of unresectable patients with a similar tumour burden. Twenty-three patients were found to have unresectable disease. Fifteen patients underwent curative resection. In the unresected group, the median survival was 27 months, with a 5-year actuarial survival of 29%. In the resected group, the median survival had not been reached and the 5-year actuarial survival was 73%. However, in this group, only five patients remained disease free, with a median time to recurrence of 21 months.

To date, no prospective randomized trial has compared hepatic resection to either no
treatment or to best medical therapy. Given the rarity of these tumours and the long natural history of neuroendocrine hepatic metastases, definite evidence for the role of hepatic resection in these patients is only likely to come from multicentre national and international trials. However, at present, the available evidence suggests that all patients with resectable liver metastases should undergo hepatic resection.

Unfortunately, relatively few patients are likely to be suitable for hepatic resection. Carty et al.\textsuperscript{29} and Dousset et al.\textsuperscript{78} found, respectively, that only 40% and 35% of patients with metastatic disease were candidates for hepatic resection. Preoperative imaging dramatically underestimated tumour burden and, overall, only 30% and 35% of patients underwent curative resection. In the initial series from the Mayo Clinic,\textsuperscript{74} only 9% of patients referred with metastatic disease were considered candidates for hepatic resection. Galland and Blumgart also found that only 2 of 30 patients with neuroendocrine hepatic metastases were suitable for resection.\textsuperscript{80} Thus the majority of patients presenting with hepatic neuroendocrine metastases will not be suitable for hepatic resection. Alternative therapies will be required for these patients.

**Hepatic artery embolization**

It has long been known that primary and secondary hepatic tumours receive most of their blood supply from the hepatic artery, whereas the hepatic parenchyma is predominately supplied by the portal venous system. Hepatic metastases may therefore be treated by interruption of hepatic arterial blood supply. This was initially performed by formal hepatic artery ligation; however, hepatic artery embolization is now the method of choice. A number of embolic agents have been used including gelatin sponge, polyvinyl alcohol foam and absolute alcohol. Embolization is frequently associated with right upper quadrant pain and nausea. Most patients experience a pyrexia and transient elevation of liver enzymes. More serious complications include gallbladder ischaemia, liver abscess, acute pancreatitis, acute renal failure and carcinoid crisis. Patients are usually managed with intravenous fluids, somatostatin analogues and opiate analgesia. Some authors also recommend the use of prophylactic antibiotics. Contraindications to hepatic artery embolization include excessive tumour burden, persistently abnormal liver function and portal vein thrombosis. (Figs 9.23 and 9.24).

Hepatic artery embolization was first used for the treatment of neuroendocrine metastases in 1977. Allison et al.\textsuperscript{81} reported a series of two patients with carcinoid tumours embolized a total of four times. These patients had complete palliation of their symptoms during a follow-up of 6 months. Maton et al.\textsuperscript{82} treated nine patients by hepatic artery embolization. They reported one death and one liver abscess. All surviving patients experienced symptomatic relief. Mean survival following embolization was 19 months. Carrasco et al.\textsuperscript{83} treated 25 patients with hepatic carcinoid metastases by embolization. This study demonstrated an 87% symptomatic response rate and a median response duration of 11 months; however, this was associated with a 9% mortality secondary to complications of embolization. As yet there is little evidence that hepatic artery embolization improves survival. Mitty et al.\textsuperscript{84} reported a 9-year follow-up of 18 patients treated with embolization. In this study mean survival was prolonged by 2 years compared with that of historical controls. However, Coupe et al.\textsuperscript{85} reported a series of 63
consecutive patients from the Hammersmith Hospital, 30 of whom underwent embolization. No difference in survival was seen between these two groups of patients.

![Figure 9.23](image1)

**Figure 9.23** Hepatic angiogram showing a tumour ‘blush’ in a carcinoid metastasis prior to therapeutic embolization.

A mixture of cyanoacrylate and ethiodized oil has been used for embolization. Cyanoacrylate is a low viscosity liquid that polymerizes on contact with blood or endothelium. The use of this mixture allows peripheral, complete and permanent arterial occlusion. Winkelbauer et al. have used this technique to treat six patients with hepatic carcinoid metastases. All patients achieved a complete symptomatic response and all were alive at a mean duration of 17 months following the procedure.

Chemoembolization involves the use of ethiodized oil as a carrier for various cytotoxic drugs. Hepatic

![Figure 9.24](image2)

**Figure 9.24** Angiogram of the same patient shown in Figure 9.23 after completion of a successful embolization.

arterial infusion is followed by arterial embolization. The encapsulation of drugs in microcapsules capable of slow deterioration is also of interest. In addition to vascular occlusion, encapsulation allows the slow release of cytotoxic agents in direct proximity to
tumour deposits. A number of authors have reported their experience of these techniques, although it is uncertain whether there is any advantage over embolization alone.\textsuperscript{87–89}

**Hepatic cryotherapy**

Cryotherapy was initially developed for the treatment of skin tumours. However, the development of modern cryotherapy delivery systems, together with the introduction of intraoperative ultrasound, has allowed the application of cryotherapy techniques for the treatment of hepatic tumours. Hepatic cryotherapy involves the delivery of liquid nitrogen to the tip of relatively thin insulated probes. Intraoperative ultrasound guides probe placement and the monitoring of ice formation during the freezing process. Cryotherapy has been widely used for the treatment of primary\textsuperscript{90} and secondary hepatic tumours, predominately colorectal metastases.\textsuperscript{91,92}

The first series describing the use of cryotherapy for the treatment of neuroendocrine hepatic metastases was published by Cozzi et al. in 1995.\textsuperscript{93} A total of six patients were treated. Four patients were symptomatic and three of these patients had elevated tumour markers. All patients were alive and asymptomatic with a median follow-up of 24 months. Patients with elevated preoperative markers showed a dramatic reduction in tumour markers following treatment. In addition, all patients had a complete radiological response. This group published their experience of a total of 13 patients with neuroendocrine hepatic metastases treated by hepatic cryotherapy.\textsuperscript{94} Twelve patients were alive with a median follow-up of 13.5 months. One patient died of bronchopneumonia 45 months following cryotherapy, but without evidence of tumour recurrence. Three patients had developed recurrent disease. One patient developed a recurrence in one of seven liver metastases and this was subsequently treated by hepatic cryotherapy. This patient went on to develop a sacral recurrence of his rectal carcinoid which was also resected. Two other patients had developed recurrent liver metastases. However, the remaining nine patients were alive with no evidence of recurrent disease. Seven of these 13 patients had had symptoms related to ectopic hormone production. In all patients symptoms were significantly alleviated and postoperatively five patients were completely asymptomatic. In this series, two patients with carcinoid metastases developed a coagulopathy postoperatively and required further laparotomy together with the replacement of clotting factors.

Bilchik et al. have reported a series of 19 patients with neuroendocrine hepatic metastases treated by hepatic cryotherapy.\textsuperscript{95} All patients were referred because of persistent endocrine related symptoms refractory to other treatments. All patients had advanced disease and cryosurgery was considered palliative as evidenced by residual liver disease, lymph node involvement, residual primary disease or unknown primary site. The median duration of symptom-free survival was 10 months. The median duration of overall survival was greater than 49 months. Recurrent symptoms following cryotherapy were effectively palliated in three patients using somatostatin and in five patients by chemotherapy. All these patients had previously been refractory to treatment.

Cryotherapy has the advantage of being able to treat bilobar disease and lesions close to major blood vessels. This treatment appears to be safe and to provide good palliation of symptoms related to ectopic hormone production. In some patients it appears that long-
term disease-free survival may be obtained. However, given the long natural history of neuroendocrine tumours and the relatively short follow-up of patients treated by hepatic cryotherapy, evidence for prolonged survival is as yet unavailable.

**Liver transplantation**

Malignant tumours initially represented one of the main indications for orthoptic liver transplant (OLT). However, it rapidly became clear that this was associated with high rates of disease recurrence. The results of hepatic transplantation for metastatic tumours are particularly poor. The two largest series describe 2-year survival rates between 14% and 19%, with 5-year survival rates not exceeding 5%. 96,97 In contrast, patients with hepatic neuroendocrine metastases have been considered more likely to benefit from hepatic transplantation. In 1989, the Pittsburgh group reported a series of five patients with neuroendocrine hepatic metastases, three of whom were alive at 7, 16 and 34 months following surgery.98 That same year, the group at King’s College, London, reported a series of four patients with two patients alive and well 38 and 22 months following surgery.99 Routley et al. subsequently described a series of 11 patients who had undergone OLT for neuroendocrine hepatic metastases.100 In six patients the indication for transplantation was pain due to hepatomegaly and in five patients symptoms due to excess hormone production. All patients initially obtained complete relief of symptoms. However, six patients developed tumour recurrence at a median of 11 months. Five patients had died, four from recurrent disease and one from chronic rejection. Four patients were alive with no evidence of disease recurrence. Overall actuarial survival was 82% at 1 year and 57% at 5 years. In this study, tumour recurrence for patients with carcinoid tumours was more frequent. The reasons for this were unclear. However, it was thought that this may have reflected the fact that transplantation was carried out later in the course of the disease process in carcinoid patients or due to differential effects of immunosuppression on tumour growth.

Dousset et al.79 reported their experience from Hôpital Cochin in Paris. They describe the results of OLT in nine cases. One patient underwent upper abdominal exenteration with liver replacement for a large pancreatic tumour. With this exception, all patients had previously undergone resection of the primary tumour. In this series, despite extensive preoperative imaging, extrahepatic tumour was found in four patients and this was resected. There were a total of five deaths related to transplant surgery. One patient died from primary nonfunction. Two patients died as a result of portal vein thrombosis and one patient died at day 7 from overwhelming septicaemia. A further patient died at 8 months from chronic rejection. Of the remaining patients, one patient died at 17 months as a result of bone and liver recurrence. Three patients were alive at 15, 24 and 62 months, but the longest survivor had developed bone and liver metastases. In some patients long-term palliation was achieved. However, clearly there was a high operative morbidity and mortality. Many patients considered for OLT will have undergone previous upper abdominal surgery or arterial embolization, adding to the technical difficulties of the procedure. The authors have recommended that transplantation should only be offered to patients with symptomatic disease that has failed to respond to all other therapies. In addition, they conclude that the finding of extrahepatic disease at
laparotomy should probably result in the abandoning of the transplant procedure.

More encouraging results have been reported from the Hanover group.\textsuperscript{101} In this series, 12 patients underwent OLT. There was one operative death. Two patients died from tumour recurrence, one at 6 months, the other at 5 years post-transplantation. Nine patients were alive with a median survival of 55 months. Four of these patients were disease-free 2, 57, 58 and 103 months post-transplantation. All patients experienced good symptomatic relief and postoperative hormone levels were within normal ranges.

The largest series of patients undergoing liver transplantation for the treatment of neuroendocrine hepatic metastases comes from France. Le Treut et al. have published the results of a multicentre review including all cases of OLT for metastatic neuroendocrine tumours performed in France between 1989 and 1994.\textsuperscript{102} The cases of Dousset et al. described above were included in this series. A total of 31 patients were treated by OLT. Six patients (19\%) died following surgery. Twelve patients subsequently died; four of these deaths were due to delayed technical or other non-tumour complications. All seven patients that had undergone upper abdominal exenteration died from immediate or delayed surgical complications. At the time of their publication, 13 patients were alive and in eight of these there was no evidence of recurrent disease. The overall actuarial 1- and 5-year survival was 58\% and 36\%, respectively. Disease-free survival was 45\% and 17\% at 1 and 5 years, respectively. However, the survival rate for carcinoid tumours was significantly higher with a 5-year survival rate of 69\%. This reflected a lower postoperative mortality for patients with carcinoid tumours and the fact that disease recurrence was more compatible with long-term survival. Overall survival figures are not dissimilar from the 25 to 35\% 5-year survival reported for non-transplant treatments.\textsuperscript{76,103,104} However, direct comparisons may be misleading, given that liver transplant is generally performed only when other therapies have become ineffective.

There is now a broad consensus regarding the indications and timing of liver transplantation for patients with neuroendocrine hepatic metastases. In general, the primary tumour should be removed before liver transplantation. This allows a full laparotomy to be performed and extrahepatic disease may be identified at this time. Patients with stable or controlled disease should be excluded. Inevitably some patients may present later with extrahepatic disease and then no longer be candidates for transplantation. However, transplantation continues to be associated with high surgical mortality and many patients can be maintained on medical therapy for a prolonged period of time. Finally, if extrahepatic disease is identified at the time of transplant, the procedure should probably be abandoned. Thus patients with symptomatic disease that have failed to respond to all other treatments may be considered candidates for hepatic transplantation. In selected patients transplantation offers good palliation and for a small proportion of patients there may be the possibility of cure.

\section*{Medical treatment}

\subsection*{Chemotherapy}

Chemotherapy has only a very limited role to play in the treatment of patients with neuroendocrine hepatic metastases. For patients with endocrine pancreatic tumours,
single agent chemotherapy generally has poor response rates of between 7 and 25%. The combination of streptozotocin and doxirubicin has been more effective, with tumour regression observed in up to 69% of patients. This was often associated with sustained regression with a median duration of regression of 18 months. When the same combination of chemotherapeutic drugs was applied to patients with carcinoid tumours, response rates were generally only 10–20% with only a very brief response. All patients suffered serious and severe side effects including nausea, vomiting, neutropaenia and cardiomyopathy. Given that many patients are relatively asymptomatic and the range of alternative therapies available, chemotherapy should not generally be recommended for patients with metastatic carcinoid tumours.

There may be a role for chemotherapy for the treatment of anaplastic neuroendocrine tumours. Moertel et al. have treated 18 patients with anaplastic neuroendocrine tumours using a combination of etoposide and cisplatin. An objective tumour response was observed in 12 of 18 patients (67%). The median duration of response was 8 months. Thus, the overall regression rate was similar to that observed for small cell lung cancer, although again severe side effects were observed.

Hepatic artery embolization has been combined with the administration of systemic chemotherapy. Moertel et al. found a response rate of 60% in 23 patients treated by embolization alone compared to 80% in 42 patients treated by hepatic artery embolization and sequential chemotherapy. The median duration of response with occlusion alone was 4 months, compared to 18 months with combined treatment. The median survival was 27 months with embolization compared to 49 months for patients treated with sequential chemotherapy. Although this was a non-randomized study, the results do suggest that there may be a role for chemotherapy when combined with other treatment modalities.

**Somatostatin analogues**

The somatostatin analogue octreotide is now widely used for the treatment of patients with carcinoid syndrome. Somatostatin inhibits the release of hormones from the tumour and also directly inhibits gastric, pancreatic and intestinal secretion. Somatostatin has a half-life of approximately 2 minutes and so is not suitable for clinical use. Octreotide has a half-life of approximately 2–3 hours when given by subcutaneous injection. Octreotide has been shown to be effective in the treatment of both carcinoid diarrhoea and flushing. Objective and symptomatic improvement occurs in over 70% of patients for a median duration of 12 months. Loss of therapeutic response eventually occurs and this is thought to be due to either downregulation of somatostatin receptors or the development of receptor-negative tumour clones. Doses of 50–200 µg usually allow symptomatic control, although higher doses may be required as treatment progresses. Octreotide is usually well tolerated. However, side effects do occur and these include diarrhoea, steatorrhea, flatulence, nausea, vomiting, impaired glucose tolerance and the development of gallstones. Octreotide therapy may also influence tumour growth. Evidence comes from the results of two prospective studies. In the first of these, 34 patients with carcinoid and pancreatic neuroendocrine metastases were shown to have progressive disease on the basis of CT scan. All patients were treated with octreotide. No objective tumour regression was observed. However, following repeat CT scans, 50% of
patients were found to have stable disease. The median duration of response was only 5 months.\textsuperscript{110} In a further study, 52 patients with progressive diseases were similarly treated with octreotide.\textsuperscript{111} Again no objective tumour regression was observed. However, 36% of patients showed stabilization of disease with a median duration of response of 18 months.

One of the main disadvantages of octreotide is the need for frequent subcutaneous injections. New long acting preparations are now available and are clinically effective.\textsuperscript{112} Lanreotide is a recently developed somatostatin analogue which also has a slow release formulation. It is administered as an intramuscular injection every 2 weeks. Lanreotide has been shown to be as effective as octreotide in controlling symptoms and it may also have some antitumour activity.\textsuperscript{113–115}

**Interferon**

Interferon was first used for the treatment of patients with neuroendocrine metastases in 1982. The mechanism of action of interferon is thought to involve cell cycle blocking in GO and G1 phase, induction of 2′-5′-A-synthetase and a reduction of mRNA for the synthesis of hormones and growth factors. In addition, alpha-interferon induces increased MHC class I expression of tumour cells together with a generalized upregulation of the immune system. The majority of experience comes from the endocrine oncology unit in Uppsala, Sweden.\textsuperscript{115} This group have treated over 350 patients with alpha-interferon. Of 111 patients with carcinoid tumours, a biochemical response was noted in 42% of patients, tumour size was reduced in 15% of patients and stabilization of tumour growth was seen in 39% of patients. The median duration of response was 34 months. Of 47 patients with metastatic endocrine pancreatic tumours, 51% of patients showed a biochemical response, 12% showed tumour reduction and disease stabilization was observed in 24.5% of patients. The median duration of response was 20 months. The main side effects of interferon are flu-like symptoms such as myalgia, fever and fatigue.

**Receptor targeted therapy**

The uptake of\textsuperscript{111}In-labelled octreotide and\textsuperscript{123}Ilabelled MIBG for scintographic scanning has led to the development of receptor targeted therapy. Carcinoid tumours have shown a biochemical response and reduction in size following treatment with repeated high dose \textsuperscript{111}In-octreotide.\textsuperscript{116} Similar results have been achieved with \textsuperscript{123}I MIBG.\textsuperscript{68,69,117} The choice of agent may be guided by uptake at diagnostic imaging. These therapies appear highly specific, are tolerated with minimal side effects and patients are able to undergo repeated treatments, followed by further scanning. The development of these therapies is likely to hold significant promise for the treatment of patients with disseminated neuroendocrine metastases.\textsuperscript{118}

**Summary**

There are an increasing number of diagnostic procedures and therapeutic options
available for the management of patients with neuroendocrine metastases. At present, all patients should be considered for liver resection. However, only a relatively small proportion of patients will be suitable for resectional surgery. Hepatic arterial embolization or hepatic cryotherapy should then be considered. Liver transplant should be considered for patients with progressive symptomatic disease confined to the liver when all other treatment options have failed.

Accurate staging is of critical importance when considering patients for any form of surgical intervention. Octreotide receptor scintography is therefore likely to have a major impact on the management of these patients. For patients with disseminated disease, chemotherapy has relatively little role to play. Symptomatic patients may benefit from octreotide therapy; however, receptor targeted therapies are likely to hold promise for the future.

Patients with neuroendocrine tumours are rare and the experience of individual centres is therefore limited. Randomized trials will be required to define more clearly the role of each of the above treatment modalities and the role of multimodality therapies. Given the long natural history of the disease, such trials are likely to require large numbers of patients. Optimum therapy will require a multidisciplinary team approach involving a physician, an oncologist, an interventional radiologist, a nuclear medicine physician and a surgeon. All patients with neuroendocrine metastases should therefore be cared for in centres of expertise and every effort should be made to enter patients into nationally or internationally co-ordinated clinical trials.

Key points

- **Diagnostic imaging includes:**
  - Ultrasound
  - CT (± arterio portography)
  - MRI
  - Radiolabelled octreotide scintography
  - MIBG scintography.

- **Surgical strategies include:**
  - Resection
  - In situ ablation
  - Liver transplantation.

- **Non-surgical strategies include:**
  - Hepatic arterial embolization
  - Symptom control with octreotide
  - Therapeutic radionucleotide-MIBG ablation
  - Therapeutic radionucleotide-octreotide ablation.

- **Non-proven or therapies of little benefit:**
  - Hepatic artery surgical ligation
  - Cytotoxic chemotherapy
  - Interferon.
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Diagnosis and management of haemangiomas of the liver

Enrique Moreno Gonzalez, JC Meneu Diaz and A Moreno

Introduction

The first description of the morphology of a hepatic haemangioma was made by Amboise Paré in 1570, and nearly 300 years later it was fully characterized by Frerich.2

Haemangiomas are the most frequently found benign tumours in the liver,3–16 and these are usually congenital.17

Over the last decade there has been growing interest in an understanding of the aetiological and epidemiological factors involved in the development of haemangiomas, as well as those factors which have an influence on their growth.18 Due to progressively better knowledge of surgical techniques for resecting solid hepatic tumours, indications for surgical excision have increased, thus reducing options for conservative therapy. However, until 1963 there were only 80 reports of resection of hepatic haemangiomas in the medical literature.6 More recently, minimally invasive surgical procedures have spurred interest in more patient acceptable types of treatment. Similarly, non-surgical techniques have gained protagonists due to their simplicity, although their effect is often short-lived combined with a high number of tumour relapses that then ensue.

Presentation

Haemangiomas are one of the most frequently observed lesions found in autopsy studies, appearing on average in 0.7% to 7.3% of cases,19,20 with an overall average of 3.3% out of 50 000 autopsies.21,22 In 1910, Adami23 observed 20 cases in a total of 1400 autopsies (1.4%).

Unsuspected haemangiomas which have been identified during surgery undertaken for other conditions constitute from 0.30% to 3% of cases. However, this incidence depends on the age and sex of those groups studied. For example, Moreaux,22 reporting on 3800 cholecystectomies found the proportion to be 0.23%. However, by the fifth decade the female/male ratio, initially 4:1, rises to 9:1.4,11,24 If we disregard age, and consider women only, the percentage is 4%. Between 2%22 and 10% of haemangiomas are multiple.20

Haemangiomas present most often between the third and sixth decade of life, with a predominance in the fourth decade. Without doubt, this condition is more frequent in women than in men (ratio 4:1–6:1),24 and the main reason for this finding is female
hormone activity, which explains the increase in size of haemangiomas seen during pregnancy. Furthermore, there is a greater incidence of intratumoural haemorrhage or tumour rupture with haemorrhage in the free abdominal cavity during pregnancy, and when there is increased hormonal activity during the menstrual cycle, an increase in tumour diameter has been observed at this time.

The relationship between hormonal activity and changes in the development of haemangiomas has been shown after the administration of oestrogens and progestogens. This influence was observed not only on tumour growth, but also with the link to tumour relapse after surgical excision. In spite of all the above, there is still a great deal of scepticism about the role of hormonal effects on morphological changes in these tumours.

Another explanation for volumetric changes in these tumours is related to changes in arterial flow and greater vascular stasis in the capillary bed of haemangiomas, which could also be related to physiological, cyclical hormonal activity in women, or new states of greater hormonal activity such as pregnancy. In any case, it is not scientifically proven that organs which may change vascular flow—or in which this may be altered—change diameter during these two stages in female physiology.

**Pathological anatomy: macroscopic and morphological features**

Generally, haemangiomas are tumours with a red wine colouring which are elevated on the hepatic capsule. They have a shiny, smooth but irregular surface which, when large in diameter, has a lobulated appearance. Clearly delineated on the adjacent hepatic surface, from which they are separated, they are contained within their own capsule. They become depressed and reduce their size on manual compression, recovering their appearance and diameter when this pressure is removed.

Haemangiomas may measure in size from a few millimetres up to several centimetres, and are generally single, less frequently multiple, and are distributed in random manner. Where multiple tumours are seen they are most often bilobar. Large haemangiomas are located most often on the right hepatic lobe, often concomitantly with others of smaller diameter in the contralateral lobe. Nevertheless, the presentation of large haemangiomas in both lobes is not exceptional. The definition of giant haemangioma is accepted when the tumour diameter reaches 10 cm. Nevertheless, haemangiomas of more than 30 cm have been observed which occupy up to half the abdomen, displacing other intra-abdominal viscera towards the opposite side. The weight of these haemangiomas varies widely, with one haemangioma of 18.16 kg having been described, and frequently weighing 5 to 6 kg. Even in cases of large tumours, diagnosis is, or may be, quite fortuitous.

On cross-section, the tumour has a fibrous capsule and septae which produce a lobulated appearance on the cut surface. In small tumours the appearance is homogeneous and the consistency firm, with greater elasticity than the normal surrounding hepatic parenchyma. Large haemangiomas have a recognizable conjunctive central vascular pedicle.

On the cut surface, giant haemangiomas frequently have areas of intense fibrosis which
are hard in consistency and which may represent evolution towards cicatrization or the substitution of extensive areas of intratumoural infarct.

Similarly, giant haemangiomas may be found to contain a cavity, which is generally single, clearly delineated by a fibrous surface, and filled by a transparent fluid of low density which is odourless and sterile. The presence of this cavity is generally explained by the transformation of areas of extensive intratumoural haemorrhage which later involute towards liquefaction and breakdown of accumulated blood.

Microscopic examination of these tumours generally reveals vascular spaces in the form of large capillary lakes which form a confluence at their centre point and are lined with flat endothelial cells. In the septa, formed by the joining of the fibrous surfaces, vascular structures in the form of blood vessels can be identified. Biliary canals which do not show any morphological or microscopic anomaly can also be observed. Most often these walls are thick, less frequently revealing myxoid structures.

From the microscopic and ultrastructural point of view, large haemangiomas possess cavernous loculi which have given rise to the name of ‘cavernous’ lobules. Other haemangiomas, generally smaller in size, have the typical characteristics of simple haemangiomas.

The association between hepatic and cutaneous haemangiomas and those found in other visceral locations, either hollow organ (oesophagus, stomach, jejunum-ileum, colon and rectum) or solid organ (spleen, kidney, brain) is not unusual, forming part of specific syndromes such as the Kasabah–Merrit syndrome. These are generally identified early in life and are exceptional in adults. Another specific hereditary syndrome is the Osler-Weber-Rendu syndrome, in which the association of hepatic haemangiomas with angiomatous multiple telangiectases define this syndrome. In addition, an association has been identified between hepatic or pancreatic cysts and other benign tumours, mainly adenomas, particularly after use of the oral contraceptive. An association with endometriosis has also been identified.

Evolution

Haemangiomas generally tend to grow slowly and progressively, in an irregular way, perhaps subject to the influence of hormonal steroids or to changes in blood flow. It is not possible, however, to explain the exceptional cases of spontaneous regression which have been documented.

Due to the high risk factor, there is much interest in the possibility of surface rupture of the haemangioma, reported in 19.7% cases, which may cause severe intra-abdominal haemorrhage. This complication is less frequently spontaneous (2–6%), mainly post-traumatic or iatrogenic, and in this case may be caused by attempted diagnosis using FNA (fine needle aspiration).

Isolated descriptions of spontaneous tumour rupture have related this to administration of oestrogens or progestogen. However, although this association is accepted in hepatic adenoma, at the present time there is an on-going debate with some authors rejecting the concept of evolution of haemangiomas being related to hormonal and steroid action drugs. In any event, spontaneous rupture is relatively frequent (5%), 28 cases having
been published by Yamamoto et al.\(^5\)

Traumatic rupture—generally in traffic accidents—is also rare, although it is more common than the spontaneous variety. Nevertheless, it should be remembered that the accentuated elasticity of the tumour parenchyma makes it more resistant to contusions than the liver tissue which surrounds it.

Puncture biopsy does, indeed, present a major risk of intratumoural and intra-abdominal haemorrhage, especially when the capsule is ruptured for some distance during puncture. For this reason, given the radiological suspicion of haemangioma, histological examination is contraindicated as it often produces a significant number of false negatives or positives due to the extraction of just fibrous tissue and cellular blood, without offering any other more characteristic histology.\(^5\)

In general, the importance of rupture of a haemangioma is not in the frequency of its occurrence (historically 1.8\%).\(^1\) At present, the frequency of rupture is accepted as being between 3% and 4%. More importantly, rupture is associated with an average mortality rate of 50%, which is higher in spontaneous cases and those which are secondary to abdominal trauma (86%) than after puncture biopsy (47%),\(^6\) or biopsy due to excision.\(^1\)

Tumour recurrence is not frequent, but has been documented.\(^2\) The most frequent cause is incomplete excision of the haemangioma, which occurs after inadequate enucleation or tumour excision when the plane corresponding to the tumour surface is used to facilitate excision. This explains why it is exceptional after anatomical hepatic resection, in which a resection margin of over 15 to 20 mm is always obtained. In these cases it is accepted that further haemangiomas appear as a result of the increase in size of others of smaller diameter which had gone unnoticed during surgery. In any case, in order to avoid tumour recurrence after excision of a haemangioma, the surgeon should ensure that resection is complete, examining both the tumour surface and the surface corresponding to the adjacent hepatic bed, extending resection of hepatic tissue to its anatomical limits and removing small remaining haemangiomas, or others of larger size, in spite of their location on the contralateral hepatic lobe.\(^1\)\(^4\)\(^6\)

The relationship of recurrence to administration of oestrogens or progestogens has been documented, especially in the case of tumour relapse or growth of small unapparent haemangiomas.\(^1\)\(^8\)

In giant cavernous haemangiomas, their histological characteristics, and tendency to extensive growth have led to thoughts about possible malignant transformation.\(^1\) Nevertheless, of the three patients with possible malignant transformation identified,\(^5\) none of these was there prior histological diagnosis of haemangioma, the subsequent diagnoses being haemangioendothelioma, haemangioendothelio-sarcoma and haemangiosarcoma, respectively. Logically, malignant transformation of haemangiomas cannot be accepted, as there is no evidence of this development elsewhere.\(^5\)

**Clinical practice**

Most haemangiomas evolve silently with no clinical symptoms, even when they eventually acquire such a large volume that they occupy 60 to 70% of the abdominal
cavity. Indeterminate symptoms are related to the finding of a haemangioma, but frequently they have nothing to do with the existence of the tumour, so that these symptoms remain even after excision. Less frequently, patients from whom large haemangiomas have been removed may sometimes admit to improved symptoms and which are more closely related to the reduction of gastric capacity, gastro-duodenal emptying, intestinal transition, bowel habit, capsular adherence to the diaphragm or parietal peritoneum.

More often than not, haemangiomas are diagnosed by chance. This may occur during abdominal palpation during an examination for no specific reason, as can happen in the case of giant haemangiomas which occupy a large part of the right hemiabdomen. Currently transabdominal ultrasound frequently detects small and middle-sized haemangiomas which had not previously produced any conditions, such as gynaecological disease, or in the search for secondary hepatic lesions. They may also be detected during investigation of other intestinal diseases (gastric tumours, diverticulosis, alterations in bowel habit), and have even been seen during the work-up of prostatism when pelvic ultrasound extends to the abdominal cavity. A hepatic haemangioma has even been diagnosed in a foetus before birth.

Pain is usually the main symptom, and this is probably due to these factors: changes produced during growth, adherence of the tumour surface to the diaphragmatic or parietoabdominal peritoneum and intratumoural haemorrhage due to rupture of vascular elements, which then gives rise to capsular distension. Another factor which may cause tumour increase is the action of hormones, in particular steroids. Increase in tumour size is generally rapid in these cases, sometimes intermittent, with regression noted during menstruation. Less frequently, pain is related to compression of adjacent viscera.

It is generally accepted that pain is the presenting symptom in 28% of patients, beginning in the epigastrium and right hypochondrium, extending to the ipsilateral iliac fossa or radiating to all abdominal quadrants in a diffuse manner.

Whether or not there are referred symptoms, during physical examination an enlargement of the hepatic lobules, or an overall increase in liver size, may be noted. Generally there is a smooth regular hepatomegaly, of soft consistency, with loss of the liver edge which is replaced by the tumour surface.

Not exceptionally in these large size haemangiomas audible murmurs may be heard on the abdominal wall overlying the tumour surface, and, on occasions a thrill may be palpated. More unusual is the appearance of collateral circulation (portacaval) over ipsilateral hemiabdomen. This may appear at any stage, which further complicates the clinical differential diagnosis.

There are a number of differential characteristics of complications which may arise during the development of haemangiomas. Tumour rupture in the abdominal cavity generally occurs spontaneously with no background history, presenting with extremely severe pain at right hypochondrium and with shoulder tip pain due to phrenic irritation and haemodynamic instability. Intratumoural rupture may produce fever and respiratory disorders due to ipsilateral pleural effusion.

Haemobilia has been described as a complication of tumour haemorrhage. Although very infrequent, its possible existence should be borne in mind due to the seriousness of its presentation which gives rise to right upper quadrant pain with jaundice and is
accompanied by melaena but no associated splenomegaly or portal hypertension.

Jaundice may also appear without tumour rupture, due to compression of the extrahepatic bile duct or tumour confluence as a result of the growth of tumours located within the central liver. Nevertheless, due to the adaptation of adjacent structures which the haemangioma compresses during its slow growth, this presentation is exceptional.

Severe fever may appear in cases of extensive tumour thrombosis, or as a consequence of largescale infarcts, followed by liquefication of extravasated blood, and the cavity may become infected in exceptional cases.72

Cavernous haemangiomas represent massive arteriovenous fistulae. This is demonstrated by the observation of the large diameter of the hepatic artery itself, and its branches which supply the tumour, or the segmental or named hepatic vein draining the tumour, as well as the significant increase in blood flow through the tumour. Nevertheless, only isolated, exceptional cases of heart failure, or aneurysmal dilatation of the draining veins, or retrohepatic vena cava have been described, in spite of frequent evidence of intense intratumoural arteriovenous shunting.

Of lesser importance is the association of joint pain due to rheumatoid arthritis in patients with hepatic haemangiomas treated with azathioprine.73

Laboratory investigations

Generally, laboratory investigations do not contribute much which could be of diagnostic assistance, or, more particularly, contribute to a differential diagnosis. It has been observed that anaemia is frequent, but only occurs in intratumoural bleeding.70 Similarly, in spite of the extraordinary size of hepatic haemangiomas, the biochemical liver function tests are always normal, as well as serum tumour markers.10,31,35,74,75

More frequently, especially in large hemangiomata, alterations in blood coagulation have been reported. Generally this is a consumption-based coagulopathy, the most evident example of which is the Kasabach-Meritt syndrome, in which thrombocytopenia prevails. This appears more frequently in giant haemangiomas as a result of platelet sequestration. It should be said, however, that no haematological alterations of any type are normally shown.45,46,60,76

Radiological diagnosis

Simple radiography

Plain abdominal radiography may show elevation of the right hemidiaphragm related to the overall increase in liver size. This is due to the displacement caused when the tumour is located in the upper level of the right hepatic lobe, or of upper middle segments. In addition, displacement of adjacent hollow viscera, the stomach, the hepatic angle of the transverse or ascending colon may also be observed. Similarly, but more difficult to detect due to their small size, phleboliths may be evident in the form of rounded calcifications which are sometimes arranged in line, following a vascular pathway, but
with no anatomical reference. These are characterized by their very small size.

More frequently calcifications can be seen which adopt the form of a central mass, large in size, and surrounded by satellite microcalcifications, which may take on the form of a crown or a radial arrangement. Calcification is present in 6 to 10% of cases and is interpreted as calcium deposit at the level of the septae, corresponding to the walls used by the arterial branches for their intratumoural arteriocapillary distribution.4,10,22,60,66,77

Perhaps the diagnostic sign of greatest importance in giant haemangioma is the existence of a large soft tissue shadow, which displaces the air pattern of adjacent hollow viscera towards a non-anatomical position.

Ultrasound

The first examination which should be undertaken is abdominal ultrasound. This will show an overall increase in liver size, and the existence of one or several tumours within. In the case of small haemangiomas the distinct margin is of great importance with regard to adjacent hepatic parenchyma, as well as their homogeneous character. In giant haemangiomas tumour heterogeneity may be noted due to the existence of septae, fibrosis, intratumoural cavitation and possible evidence of fluid content in the interior of the cavities.61,78

Haemangiomas are often homogeneous, observed as a well-defined hyperechoic mass in 77–92% of cases.79 In almost 80% posterior acoustic highlighting can be seen,39 present in lesions of 25 mm upwards. Due to their increase in size, more than 80% of haemangiomas maintain their ultrasound characteristics, the most specific characteristic being progressive increase in size.7,60,79

Nevertheless, occasionally a central hypoechoic nucleus may be observed, though with no hypoechoic halo on the tumour periphery. Atypically, hypoechogenicity may extend to the whole of the tumour mass, if this is homogeneous, then it is surrounded by intense fatty deposits in the surrounding hepatic parenchyma.

In any case, ultrasound is an important method of diagnosis, and will help to differentiate haemangiomas from primary and secondary tumours, especially when the tumour mass may be compressed by the ultrasound probe. The haemangioma becomes increasingly isoechogenic with this procedure, as echogenicity decreases due to compression of the cavernous sinuses. Such changes cannot be observed in solid malignant tumours.41,62,78

Abdominal CT scan

This is not the most appropriate study for diagnosis of haemangiomas; however, this is a method which can go hand in hand with ultrasound, so its indication is not controversial62 (Figs 10.1 and 10.2).
**Figure 10.1 (A)** CT scan. Large haemangioma localized in the right lobe of the liver. Central areas of connective tissue can be seen.

**Figure 10.1(B)** Large hypervascular mass in the right lobe of the liver. Homogeneous contrast distribution in all the haemangioma tissue is shown.

**Figure 10.2** Bilateral haemangioma. CT scan. Large mass in the right lobe of the liver also occupying segment IV of the left. Small mass in the left lobe of the liver, posterior part of segment II and III. In the right lobe needle biopsy is being performed.
Four rigorous diagnostic criteria have been described in between 50 and 55% of haemangiomas studied: 38 (1) relative hypoattenuation in comparison with the hepatic parenchyma which surrounds the lesion before administering contrast; (2) perilesional increase in contrast in the early phase; (3) progressive opacification from the periphery to the centre of the lesion, and (4) isoattenuation, which occurs between 3 and 60 minutes after administration of intravenous contrast. 80 Nevertheless, hypoattenuation is frequently seen. These findings depend, as in the case of ultrasound, on the degree of fatty infiltration within the peritumour hepatic parenchyma, as the existence of diffuse steatosis may give rise to images of isoattenuation or hypoattenuation before administration of intravenous contrast, 8,81 which is of special importance in dynamic CT. 82

From the morphological point of view, haemangiomas are clearly delineated tumours which show their richness of intratumoural capillaries after administration of contrast. After several minutes, the contrast is seen generally to be located peripherally, with either larger or smaller stellar images in the centre of the tumour, which represents the central axis of the lesion where actual walls or septa may be seen. This central portion markedly alters the level of attenuation where cavitated areas usually exist. In general, large haemangiomas can be diagnosed using an abdominal CT scan, which gives 70% sensitivity and a specificity of 65% to 75%.

**MR imaging**

This very safe test provides higher resolution than abdominal CT scans. 83 From the morphological point of view, haemangiomas are spherical in 90% of cases, much less frequently ovoid, and clearly delineated from the proximal hepatic parenchyma by well-defined edges which represent the fibrous capsular sheath. MR imaging gives 90% sensitivity, 95% specificity and 93% accuracy. 84,85

Haemangiomas show marked hyperintensity during T₂ imaging (light-bulb sign). The imaging of greatest use for diagnosis is obtained using multiecho techniques (ET: 120 milliseconds). Nevertheless, light-bulb sign specificity is not 100%, as it may be present in any hypervascular lesion, such as adenoma, hepatocellular carcinoma and endocrine tumour metastasis. The greatest use of this technique is in a differential diagnosis between haemangioma and primary hepatic tumours, especially hepatoma, as these tumours are heterogeneous in 70% of cases. 86 A low intensity signal is observed at the level of the tumour capsule in more than half of examinations, which, in contrast, is not seen in haemangiomas. In addition, in hepatoma the signal during T₂ is less prolonged.

Giant haemangiomas are most often heterogeneous in images obtained during both T₁ and T₂ imaging. In almost all cases, images appear to be similar to septae, in the form of low intensity areas during T₁, with a high intensity signal during T₂. Septal areas were identified in more than 50% of cases as a low intensity signal during both T₁ and T₂. 87

Due to the largely vascular composition, administration of contrast provides greater possibilities for diagnosis of haemangiomas. Intravenous bolus administration of gadolinium (gadopentate dimeglumine; diethylene triaminepentacetic acid) is used with a dynamic gradient of echosequences which show peritumour reinforcement after 2 minutes, which persists in late images in a similar way to that which occurs after
administration of contrast in abdominal CT scan.\textsuperscript{38,87}

**Gamma camera imaging after administration of Tc99m-labelled red blood cells (SPECT: single photon emission CT)**

At present, conventional gamma camera imaging with Tc99m-labelled red blood cells is being indicated less, due to the fact that there is no great difference in its results when compared with hepatic magnetic resonance imaging. Moreover, MRI has shown greater sensitivity, detecting lesions of less than 2 cm in diameter. It is true, however, that SPECT, in contrast, has greater specificity and predictive value than MRI, as this is practically 100\%.\textsuperscript{84} In the case of haemangiomas this is more valuable than the detection of small diameter

![Image](image.png)

**Figure 10.3** Hepatic gammagraphy performed 60 minutes after injection of autologous blood red cells labelled ‘in vitro’ with PYP\textsuperscript{99m}Tc.
Radiological (A,B) and tomographic/SPECT (C,D) imaging. In a different projection (A,B) a focus of enlargement of the vascular pool in the right hepatic lobe is observed, anterolateral, typical of angioma and a smaller one, previously located (more anterior), suspicious of another similar lesion. Tomographic imaging (C,D) showing two angiomas.

lesions, as the latter are benign lesions which would remain under observation only, once a correct diagnosis has been confirmed. Less specificity is shown in cirrhotics with portal hypertension (Fig. 10.3).

Gamma camera examination (SPECT) has 90% sensitivity, 100% specificity and precision close to 100%, which provides a higher safety level in the diagnosis of haemangiomas. In these tumours a decrease in activity and an accumulation of labelled red cells is shown immediately after perfusion, with this activity increasing to its maximum in later images. Other very highly vascularized tumours such as adenomas and focal nodular hyperplasia also, show progressive accumulation of labelled red cells. Nevertheless, the difference between these and haemangiomas is that in the latter case, the increase in activity is shown at the earliest stages.

In most giant haemangiomas (65–70%), a significant increase in perfusion can be seen in dynamic imaging. Nevertheless, in a not insignificant percentage (20–25%) this hyperperfusion is seen only in the most peripheral part of haemangiomas, the central part appearing hypoperfused, perhaps as a consequence of less capillary richness in the central portion of the lesion or the existence of extensive areas of fibrosis or cavitation. False positives also occur.

A great difference between conventional gamma camera imaging and single photon emission CT has been demonstrated, particularly as regards sensitivity, as lesions of around 3 cm in diameter may be detected with the latter technique.

**Vascular examination**

Arteriography shows the intense and extensive uptake of contrast within the tumour parenchyma, persisting in the interior of the lesion much longer than in the surrounding parenchyma. The distribution of contrast is uniform in giant cavernous haemangiomas, provided that there has been no fibrosis or cavitation in its interior. There is no evidence of particular vascular activity within the tumour capsule. Consequently, the periphery of the lesion is less easily appreciated (Figs 10.4–10.6).

Specific characteristics of haemangiomas are displacement of the intratumoural vascular trunks towards the peripheral areas of the tumour, as well as the thick diameter of the feeding branches of the hepatic artery and changes in the anatomical position of arterial and venous trunks which are displaced by tumour growth.

In multiple haemangiomas even lesions of a few centimetres may be demonstrated. In this situation all lesions within the liver will have similar characteristics, regardless of which lobule they are located in.

One of the advantages of visceral angiography is access for embolization of the arterial branches feeding the tumour, especially in the case of haemangioma. However, this procedure may be ineffective, even in cases when it has been undertaken prior to surgical excision. However, embolization has a role in the management of haemangioma.
Exceptional cases have been published on the use of embolization in the treatment of spontaneous rupture of the tumour or intratumoural haemorrhage.

Figure 10.4 Arterial splenoportography. Venous face of splenic arteriography. Very wide splenic vein. Hypervascular large mass is localized in the left lobe of the liver, producing reduction of right lobe.

Figure 10.5 Angiographic examination of large right lobe haemangioma. (A) sma: superior mesenteric artery, displaced to the left side, smv: superior mesenteric vein, displaced by the tumour mass to the midline (B) Venous phase of splenic arteriography, sa: splenic artery, sv: splenic vein. Both vessels are displaced to the left side by the tumour mass. (C) Igv: left gastric vein, rha: right hepatic artery, ca: celiac trunk. Celiac trunk and its branches are displaced to the left side about 7 cm. (D) Capillary phase hepatic arteriography, na: limits of the internal surface of the large haemangioma localized in the right lobe of the liver.
At present there are few indications for angiographic examination in this disease, which, in our opinion also goes for laparoscopy, first due to the fact that there is little gained from this procedure and, second, because angiography is being substituted by MRI, which is much more innocuous. Less important, but also less aggressive, are Doppler, colour Doppler, scintigraphy and renoscintigraphy.

Figure 10.6 (A) Large haemangioma localized in the right lobe of the liver following resection. Branches of hepatic artery (ha) and portal vein surround the surface of the haemangioma. The gallbladder can be seen on the lower part of the tumoural surface. (B) SV, splenic vein. Aspect of the right lobe of the liver after resection of a large haemangioma.

Percutaneous biopsy

In general, in hepatic tumours, percutaneous biopsy can only be indicated when there are difficulties in establishing a differential diagnosis between primary or secondary malignant tumours; i.e. this will never be established as a routine or necessary diagnostic test to confirm clinical and/or radiological diagnosis, although several groups consider percutaneous cytology very helpful.

First, if undertaken, histological diagnosis of the tumour will alter or establish the correct course of treatment, as, if it is not going to influence the final decision, it should never be indicated. Moreover, one should carefully consider all possible complications which this test may cause, such as tumour rupture, intratumoural haemorrhage either in the abdominal cavity or in the case of a malignant lesion, tumour spread along the path followed by the needle during extraction across the abdominal cavity (exceptional) or in the abdominal wall.

In general, interpretation of material extracted by fine needle aspiration is not easy. In the case of haemangiomias, diagnosis is generally reached by exclusion, as the sample extracted shows only red cells and fibrosis, often making several more attempts at puncture essential to ensure the correct histological diagnosis, with the corresponding risk of haemorrhage.

Finally, we should be aware of the possibility, already described, of rupture—especially in the case of giant haemangiomia with a very fine capsule, most often as a consequence of repeated puncturing, but also due to tumour fragility or subcapsular...
haemorrhage. We are not in favour of biopsy puncture, except in a few very specific exceptional cases. Diagnosis, in most cases, can be undertaken by morphological tests which are less invasive, both in the case of haemangiomas and in the other types of benign or primary or secondary malignant tumours.

Surgical treatment

Indications

Although it was initially considered necessary to excise these tumours regardless of their diameter or location at the present time there are selective criteria which are sufficiently robust to avoid unnecessary operations. These operations do not incur any benefit for most patients, and may, indeed, involve unnecessary risk—however small this may appear—or unjustified morbidity. There is also the possibility of greater complications to which the patient should not be exposed. No matter how expert the team of surgeons may be in liver surgery, there can be no argument for the treatment of patients without absolute indications for surgery.

It is accepted that small size haemangiomas (2 to 4 cm) diagnosed by chance should not be removed, but should merely undergo periodic review in order to gain a more adequate knowledge of their behaviour and thus act accordingly. Nevertheless, it is essential to be absolutely certain of their nature, with no doubt whatsoever as to whether they are benign or not, and to their histological diagnosis. Haemangiomas detected during the followup of a patient who has undergone removal of a malignant tumour of another abdominal organ, especially colon or rectum, may be candidates for surgical treatment when the liver lesion is not clearly characterized and elevation of a specific tumour marker (CEA) is detected.

Previous history, lack of morphological identification or negative cytology following puncture aspiration (although infrequent, if indicated at all), must be factors when considering any eventual surgical treatment.

There may be doubt in the case of small size haemangiomas detected in the course of a surgical operation undertaken for another reason. If a possible haemangioma is detected, located on the liver edge or on its surface in an easily accessible area due to the type of incision made, excision is justified. However, if the appearance of the lesion leaves no doubt about the diagnosis of haemangioma, it could be left alone, with a description in the operative note, along with the reasons for not removing the lesion. We believe that such haemangiomas should be excised, as a removal in our hands does not increase the risk of the operation. It is clear that incision biopsy of the tumour should not be undertaken, as the risk of haemorrhage, even in small lesions, is very high.

Currently, accepted indications for surgical treatment of haemangiomas are as follows: (1) tumours of diameter over 6 cm, (2) haemangiomas causing episodes of pain of great intensity in the area of the tumour which occur spontaneously and which can be correlated with intratumoural bleeding, (3) giant tumours which cause symptoms by reducing the capacity of the abdominal cavity, (4) hypotension and inexplicable anaemia, which sometimes may coincide with an increase in the size of a hepatic lobule, signs
which may be secondary to intratumoural rupture with capsular distension and (5) tumours which are difficult to diagnose, with a well-documented suspicion of malignancy, and which, even after inconclusive aspiration cytology, due to their diameter (5 to 7 cm) cannot be left without any treatment.^{32,102,106}

At present it seems difficult to be able to justify surgical treatment for large asymptomatic haemangiomas,^{24,107} first because it is not known how long it has taken to reach this size and, second, because most asymptomatic giant haemangiomas do not give rise to any special symptoms. Moreover, they do not produce complications and spontaneous rupture is exceptional, as is traumatic rupture.^{14,36,108} Special care should be taken in childhood when indications for surgical treatment are exceptional.^{109}

**Preoperative tumour embolization**

As previously stated, embolization will reduce tumour mass, as well as its arterial input, making any surgical operation easier by reducing blood loss and demarcating the border between the tumour capsule and the underlying liver parenchyma.

Nevertheless, embolization of these tumours has a short-lived effect.^{18} Arterial flow is quickly re-established by other routes, and the tumour rapidly recovers its original morphology and size.^{12,53,70,93,109} In spite of this, preoperative embolization has nevertheless been indicated in giant haemangiomas^{95} to facilitate surgical manoeuvres.

It should be remembered that large haemangiomas which consequently have a very intense arterioportal flow are difficult to embolize. This is the main contraindication for embolization. Our experience of this technique is minimal, and reports from other authors do not back up this practice. In addition, there is the additional risk of vascular occlusion progressing back along the arterial branches corresponding to the adjacent segments or contralateral hepatic lobule.

**Surgical excision**

At the present time the accepted procedure is tumour resection or enucleation,^{99} as it is not necessary to include any resection margin of healthy liver tissue to avoid tumour recurrence. The margin between hepatic haemangiomas and healthy hepatic tissue is minimal, with no infiltration or satellite nodules which would justify the inclusion of a healthy margin of tissue covering the resected tumour to ensure greater safety.^{110} This criterion is accepted equally for small surface haemangiomas or those on the anterior edge of the liver if, despite their small diameter, excision is indicated.

Anatomical resections (segmentectomies, lobectomies and extended lobectomies) \(^3,111,112\) are only indicated in exceptional cases of unilobular multiple hepatic haemangiomas, or those confined to several segments in which multiple tumourectomy would leave areas of the hepatic parenchyma poorly vascularized with the danger of biliary leaks, increasing postoperative morbidity and hindering the process of liver regeneration.\(^35,40,76\)

Total hepatectomy and liver replacement by orthotopic homotransplant is not indicated in hepatic haemangiomas in spite of their frequent occurrence.\(^113\) Nevertheless, in exceptional cases which may markedly affect liver function, or give rise to serious
haemodynamic alterations as a consequence of the presence of innumerable arteriovenous fistulae, liver transplant may be absolutely necessary as well as urgent. Perhaps the best example is the Kasabach-Merritt syndrome,\textsuperscript{45,46} provided that there are no multiple cerebral haemangiomas which are generally incompatible with survival. In our experience in 625 hepatic transplants undertaken between April 1986 and September 1998, we have seen two cases, although in the case of an adult patient the histopathological diagnosis was a haemangioendothelioma, whereas in the case of a baby girl with Kasabach-Merritt syndrome, the patient was a 39-day-old neonate weighing 2.2 kg, born after a 24 week pregnancy. While still in the incubator, she underwent surgery on the twenty-first day after birth because of a patent ductus. At the preagonal phase,

![Liver with multiple haemangiomas (Kasabach-Merrit syndrome).](image)

Figure 10.7 Liver with multiple haemangiomas (Kasabach-Merrit syndrome).

The liver was removed and replaced by total graft in a premature baby, after a 24-week pregnancy, at 2.2 kg birth weight.

she became haemodynamically unstable, and required liver transplantation. As can be seen in Fig. 10.7, the hepatic parenchyma is replaced by multiple haemangiomas of differing diameters.

Nevertheless, the indication for hepatic transplantation in the Kasabach-Merritt syndrome is dubious, as haemangiomas tend to disappear or lead to thrombosis and resolution, as happens in cutaneous haemangiomas. For this reason, it is only indicated in particularly acute situations in order to save the patient’s life. The existence of a giant haemangioma, in this syndrome could in exceptional circumstances indicate a liver transplantation.\textsuperscript{46}

In cases of diagnostic doubt, excision could be extended to obtain a sufficient resection margin. Biopsy by excision in these cases is advisable but not compulsory, especially given the complications this produces.\textsuperscript{14,17}

**Surgical excision technique**

**Incision**

Surgical incision should always be abdominal, with right subcostal laparotomy being
favoured, extended laterally under the tenth rib, in order to extirpate the cartilage and medial end of the rib (respecting the perichondral sheath and periosteum which will allow osteocartilaginous regeneration) in bulky haemangiomas which occupy the hepatic dome, sometimes with firm adhesions to the diaphragm surface, and which may be intensely vascularized (Figs 10.8 and 10.9).

In cavernous haemangiomas located on the left hepatic lobule, the most commonly accepted incision is an upper midline extended inferiorly to improve access. These tumours are large in diameter and impossible to resect through a smaller incision (Figs 10.10–10.12).

Bilateral subcostal incision is necessary in giant haemangiomas which affect central segments of the liver (IV, V, VIII). Thoracoabdominal incisions (thoracophrenolaparotomy) are not indicated. Between 10 and 20 years ago, Japanese surgeons were keen on the use of thoracolaparotomy during transplantation of hepatomas, however this incision has now fallen into disuse, and is only used in exceptional cases (Fig. 10.11A,B).

![Figure 10.8](image-url) (A) CT scan showing large haemangioma localized in the right lobe of the liver. (B) Same patient after resection of the right lobe haemangioma; the surface of the normal liver and retrohepatic vena cava can be seen. (C) Haemangioma of 32 cm diameter (same patient as in Fig. 10.9).
In spite of the advance of laparoscopy over the last few years, this technique is not indicated in the surgical treatment of giant haemangiomas due to risk of rupture, and consequent haemorrhage. Similarly, laparoscopic examination and biopsy by excision, along with direct laparoscopic ultrasound, do not offer any therapeutic benefit to these patients. In the future the possibility of undertaking laparoscopic arterial ligation, sclerotherapy and/or cryotherapy may arise. However, these procedures at present remain theoretical.

**Vascular control**

The reduction in size which occurs following arterial ligation can be dramatic, and is maximized by extending this ligature to involve the trunk of the portal vein entering the tumour.
Figure 10.10(A) CT scan. Large haemangioma localized in the centre of the liver.

Figure 10.10(B) Aspect of the central area of the liver after resection of the haemangioma diagnosed in the patient in (A). Mesohepatectomy.
Figure 10.11 (A) CT scan showing large haemangioma localized in the left lobe of the liver.

Figure 10.11(B) Haemangioma in the left lobe (same patient as in (A)).
**Figure 10.12(A)** CT scan showing very large haemangioma in the left of the liver, occupying almost 60% of the abdominal cavity.

**Figure 10.12(B)** Large haemangioma before resection.
Ligation of a main branch of the hepatic artery (right or left), and of the portal vein is essential in most cases of giant haemangioma that require anatomical resection. For this reason, control must be prehepatic using a vascular clamp or vessel loop which permits arterial and venous blood flow to re-establish itself after tumour enucleation\textsuperscript{14} (Fig. 10.13).

The fastest and easiest method of preventing afferent blood flow is complete vascular occlusion of the liver at the hepatoduodenal ligament.\textsuperscript{114} Nevertheless, the success of this manoeuvre depends on the response of the rest of the hepatic parenchyma to ischaemia.\textsuperscript{115} In our experience the Pringle\textsuperscript{114} manoeuvre can be maintained for up to 90 minutes without any serious functional effects, with only a discrete rise in hepatic enzyme levels, and a very limited drop in prothrombin factors.\textsuperscript{116} Nevertheless, in giant
cavernous haemangiomas, this is only indicated when it is necessary to shorten operating time, or in cases of bleeding through the hepatic surface in contact with the tumour, when the tumour capsule is ruptured and penetrates into the remaining liver.\textsuperscript{117} Total vascular isolation is less frequently indicated. Vascular occlusion is achieved at the level of the hepatoduodenal ligament and supra and infrahepatic vena cava.\textsuperscript{99,118} The haemodynamic changes which occur in the splenic and lower abdomen, along with the greater seriousness of the reperfusion syndrome, make this procedure too dangerous for routine use in this disease.\textsuperscript{115} In addition, this technique, while questionable in malignant hepatic tumours, is absolutely unnecessary in cavernous haemangiomas. Similarly, ex vivo procedures of bench resection,\textsuperscript{119} which occasionally play a role in the resection of malignant hepatic tumours, offer no advantage while they do give rise to a number of possible complications.\textsuperscript{14,56,106}

**Dissection and tumour removal**

Enucleation is characterized by dissection and separation of the tumour capsule from the adjacent hepatic parenchyma. Similarly, the whole of the tumour must be removed, with no residual tumour capsule.

During dissection vascular elements can be seen which enter the tumour structure. These should be ligated and divided. The segmental branches of the intrahepatic biliary tree should be preserved and small vessels displaced by tumour growth may be ligated and divided by suture-ligature stitches. Accidental ligation of larger intrahepatic vascular structures must be avoided as these could give rise to biliary fistulae. Unrecognized small biliary leaks are the most frequent cause of perihepatic infection, giving rise to subphrenic abscesses.

Dissection of the tumour surface may be undertaken by ultrasonic dissection (CUSA, Ultrajet, etc), harmonic scalpel or electrocautery. Nevertheless, in attempting to simplify the procedure we prefer to use clips to dissect through liver tissue.

**Maintaining the integrity of the biliary tree**

For several years cholangiography after tumour excision had been the rule for many surgeons to ensure the absence of biliary fistulae. Nevertheless, this procedure usually involves a cholecystectomy which is unnecessary, particularly when the bile duct is far from the tumour. Less frequently this is undertaken by transhepatic puncture, afterwards compressing the parenchyma in order to force the passage of contrast into the bile duct, or by direct puncture of the common hepatic or bile duct. Both procedures avoid cholecystectomy.

Nevertheless, identification of a biliary fistula on the raw liver surface—even if this is small in diameter—may be done by wiping with a surgical gauze. By moving this slowly away from the liver surface a small stain of bile can be seen which indicates its exact location.

Assisting biliary drainage with a T-tube is not indicated for any type of liver resection, considering the fact that this increases the morbidity of the procedure. None of the theoretical advantages of T-tube placement in fact justify it.
The raw surface is fulgurated by argon beam coagulation, thus removing any microscopic capsular remains which could have been left behind. Nevertheless, caution is necessary, as this may disrupt small suture-ligatures. This is because reabsorbable polyglycolic acid is sensitive to the high temperatures of fulguration.

**Drainage in the residual cavity**

The use of postoperative intra-abdominal drainage has been questioned over the last few years. The basis for avoiding drainage is that perfect haemostasis, absence of biliary fistula, and the avoidance of poorly vascularized tissues will reduce the risk of postoperative collections. For this reason, once confirmed by waiting a few minutes and rinsing with warm saline, it is not necessary to drain the operative field.

In addition, the surgical field is located in the free abdominal cavity, so that the transudate produced may be reabsorbed through the peritoneal mesothelium. On the other hand, drainage keeps the external space in contact with the inside of the abdominal cavity, with the attendant risk of subsequent infection.

**Operative mortality**

Enucleation or resection of cavernous haemangiomas can only be undertaken in the absence of serious complications and mortality. However, there are reports of between 2 and 5% operative mortality at 30 days after operation. These figures seem excessive, as there is no justifiable reason for mortality, i.e. the mortality rate should be as close to 0% as possible.

These patients have normal hepatic parenchyma, and are generally between the third and sixth decade of life, without any deranged hepatic function and with normal coagulation studies. If patients are selected correctly, there should be no operative deaths.

Factors which may be related to postoperative mortality are: co-existence of cirrhosis of the liver, respiratory failure, kidney failure and/or cardiopathy. For this reason it is questionable whether patients in poor physical condition at an advanced age, or those with cardiopulmonary disease or kidney or liver failure, even if moderate, should be treated or not.

In our experience, out of a total of 78 giant cavernous haemangiomas, no patients died in the postoperative period.

**Tumour recurrence**

Provided the considerations described above are observed, recurrence of the excised lesion within the liver is exceptional and must not be confused with the appearance of a haemangioma in the remaining hepatic tissue, far from the surgical field.

We have never observed a case of tumour recurrence, and we advise surgical treatment whenever possible.15
Other therapeutic options

Prevention of further growth
This is advisable in the case of giant cavernous haemangiomas in which, for the reasons mentioned above, excision is not indicated (small diameter tumours, asymptomatic patients or considerable risk factors).

This approach applies to the majority of patients. Complications relating to growth of haemangiomas occur in approximately 20% of patients, resulting in subsequent excision when symptoms occur. The occurrence of rupture and haemorrhage is exceptional, and malignant transformation does not occur.

One of the dangers of not monitoring these tumours is, without doubt, erroneous diagnosis, since the image of a cavernous haemangioma may be confused with other very vascularized tumours, such as hepatoma when located on a non-cirrhotic liver, when there is no background of viral infection and plasma levels of alphal-aphetoprotein are normal. These conditions are not frequent in hepatomas, nor are they, however, exceptional.

However, conservative management is acceptable when the diagnosis is absolutely clear and there are no indications to operate. Nevertheless, in spite of most surgeons agreeing with this approach, the reality is that even among experienced liver surgeons, 20–40% of haemangiomas remain undiagnosed with excisional biopsy.

Radiotherapy
This has been advocated in diffuse haemangiomas or in unresectable voluminous haemangiomas. Until 1970, before the advent of modern liver surgery, this form of therapy was still indicated, based on the possibility of provoking sclerosis of the tumour parenchyma with consequent reduction in its volume. For this reason it was used in patients who complained of pain in upper right quadrants due to capsular distension as a result of progressive tumour growth, or following episodes of intratumoural haemorrhage.

Initially conventional external beam radiotherapy was used, with the risk of radiation hepatitis or centrilobular thrombosis when dosage exceeded 2500 to 2800 rds. For this reason it was superceded first by cobalt therapy and then subsequently by the linear accelerator. Use of the linear accelerator enables better limitation of the field, both on the surface and deeper within the liver, thus reducing undesirable effects on the surrounding healthy liver parenchyma.

Following radiotherapy, reductions in volume of haemangiomas ranged between 20% and 40%, with approximately 30% improvement in symptomatology. For this reason, some authors continue to advocate its use.

However, radiotherapy is associated with a high rate of complications such as radiation hepatitis, and tumour rupture only a few months after completion of treatment, probably due to the increase in capsular fragility. Isolated cases of malignant transformation induced by radiotherapy have been described, as well as the development of malignant
tumours at other sites after administration.\textsuperscript{122}

**Selective hepatic dearterialization**

Although the role of hepatic dearterialization was described 20 years ago, at present it is not widely indicated for the treatment of liver tumours.\textsuperscript{70,123}

The demonstration of intense vascularity in liver tumours logically leads to selective, permanent occlusion, which both decreases the arterio-venous shunt and reduces the size of the tumour.

However, the effect of dearterialization is temporary, and blood flow is re-established through an intricate network of collateral branches.\textsuperscript{17}

**Embolization**

Apart from its transitory nature, morbidity of embolization is high because of tumour necrosis, sometimes even leading to the formation of intrahepatic abscesses.

Short-term results are difficult to evaluate, but in the long term tumour size may be reduced, with a reduction in symptomatology as well, although only in exceptional cases. For this reason, at present embolization is not a procedure that can be widely recommended.\textsuperscript{17,53,109}

Sclerosing by means of direct injection of hypertonic solutions is of only historical value.\textsuperscript{124}

**Key points**

- **Presentation of hepatic haemangiomas:**
  - Incidental finding (US or CT)
  - Pain (28%)
  - Spontaneous or post-traumatic rupture
  - Fever, jaundice, cholangitis uncommon
  - Cardiac failure due to A-V fistula (rare).
- **Investigation of hepatic haemangioma:**
  - US
  - CT
  - MRI
  - Technetium-labelled red cell scan
  - Angiography.
- **Do not biopsy.**
- **Indications for surgical resection:**
  - >6 cm diameter
  - Pain not responding to analgesic drugs
  - Risk of spontaneous rupture
  - Giant tumours compressing other viscera
  - Anaemia
To exclude malignancy.

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Management strategies for benign cysts and polycystic disease of the liver

Francis Sutherland and Bernard Launois

Biliary cysts and polycystic liver disease were for a long time relatively unknown; they were only discovered when symptoms or complications occurred. With the development of improved imaging techniques the asymptomatic forms of this disease were first appreciated.

Simple biliary cysts and polycysts have in common three characteristics: they are cysts that normally do not communicate with the biliary tract; the surface of the cysts is composed of cuboidal or columnar epithelium, identical to normal biliary epithelium, resting on thin connective tissue and without precise separation from displaced hepatic parenchyma; the intracystic liquid is relatively acellular and the composition is similar to independent secretions of biliary cells. These criteria facilitate separation from the other intrahepatic cystic formations, in particular hydatid cysts and biliary cystadenomas.

The congenital origin of biliary cysts is the same for the simple cysts and the polycysts of polycystic liver disease. They develop from embryonic canalicular vestiges formed by an excess of progenitor cells from the cranial hepatic pouch at the time of their differentiation towards biliary cells and hepatocytes. These vestiges are known under the name biliary microhamartomas or von Meyenburg complexes.

Natural history of simple biliary cysts

Simple biliary cysts are found in 1.6 to 3.6% of subjects during ultrasound examination for other indications. Their frequency increases with age; simple biliary cysts are unusual before the age of 10 years, and attain the maximum frequency between 50 and 60 years. They are more frequent in women by a 5:1 ratio. This female predominance is even more accentuated for very large cysts and cysts that are symptomatic or complicated. The majority of cysts detected by ultrasound are small; 60% have a diameter less than 2 cm and fewer than 20% are more than 1 cm in diameter. In 30% of cases the cysts are multiple, from two to five, without systematic topography. Giant cysts are rare.

Simple biliary cysts are lesions that may or may not increase in size. During successive ultrasound examination fewer than 20% of cysts are noted to have an increase in their volume and only one time in four does growth attain double the initial volume estimate. Only in rare cases does size increase occur rapidly, in less than a year.

The majority of biliary cysts are asymptomatic and their discovery is incidental. The
relationship between symptoms of abdominal pain and the presence of a biliary cyst must be accepted with caution and one must consider this only for large cysts where the diameter exceeds 8 cm.\textsuperscript{6,7} The temporary disappearance of the symptoms after needle aspiration can serve as an argument in favor of responsibility of the cyst for symptoms. Otherwise it is a diagnosis of exclusion after ruling out biliary, stomach and colon pathology. Complications are unusual: compression of the biliary tree, vascular compression (vena cava or hepatic veins), intracystic hemorrhage, biliary fistula, rupture and cyst infection. Malignant degeneration is extremely rare because, unlike cystadenomas, the epithelial borders of the biliary cysts do not undergo active proliferation.

In summary, one can emphasize that simple biliary cysts are common, with little or very slow growth, and they rarely produce symptoms or complications.

The factors that cause the development of subsidiary small cysts, giant cysts, symptomatic cysts and the complicated cysts have not been established.

Natural history of the polycystic liver in the adult

This term is designated for the presence of more than three cysts and is often reserved for the genetic forms of the illness in the setting of polycystic liver and kidney disease. In fact, polycystic liver disease can be observed in the absence of renal cysts or can be associated with benign kidney cysts, of which the prevalence is equally increased. In the course of genetic polycystic disease the kidney disease always proceeds the hepatic disease.

The appearance of the liver cysts generally occurs after the renal cysts and the liver cysts are never detected before the age of 15 years. The number of cysts and their size increases progressively with age. The percentage of patients suffering from symptoms is less than 20% before the age of 30 and exceeds 75% after the age of 60 years.\textsuperscript{9}

Three factors are associated with an increased number of cysts and progressive disease: female sex, number of pregnancies and presence of polycystic kidney disease. The severity of the polycystic renal disease correlates with the expansion of liver cysts explaining the frequency of symptomatic polycystic liver disease in dialysis patients.\textsuperscript{10}

In the absence of biliary or vascular compression or other associated hepatic disease the development of cysts in not accompanied by a reduction in the volume of liver parenchyma quantified by CT scan, even when the cystic volume surpasses the liver parenchyma volume.\textsuperscript{11} This preservation of the liver parenchymal mass explains the absence of liver function abnormalities. Complications like biliary compression with cholestasis, vascular compression and intraperitoneal rupture are unusual. Like the simple biliary cyst, the alteration in the tissue covering the epithelium with atrophy and then erosion of the epithelium are probably responsible for intracystic hemorrhage, biliary connections and bacterial infection with suppuration. The last problem is serious; it is the major cause of death from liver disease in adult patients suffering from polycystic kidney disease on dialysis.\textsuperscript{10}
Diagnosis of biliary cysts

The diagnosis of biliary cysts is usually simple and relies on ultrasound (or the CT scan) examination that shows a round clear image, without septae, strictly anechoic, and with accentuation of echoes beyond the cyst. The differential diagnosis includes a young hydatid cyst, non-calcified and not containing daughter cysts. The hydatid serology is negative in 10 to 15% of hydatid cysts, and this occurs more frequently in the young forms. The diagnosis rests on the search for scoleces in the cystic liquid removed by a fine needle under ultrasound control after 3 weeks of treatment with albendazole. An intracystic hemorrhage modifies the ultrasound appearance of biliary cysts. False septae can appear after hemorrhage that correspond to fibrinous deposits; the contents of the cyst are then not strictly anechoic. Magnetic resonance imaging gives an excellent evaluation of liver cysts, permitting differentiation of complicated biliary cysts from hydatid cysts and cystadenomas. Biliary cystadenomas without septa can occasionally appear identical to a simple cyst. Cyst fluid analysis for tumor markers CEA and CA19–9 can distinguish the difference.12

Certain hepatic metastases appear cystic, particularly neuroendocrine tumors, sarcomas and epidermoid carcinomas. These cystic lesions are always associated with tissue lesions, and this allows differentiation from simple biliary cysts.

Management of simple biliary cysts

No treatment

The best treatment is no intervention in cases of asymptomatic, moderately symptomatic or noncomplicated disease. The discovery by imaging of an asymptomatic cyst can result in the demand for intervention from a hypochondriac patient. It is important to resist the temptation to offer these patients surgery.

Sclerotherapy

The non-surgical treatment is needle puncture; however, aspiration alone results in recurrence of all cysts within 2 years.13 More recently, the use of aspiration followed by sclerotherapy has gained popularity. A number of sclerosants have been tried including pantopaque,14 tetracycline, minocycline and alcohol.15–17 The use of formalin has been abandoned because of reports of sclerosing cholangitis in cases of bile duct communication. Good success has been reported with alcohol.16,18–23

This technique produces a chemical cystitis which destroys the epithelial layer of the cyst wall and results in a secondary reactive sclerosis. Epithelial lining cells are fixed and non-viable after 1–3 minutes of contact with 95% alcohol.16 Inflammatory cells have been noted as deep as 0.5 mm from the surface.16

The technique most often reported involves ultrasound or CT guided placement of a pigtail catheter in the cyst, followed by a cystogram to rule out biliary communications.
The cyst fluid is usually completely clear, ‘sweetwater cyst’, and in such a circumstance the chance of biliary communication is low. However, because any communication risks catastrophic sclerosis of the biliary tree, a radiograph is prudent. A cystogram may also demonstrate if there is a significant leak that could result in spillage of the sclerosant into the peritoneal cavity. If the cyst fluid is not clear the diagnosis should be questioned, as this suggests infection or malignancy. Fluid should routinely be sent for cytology to rule out cancer, culture to rule out infection, and microscopy to rule out hydatid scolices. As much of the fluid as possible should be removed from the cavity to prevent dilution of the ethanol. Ninety-five per cent ethanol is utilized and the amount recommended varies in the different studies; usually about 10–30% of the aspirated volume up to 100 ml is instilled. The alcohol is left for 20–30 minutes and then drained, during which the patient’s position is changed to allow complete contact of the sclerosant with the cyst endothelium.

Most authors recommend immediate removal of the catheter and report successful treatment of the cyst with one treatment. These procedures can be performed on an outpatient basis or with overnight stay. Immediate follow-up usually reveals a residual cyst cavity that may increase in size for several weeks but thereafter either remains stable or decreases in size for up to 2 years. The walls of the cyst are thickened and infolded. Repeat sessions for large cysts may be necessary and some authors report leaving the catheter in place and using the amount of drainage to guide the number of trials of sclerotherapy to use (up to 11 repeat sessions).

Pain is reported as the most frequent complication, present in up to 100% of patients. This has resulted in modification of technique in some series by either premedicating the patient with pethidine or the use of a local anesthetic agent either injected before or mixed with the sclerosant. The presence of pain may be the indicator of a significant leak into the peritoneal cavity. In this circumstance postponing the procedure for 24 hours will allow the leak to seal and the sclerotherapy to proceed uneventfully. The catheter may be either left in situ or removed and reinserted the following day. Because of the leakage problem, pigtail catheters placed by the Seldinger technique are preferable to simple needle puncture. Some authors report placing the catheter through liver tissue to reduce the possibility of leakage from the cyst.

Postsclerotherapy infection has been reported in the literature and we have seen infection in two patients that eventually required operative intervention. Because treatment involves a large dead space the risk of infection is real and strict aseptic technique must be followed. Antibiotic prophylaxis should be considered. The longer the catheter is left in place, the increased likelihood of contamination of the cyst cavity. For this reason we feel immediate removal after sclerotherapy is best. Treatment of a postsclerotherapy infection in the residual cyst cavity can be effected by replacement of the drain and intravenous antibiotics. Infection and recurrence may be related to the size of the cysts, with the very large cysts more susceptible to both. After these problems surgical treatment is made more difficult.

Other problems with percutaneous therapy include bleeding and bile duct fistulization. Indeed, any connection with the biliary tree from this procedure likely occurs by transgression of the bile duct during needle placement. At the first sign of bile or significant bleeding the procedure should be terminated and open surgical management
considered if problems progress. Histologic examination of previously resected cysts that have been treated with alcoholization demonstrates pronounced fibrosis of the cyst wall.\textsuperscript{18} This raises the theoretical question of possible damage to the compressed vasculobiliary structures in the cyst wall; however, to date this kind of problem has not been reported.

Elevation in the blood alcohol level after sclerotherapy has been investigated by a number of authors.\textsuperscript{18–20} Most report very low or negligible ethanol levels.\textsuperscript{18} Repeated application of alcohol, prolonged procedures or the use of a large amount of alcohol in a large cyst may result in more elevated levels.\textsuperscript{20} At the termination of the procedure maximal amounts of alcohol should be removed from the cyst cavity and the patients should be advised not to drive a vehicle.\textsuperscript{19}

Perhaps the major problem with cyst alcoholization is the inadvertent treatment of malignancy as a result of the inability to histologically confirm the diagnosis, as reported by vanSonnenberg et al.\textsuperscript{19} Almost all reports of hepatic cyst treatment contain cases of simple cysts being mistaken for malignant cysts, either cystadenomas or cystic metastasis. The Lahey clinic series found two out of 18 non-parasitic cysts were neoplastic.\textsuperscript{25} Furthermore, 3\% of all liver metastases are cystic.\textsuperscript{26,27} After successful sclerotherapy the cyst may appear as a convoluted, echodense network,\textsuperscript{18} that may make differentiation from a malignancy difficult. Careful preoperative screening will diminish but not eliminate this problem.

The results of percutaneous sclerotherapy are promising, with most authors reporting an initial success rate from 80 to 100\%.\textsuperscript{16,18–23} The analysis of the different studies is complicated by a number of factors. Many series include patients with polycystic liver disease and hydatid disease where the outcomes are likely to be different. Most series are small, ranging from 10 to 30 patients. How success is defined varies from symptomatic relief, to ablation of the cyst, to a reduction in volume.\textsuperscript{18} Serious complications are rare but a number of patients do go on to surgical therapy.\textsuperscript{18} Follow-up ranges from 6 months to 2 years and small residual cystic cavities occur in up to 28\% of patients.\textsuperscript{18} Larger studies with long follow-up and standardized outcome measures including quality of life scales will help establish the usefulness of this technique.

How to decide which patients are candidates for percutaneous sclerotherapy is at present unclear. Patients with contraindications to surgery, including poor cardiopulmonary tolerance, are among the best candidates. It should also be considered in patients who have had extensive previous upper abdominal surgery, where adhesions may make laparoscopy or open surgery difficult. Furthermore, in this situation surgical fenestration may be predisposed to recurrence because of early isolation of the cyst cavity and a limited resorptive surface area. Another situation where alcohol sclerotherapy offers an advantage is in the patient with failed surgical management of a large cyst, a cyst that is situated deep in the hepatic parenchyma or a cyst that is located in segments VII and VIII.

**Open surgical treatment**

Until recently problematic large hepatic cysts have been exclusively treated by open surgery. It has been recognized that external drainage or aspiration is associated with
complications and recurrence. Unroofing/fenestration of the cyst has emerged as the most popular treatment. Initially the cyst should be aspirated and the contents examined for hydatid scolices; cytology and culture should also be performed. Cloudy fluid should be sent for gram stain to rule out infection. The unroofing technique involves removal of the protruding dome of the cyst back to hepatic parenchyma, exposing the secretory epithelium to the peritoneal cavity. As much cyst wall as possible should be removed and results are best when at least one third of the cyst wall is excised. The edges should be sutured to prevent bleeding and bile leakage. The fluid is usually absolutely clear unless there has been previous bleeding, infection or biliary communication. Careful inspection of the inside of the cyst wall and biopsy of any irregular, papillary or solid elements is essential to rule out malignancy. Several series have included cases of previously unrecognized malignancies that were diagnosed at surgery and treated with resection rather than unroofing. The resected specimen of cyst wall should be examined histologically to rule out unusual malignancies such as cystadenomas or cystic liver metastasis. Electrocoagulation of the remaining cyst wall may decrease secretory epithelium and prevent recurrence. However, it carries with it a risk of damaging underlying blood vessels or bile ducts. Argon beam electrocautery is safer as thermal damage is more superficial; care should still be taken as there is still a theoretical risk of injuries. Because success depends on creating a permanent communication between the cyst and the peritoneal cavity, the placement of omentum in the cyst cavity may facilitate drainage and prevent recurrence. This is particularly applicable in posteriorly placed cysts where peritoneal drainage may be interrupted by the formation of adhesions to the diaphragm.

The abdomen should be closed tightly and in most cases drains are not necessary. Significant ascites is rarely a problem and results of this procedure are generally reported as excellent, with only rare recurrences in most series. The unusual discovery of bile within the cyst cavity should prompt a search for the leaking ductule and closure with oversewing. Cyst jejunostomy is not indicated as it is associated with significant septic complications.

Other therapy recommended for symptomatic solitary cysts has included local excision (cystectomy) and anatomic or non-anatomic hepatic resection. This form of therapy is still recommended by some authors who cite high radiologic recurrence rates with unroofing. However, radiologic recurrence must not be confused with symptomatic recurrence. The presence of a small residual cyst cavity is common and the significance in terms of symptomatic recurrence is unproven. Morbidity and mortality rates for major hepatic resections are well established: approximately 30% and 5%, respectively. Hepatic cystectomy performed on large cysts is risky as the surrounding parenchyma is compressed and vasculobiliary structures are often in the walls, as shown in Fig. 11.1. With a cyst deep in the liver it may not be obvious on initial inspection that part of its wall contains one or two hepatic veins or the inferior vena cava. The possible place for resection may be when there is suspicion that the cyst is neoplastic in origin, or if it is in a superficial location where it can be wedged out. When treating a benign disease that does not affect the patient’s longevity one must be careful not to utilize therapy that is riskier than the disease.
The best opportunity to discover malignancy within a simple cyst is by careful inspection of the cyst wall at open surgery. The risk of malignancy in a simple biliary cyst is small, but eight cases of adenocarcinoma and five cases of squamous cell carcinoma have been reported. Most patients present late with jaundice from invasion of the biliary tree. Prognosis in these circumstances is very poor, with no survivor beyond 14 months.

The recurrence of a ‘simple biliary cyst’ after adequate treatment must raise the possibility that the initial diagnosis was incorrect and a cystadenoma or other tumor was actually present. While this may be more frequent in situations where the cyst was managed without histologic evaluation, it may also occur where the initial histology showed a flat cuboidal epithelium without papillary projections. For this reason all patients should be followed long term.

**Laparoscopic surgical treatment**

Laparoscopic management of the hepatic cysts is emerging as a new, less invasive therapeutic option. This procedure, as in open surgery, involves wide unroofing of all non-parenchymal cyst wall to allow fluid produced from the epithelial cells of the cyst wall to drain into the free peritoneal cavity where it can be absorbed, as shown in Fig. 11.2. The cyst edges are more difficult to secure than in open surgery. They can be cauterized and sutured or, alternatively, the endoscopic vascular stapler can be used to resect the cyst wall. This technique is perhaps technically easier and faster than intracorporeal suturing and secures blood vessels and bile ducts effectively. The creation of a flap of omentum off the transverse colon to pack in the cyst cavity may decrease the risk of recurrence. Drainage of the cavity has been suggested to help diagnose and treat bile leakage, with many authors removing drains early after only 24 hours. However, bile leakage is rare and drainage is probably not necessary, as with the open procedure.
The gallbladder should be removed if it contains stones or is adjacent to the cyst wall being resected. The rationale for cholecystectomy is to prevent the need for reoperation in a scarred area and eliminate the risk of torsion of a free-floating gallbladder. Furthermore, a symptomatic gallstone can produce pain that is indistinguishable from hepatic cystic disease. An intraoperative cholangiogram is useful in identifying any connection with the biliary tree, which can then be oversewn.

The selection of patients with symptomatic hepatic cysts for laparoscopic treatment is important. Extensive previous upper abdominal surgery is a relative contraindication. The position of the cyst is paramount. Cysts accessible for laparoscopic therapy are located in segments II, III, IVb, and V. Cysts in segments VI and IVa are more difficult to access and conversion may be required. Cysts in the upper segments of the right liver (VII and VIII) are difficult to approach and are associated with a higher rate of recurrence. Cysts in these locations may best be approached by the open technique. Watson and Jamieson have reported successful treatment of a patient with a posterolateral cyst by placing the patient in the lateral position to gain access to the cyst wall.

One of the limitations of laparoscopic unroofing is a restricted examination of the interior of the cyst wall. Visual inspection without palpation may not be adequate to rule out malignancy. This problem may be partly resolved by the use of laparoscopic ultrasound to image the cyst wall. However, in any case where there is a possible diagnosis of a cystadenoma or other malignancy, an open technique with direct examination and biopsy or the cyst wall may be preferable.

The results of laparoscopic unroofing of liver cysts are encouraging. Nevertheless, symptomatic recurrence can occur and complication rates of around 10% are reported. However, as with sclerotherapy, most studies have only a few patients and follow-up is short (usually less than 12 months). Strict outcome measures are lacking.
Management of polycystic liver disease

Most frequently multiple cysts in the liver present with a variable number of very large cysts (in general from one to five) associated with much smaller cysts. In the patients with isolated symptomatic large cysts symptoms are comparable to the patients with simple biliary cysts. The treatment consists of treating each one of these voluminous cysts the same as for the isolated simple biliary cysts. The treatment of deep small cysts is often ineffective: alcoholization of each of these cysts is possible but surgical fenestration is simpler and more adaptable.

The fenestration operation was first proposed by Lin in 1968. The procedure involves progressive unroofing of liver cysts, starting on the surface and working to the cysts placed deep in the parenchyma. It is generally reported as successful in relieving symptoms, but is associated with a significant postoperative morbidity of around 50%. Recurrence of symptoms is not unusual as cysts in the remaining liver reform and grow.

The situation is different when all the liver is occupied by multiple small cysts, because it is not possible on the preoperative examination to identify which of the cysts are responsible for the symptoms. The symptomatology of these patients is very different and is associated with painful abdominal distention, early satiety associated with vomiting, loss of muscle bulk and sometimes profound malnutrition. Dyspnea, ascites and edema of the lower extremities may also occur. The treatment consists of fenestration of as many cysts as possible to obtain a total collapse of the liver. This intervention is long because it is necessary to fenestrate the deep cysts pocket by pocket by traversing the more superficial cysts. It must be done very delicately because the vasculobiliary structures are distorted between the cystic layers. It is almost always followed by ascites that can be prolonged and must be accompanied by a rigorous fluid and electrolyte replacement that can attain several liters. The laparoscopic approach is not adaptable to this approach. Surgical fenestration of polycystic liver disease is efficacious in about 75% of patients over the short term; it is accompanied by parenchymal hypertrophy in the remaining liver. Failures are observed in patients where there is no zone of non-cystic hepatic parenchyma and/or a very active cyst secretory epithelium.

In the past, several authors have reported success with the fenestration/resection surgical approach. This technique usually involves a non-anatomic resection of either the right or left lobe of the liver, with the addition of unroofing the remaining cyst on the opposite side. The operation is tailored to the patient’s anatomy in an attempt to preserve hepatic parenchyma. This is particularly useful when the cyst distribution is asymmetrical, as shown in Fig. 11.3.

Proponents of resection/fenestration report very adequate reduction of liver volume and prolonged relief of symptoms. However, there is significant risk of intraoperative hemorrhage. The most dangerous structures are the hepatic veins. Anatomy is always very distorted with intrahepatic and extrahepatic bile ducts and blood vessels
compressed between contiguous cyst walls. While control of the hepatic pedicle with a Pringle maneuver is usually possible, control of the hepatic veins from above may be impossible because of intervening liver and cyst tissue. Because of difficulty with exposure once hemorrhage begins it may be very hard to control. With the absence of landmarks there is also the ever present danger of occluding the remaining hepatic vein, creating the acute Budd-Chiari Syndrome. These resections should be performed with care by experienced liver surgeons; intraoperative ultrasound can be a useful tool for choosing safe sites for fenestration or identifying hepatic veins. Collapse of as many superficial liver cysts as possible before the resection is started may aid in exposure. The advantage is more prolonged relief of symptoms with the reduction of cyst surface area and less difficulty with postoperative ascites.

Gigot et al. have produced a useful classification scheme of adult polycystic liver disease according to the number and size of liver cysts and the distribution of liver parenchyma, as shown in Table 11.1. The classification is based on the preintervention CT scan. Therapy should be tailored to the classification. Type I patients have a minimal number of large cysts; Bismuth classified these patients as ‘multicystic liver disease’, as opposed to polycystic liver disease (types II and III). These patients may benefit from a laparoscopic unroofing with omental interpositions, as in patients with solitary cysts. This minimally invasive approach offers immediate relief of symptoms and is probably

Table 11.1  
Gigot classification of adult polycystic liver disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>limited number (&lt;10) of large cysts (&gt;10 cm)</td>
</tr>
<tr>
<td>II</td>
<td>diffuse involvement of liver parenchyma by multiple, medium-sized cysts with remaining large areas of non-cystic liver parenchyma</td>
</tr>
<tr>
<td>III</td>
<td>diffuse involvement of liver parenchyma by small- and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts</td>
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associated with the least postinterventional problems. Patients that have a single dominant cyst that can be accessed by percutaneous needle insertion may also benefit from alcohol sclerotherapy. This approach is particularly attractive in elderly patients with co-morbidities, where surgical intervention may be hazardous.

![Figure 11.4 Mild type II polycystic liver disease.](image)

Patients with type II cysts (diffuse involvement of the liver by medium-sized cysts) can benefit from either fenestration or fenestration/resection (Fig. 11.4). Both approaches have their proponents. Fenestration has the advantage of being perhaps a less aggressive and easier approach. The risk of massive intraoperative hemorrhage may be less than with resection, and if the cyst walls are thin there is a satisfactory reduction in size that can result in prolonged relief of symptoms. Problems do exist in that some patients have a relatively rigid liver skeleton, probably based on fibrotic reaction, that does not allow collapse after decompression (type III). Furthermore, extensive fenestration without resection exposes large amounts of a secretory biliary type of endothelium to the free peritoneal surface.\textsuperscript{45,48} The resulting fluid load may overwhelm the peritoneal cavity’s absorptive capacity and result in ascites. The long-term results are probably not as favorable as resection/fenestration.\textsuperscript{48}

Patients with the most severe form of adult polycystic liver disease are the patients with Gigot type III anatomy. Here no part of the liver is spared from involvement and the cysts are small, making fenestration difficult. There are often no large areas of uninvolved hepatic parenchyma. Furthermore, the liver is often quite rigid, with significant fibrosis of cyst walls, limiting the amount of collapse that occurs with fenestration.\textsuperscript{50} Gigot et al. have demonstrated a significant post-therapy increase in size of residual cysts over the long term in type III disease.\textsuperscript{50} Farges and Bismuth reported recurrence of symptoms in three out of five patients they treated with numerous small
cysts and no large areas of parenchyma (Gigot type III). Resection has been shown to effectively decrease liver volume in these patients, however, the risks are high. Turnage reported significant morbidity and postoperative death in three out of five patients with this type of polycystic liver disease treated with resection and/or fenestration.

There are several reports of successful transplantation of patients with polycystic liver disease. This therapy has been generally reserved for end stage patients with a syndrome described as lethal exhaustion. These patients have reached the end of their functional lives and can no longer carry the weight of their enlarged livers. Fatigue, cachexia and narcotic addiction are often present. Many of these patients present late or after a series of partially successful fenestration operations. Renal failure and a need for kidney transplantation may also prompt the decision to transplant the liver, using the same donor for both organs. Postoperative morbidity with these type of procedures is high and mortality is 25–30%. Patients are often in poor condition for this type of major surgical intervention and this is a persuasive argument for more aggressive therapy earlier in the course of their treatment. Recent reports suggest improvement in survival following transplantation. Successful living donor liver transplantation has now been reported in a patient with polycystic liver disease. These are among the most difficult and rare cases and should be handled in experienced centers that can offer both forms of therapy, resection and transplantation.

The decision on the best type of therapy for each patient depends very much on the stage at which the patient presents and the type of cysts present, including size and position. Clearly, patients that are presenting late after previous surgical interventions, with massively enlarged livers and/or chronic renal insufficiency, should be treated differently from the patient presenting for the first time with pressure symptoms from a large dominant cyst.

Prevention and management of biliary complications

Biliary complications are among the most frequent postoperative problems. They most commonly present in the early postoperative period with a bile leak and/or biliary ascites. These leaks no doubt result from an inability to secure small bile ducts in the resected cyst walls. They also appear to occur with equal incidence with fenestration and fenestration/resection procedures. Their prevention starts with meticulous surgical technique which includes oversewing any thick cyst wall. Leakage can be assessed intraoperatively by applying dry sponges on the raw areas and looking for bile staining, or by performing an intraoperative cholangiogram after cholecystectomy (a recommended procedure in all cases). Very small leaks may not be discovered on cholangiogram so injecting air or a dilute solution of methylene blue into the bile duct with direct vision of the resected area may be efficacious. Fibrin glue (Tissucol) may also be applied to large areas to prevent small leaks.

In rare circumstances a cyst may be found to contain bile stained fluid, indicating a biliary connection. Some authors in this circumstance have recommended cyst jejunostomy. We feel this is inappropriate and can be associated with significant infectious complications. Sewing a piece of bowel to a cyst creates a large, contaminated,
poorly drained cavity that connects with the biliary tree. It predisposes the patient to developing abscesses and/or cholangitis.\textsuperscript{28,57} In the same manner that cyst jejunostomies for choledocal cysts have been abandoned so should this practice with biliary cysts. Direct suture closure of the connection with the biliary tree and decompression of the common bile duct with a T-tube, transcystic duct drain or internal biliary stent are preferred. If the cyst is superficial consideration should be given to a nonanatomical resection of the entire cyst area.

Once a biliary leak has been detected postoperatively management begins with fluid and electrolyte resuscitation and intravenous antibiotic therapy. CT or ultrasound guided placement of a percutaneous drain may be the only therapy required. Endoscopic retrograde cholangiography has proven very useful in these circumstances, first in diagnosing the site of leakage and then treating the leak by placing an endoscopic stent to reduce bile duct pressure.

**Prevention and management of postoperative ascites**

Postoperative ascites has emerged as a significant problem in the therapy of polycystic liver disease. It is present in up to 70\% of cases and may be more common in patients with renal insufficiency and in patients with the type III disease.\textsuperscript{45} This may be the result of a higher secretion rate and a larger exposed surface area and/or blockage of diaphragmatic lymphatics from the extensive fibrosis associated with this disease type.

Minor postoperative ascites is best ignored as the absorptive capacity of the peritoneum will increase and the fluid will likely resorb within one or two weeks. Massive ascites, however, presents a significant problem. It can compromise respiration and postoperative mobilization. There is an ever present risk of infection. Furthermore, it may have deleterious effects on already compromised renal function. For this reason several groups do not offer surgical therapy to patients with renal insufficiency until after correction with kidney transplantation.\textsuperscript{46}

Awareness of the problem is probably most important. One should attempt to minimize the amount of residual epithelium by extensively removing as much of the cyst walls as possible or by resecting a segmental area. Postoperative ascites is probably reduced in the resection/fenestration operation compared to fenestration alone, as less of the secretory epithelium is left in contact with the peritoneal cavity. Cyst cavities exposed to the peritoneum can be fulgurated by electrocautery or argon beam coagulation (Bard Electromedical Systems, Englewood, CO). Que et al.\textsuperscript{48} reported only mild postoperative ascites in 7 of 31 of their patients treated with resection/fenestration and fulguration. There is an undefined risk of causing damage to the bilio-vascular elements in the cyst wall, so care should be taken.

Secretion from biliary epithelium may be pharmacologically reduced with either H2 antagonists (ranitidine) or somatostatin and its analogs. Several groups have reported a beneficial effect of these drugs in decreasing postoperative ascites;\textsuperscript{47} however, this therapy remains unproven. Other groups have reported treating this problem with repeated peritoneal tapping.\textsuperscript{58} There is also a report of placement of a LeVeen shunt for intractable ascites.\textsuperscript{19} Tapping and draining should be used as a last resort as this risks
infection. Letting time pass will often solve this problem.

Summary

Benign cysts of the liver are common, but rarely cause problems requiring surgery. However, where cysts or polycysts produce disabling symptoms, or if a cystic malignancy is suspected, intervention is required. Because of the rareness of these lesions most clinical series are small and there are no randomized or case-control trials of the different treatment options. Thus, clinical decisions must be based on the lowest level of evidence, the case report or small clinical series. In this situation one must rely on reports from referral institutions with the largest numbers of patients treated. One must also rely on one’s own clinical judgment and experience. Whensubjecting these patients to surgery, extensive liver resection and biliary reconstruction may be required. Referring a patient with one of these rare conditions to a center with specialized expertise may be in the patient’s best interest.

Key points

• The vast majority of simple hepatic cysts are small and asymptomatic and should be left alone.
• Abdominal pain should only be attributed to large (>8 cm) cysts.
• Indications for drainage/resection of simple cysts include:
  Resolution of pain after aspiration
  Compression of biliary tree, cava or portal system
  Intracystic hemorrhage
  Biliary fistula
  Spontaneous/traumatic rupture Infection.
• Indications for fenestration in polycystic liver disease:
  Painful abdominal distension
  Early satiety associated with vomiting
  Malnutrition, loss of muscle bulk
  Dyspnea, ascites and ankle edema.

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Management of choledochal cysts
Matthew Jones and David Lloyd

Incidence

Cystic dilatation of the extrahepatic bile ducts is a rare abnormality in Western countries, with an incidence which has been estimated at around 1 in 15,000 live births. The incidence is much higher in the Far East, and in Japan choledochal cysts may account for up to 1 per 1000 hospital admissions. The male to female ratio has been variably reported as being between 1:2 and 1:4. More than 60% of cases present before the age of 10, and an increasing number are presenting antenatally as a result of routine ultrasound scanning.

History

Abnormalities in the anatomy of the common bile duct were originally described by Vater, but Douglas gave the first detailed account of a patient with massive dilation of the bile duct. He described a 17-year-old girl with the now classic triad of pain, jaundice and a right-sided abdominal mass. This was managed by percutaneous aspiration of 900 ml of bile, but unfortunately the girl died 1 month later. The subsequent postmortem examination confirmed the presence of a choledochal cyst.

Aetiology

The liver and biliary tree arise as a ventral outgrowth (the hepatic diverticulum) of the endodermal epithelium from the caudal part of the foregut early in the fourth week of gestation. The hepatic diverticulum initially consists of solid endodermal cell strands, which later canalize to form the biliary tree. It is widely accepted that the majority of choledochal cysts are congenital lesions, and this is supported by the increasing number which are being detected by antenatal ultrasound scanning, sometimes as early as 17 weeks of gestation.

There are several theories as to the aetiology of these lesions, but the most popular
concerns the presence of an abnormality at the pancreaticobiliary junction. This was first proposed by Babbitt who found that there was a common channel between the lower end of the common bile duct and pancreatic duct, in 19 cases of choledochal cyst. He suggested that this predisposition to reflux of pancreatic secretions up the biliary tree might lead to chronic mucosal damage and thus ductal dilatation. This finding has been corroborated by several other authors, who have shown that a common channel may be present in as much as 75% of choledochal cysts. In such cases the biliary amylase is usually elevated. Babbitt’s theory is further supported by an experiment in dogs, in which the pancreatic duct was anastomosed to the gall bladder, resulting in dilatation of the biliary tree and mucosal destruction. A study of human foetuses by Wong showed that the pancreaticobiliary junction does not become incorporated in the duodenal wall until the eighth week of gestation. It is clear that any arrest in this process would tend to result in the creation of a common channel and thus pancreaticobiliary reflux. However, it is unlikely that a common channel is the sole explanation for choledochal cysts as there are many of these lesions in which it is not present.

Other aetiologies which have been suggested include ‘weakness of the bile duct wall’, ‘a primary abnormality of ductal proliferation’ and ‘congenital duct obstruction’. Such theories are largely speculative, but they are supported by a study in newborn lambs, which showed that lesions similar to choledochal cysts could be produced by simple ligation of the bile duct. Moreover, it has been shown that biliary amylase is not elevated in choledochal cysts which present as a result of antenatal diagnosis, implying the absence of pancreaticobiliary reflux in these patients. This would tend to suggest that such cysts are truly congenital, as opposed to those cysts which present later, and are therefore ‘acquired’ as a consequence of a common channel anomaly.

Petersen et al created a murine model for extrahepatic biliary atresia by infecting newborn mice with rotavirus group A. Amongst the various pathological features produced by this model was a single mouse, which developed a ballooning dilatation of the biliary tree. This model is particularly interesting in that it suggests a possible infectious aetiology for some of these lesions. On balance, however, it seems likely that there are a number of possible mechanisms, any or all of which might result in the formation of choledochal cysts.
Figure 12.1 Classification of choledochal cysts.

Pathology

Macroscopic
The macroscopic appearance of choledochal cysts differs widely. They may affect any part of the biliary tree, and the bile duct dilatation may vary from no more than 2 cm, to a giant cyst containing more than a litre of bile. A number of schemes have been devised to
classify these lesions, the most widely used of which is that proposed by Alonso-Lej et al. in 1959. They divided the cysts as follows (Fig. 12.1):

- Type Ic: cystic
- Type If: fusiform
- Type II: diverticulum
- Type III: choledochocoele (dilatation of intraduodenal bile duct)
- Type IV: extra and intrahepatic dilatation
- Type V: intrahepatic dilatation.

The relative frequency of different cyst types varies from series to series, but there is a general consensus that type Ic accounts for about 50%, type If for 25%, type IV for 10% and type V for 5% of cysts. Types II and III are very rare. Since then, other authors have devised classifications based on the cholangiographic findings of intrahepatic duct or pancreaticobiliary malunion, i.e. the so-called common channel. These later classifications have the merit of relating the anatomical findings to a possible underlying aetiology, however in practice the choice of classification has little impact on subsequent patient management.

A number of unclassified anatomical variants have been described, most of which relate to the presence of aberrant hepatic ducts, cysts without apparent connections to the biliary tree, and associated hepatic duct strictures. The existence of these variants emphasizes the importance of adequate peroperative investigations, in order that they be identified and treated appropriately.

Microscopic

The wall of a choledochal cyst is thickened and may vary from 2.0 to 7.5 mm in thickness. It is composed of fibrous tissue with scanty fibres of smooth muscle and elastic tissue. The cuboidal biliary epithelium may be present, but typically there is extensive ulceration, and only small patches of cells remain. The degree of histological damage appears to correlate with age. In infants with asymptomatic cysts there is fibrosis and epithelial loss, but relatively little inflammation. However, in longstanding cysts there is a marked acute and chronic inflammatory infiltrate. In some of the oldest patients the cysts may show evidence of metaplasia, dysplasia and early adenocarcinoma.

Immunohistochemical studies in ‘cystic’ choledochal cysts have shown a reduced number of ganglion cells, irrespective of the diameter of the cyst. By contrast, in ‘fusiform’ cysts, the number of ganglion cells varies according to the severity of the clinical presentation and the age of the patient. This would tend to support the hypothesis that ‘cystic’ cysts are truly congenital, whilst ‘fusiform’ cysts are generally acquired.
Presentation

Choledochal cysts may present at any age, but the majority (up to 60%) are diagnosed before the age of 10. The clinical manifestation of choledochal cysts differs according to the age of presentation. Choledochal cysts used to be uncommon in neonates, but more recently the incidence has been increasing owing to the widespread use of antenatal ultrasound scanning. These infants are initially asymptomatic, although a mass may be palpable in the right upper quadrant. For a while there was some question as to whether such cysts might be managed non-operatively. However, it has become increasingly apparent that early intervention is the best course of action, as the majority of these infants go on to develop cyst enlargement and/or obstructive jaundice. In some cases this may be due to ductal obstruction by an inspissated bile plug.

In older children, the commonest presenting symptoms are jaundice (75%), abdominal pain (50%) and an abdominal mass (30%), although the classic triad of all three occurs in less than half of cases. In general children tend to present in one of two ways: children with ‘cystic’ choledochal cysts usually present with a palpable right upper quadrant mass and intermittent obstructive jaundice, whilst those with ‘fusiform’ choledochal cysts usually present with recurrent abdominal pain due to pancreatitis. It has been reported that the bile ducts are significantly more dilated during the symptomatic phase than the asymptomatic phase, and that this may be the result of acute ductal obstruction by protein plugs. In 1–2% of cases, choledochal cysts may present acutely as a result of cyst rupture with subsequent bile peritonitis. The cause of rupture is usually unknown, and is thought to be spontaneous.

Choledochal cysts in adults appear to behave somewhat differently. Although adults may still present with typical features, they are more likely to have developed such complications as calculi, cirrhosis, portal hypertension, hepatic abscesses, bleeding cyst erosions, cholangitis and adenocarcinoma, any of which may be the presenting feature.

The differential diagnosis of choledochal cysts depends upon the mode and timing of presentation, and includes duplication cysts, biliary atresia, spontaneous perforation of the common bile duct, rhabdomyosarcoma, simple hepatic cysts, mucocoele of the gallbladder, hepatic tumours and lesions of the pancreas, kidney and adrenal gland.

Diagnosis

The diagnosis of choledochal cyst is generally straightforward once the possible diagnosis is considered.

Ultrasonography is usually the first-line investigation of choice. As has been previously mentioned, an increasing number of cysts are being detected antenatally as a result of routine antenatal scanning, and some cysts are being detected as early as 17–19 weeks of gestation. Ultrasonography can determine the size, position and shape of the cyst, as well as the anatomy of related structures (Fig. 12.2). However, it is less useful in
the case of fusiform cysts, as there

Figure 12.2 Ultrasonography of choledochal cyst.

are limitations in its ability to demonstrate the ductal anatomy at the pancreaticobiliary junction.

A plain abdominal radiograph may show a right upper quadrant mass which displaces bowel, and may reveal some radio-opaque calculi if these are present. Cholangiography provides the most accurate information about the cyst and its associated ductal anatomy. A cholangiogram may be obtained either by the ‘percutaneous transhepatic’ route (PTC) or by the endoscopic retrograde route (ERCP). However, these are invasive investigations with a significant complication rate, and although they provide excellent anatomical delineation, they rarely produce information which alters the subsequent management of the cyst. The risk of developing necrotizing pancreatitis after ERCP is such that this investigation is contraindicated in patients with active pancreatitis. Most surgeons agree that it is essential to have highly accurate information about the ductal anatomy, and that such information can only be obtained through some form of cholangiography. However, this information is best obtained by operative cholangiography, which is simple, safe and accurate. These studies are usually best performed by injecting contrast material directly into the common hepatic and distal common bile ducts, since contrast which is injected directly into the cyst itself tends to be excessively diluted and may not adequately display the ductal anatomy.

Computerized tomography (CT) scanning provides clear images of the cyst and adjacent structures. Its particular value is that it may reveal associated pathology within the parenchyma of related organs. Recent advances in spiral CT cholangiography may enable 3D reconstruction of the biliary tree and provide further anatomical information.

Hepatobiliary scintigraphy with technetium-99m labelled iminodiacetic acid (IDA) derivatives will often show the cyst, and is particularly helpful at establishing that the cystic structure is an intrinsic part of the biliary tree. A typical scan shows an initial filling defect in the liver, followed by a gradual increase in concentration within the cyst, which may take up to 24 hours to become apparent in patients with obstructive jaundice. IDA scanning is also helpful at assessing hepatobiliary function and anastomotic patency.
postoperatively.

Magnetic resonance imaging (MRI) has been used with increasing success (Fig. 12.3). MR cholangiopancreatography (MRCP) is non-invasive and will produce clear images of the biliary tree (Fig. 12.4), which may even demonstrate the ‘common channel’. At present most images lack the clarity and definition of those obtained by conventional cholangiopancreatography, although this is likely to become less of a problem as technology improves.

![Figure 12.3 MR scan of choledochal cyst.](image)

A variety of other diagnostic modalities have been suggested, including endoscopic ultrasonography, angiography, laparoscopy and intraoperative cyst endoscopy. All of these may provide useful information in selected cases, but in general they add little to the sum total of information available by more conventional means. Our preferred investigations are ultrasonography and MRCP, with an ontable cholangiogram where necessary.

Treatment

All choledochal cysts will require operative treatment. There is no role for long-term observation because of the risk of gallstones, pancreatitis, cholangitis, cirrhosis and malignancy. The theoretical requirements of an ideal operation are:

1. To allow free hepato-enteric bile flow.
2. To remove all cyst mucosa (with its associated malignant potential).
3. To exclude any ‘common channel’ and prevent pancreaticobiliary reflux.
4. To minimize the subsequent risk of cholangitis.

These criteria are met by the operation of ‘cyst excision and hepaticojejunostomy’, which has become the mainstay of choledochal cyst surgery. This operation is not suitable for all cases of choledochal cyst and may not always be possible in the acute situation, however there are many large series which testify to its continuing success.
Cyst excision and hepaticojejunostomy

**Preparation**

The patient will require a full preoperative workup, which should include a full blood count,

![MR cholangiogram of choledochal cyst](image)

**Figure 12.4** MR cholangiogram of choledochal cyst.

...coagulation profile, liver function tests and crossmatching. Any abnormalities in the above will need to be corrected in so far as this is possible. A full bowel preparation should be carried out, and systemic antibiotics should be commenced prior to starting surgery.

**Access**

Optimal access can be had with the patient placed in a supine position and with his/her back slightly extended. This can be achieved by placing a small radiolucent roll under the small of the back. A high transverse or subcostal incision provides excellent exposure. If possible, this incision should not cross the midline in order to reduce postoperative discomfort.

**Procedure**

A laparotomy is carried out, in which the appearance of the liver, spleen, pancreas and biliary tree are noted (Fig. 12.5). Fluid may be aspirated from...
the choledochal cyst for evaluation of microbial content and estimation of biliary amylase, elevation of which implies the presence of a common channel.\textsuperscript{4,15} Operative cholangiography\textsuperscript{4,22,52} and/or cyst endoscopy\textsuperscript{5,33,40} will help to define the anatomy of the cyst, and is particularly useful at revealing the presence of proximal ductal stenoses,\textsuperscript{25} calculi and aberrant ducts.\textsuperscript{27}

The choledochal cyst and gall bladder are mobilized, keeping to a plane of dissection which lies between the peritoneum and cyst wall. This plane is entered anteriorly, and is then extended around the sides of the cyst, taking great care to avoid damaging the hepatic artery, which may be very adherent to the cyst wall. The cyst is lifted forwards from the portal vein and is encircled proximally and (where possible) distally. The common hepatic duct is then divided at the level of the bifurcation and the cyst and gallbladder are reflected forwards (Fig. 12.6). This allows the dissection to proceed distally, as far towards the pancreaticobiliary junction as possible, whilst avoiding damage to the pancreas and related structures. At this point the bile duct is divided and the cyst and gallbladder are removed en bloc. The distal end of the common bile duct is either ligated or oversewn, depending on size.
The common hepatic duct is carefully examined to exclude any proximal stenoses. If these are present, they can usually be resected from the divided end of the duct.\textsuperscript{25} The common hepatic duct is then anastomosed to a 40 cm retrocolic roux loop of jejunum with interrupted absorbable sutures. It is important to achieve a wide anastomosis, which is proximal to any ductal strictures.\textsuperscript{25,52} The abdomen is then closed, leaving a small suction drain in place.

**Alternative procedures**

**External drainage**

In very complicated cases, particularly where there is obstruction, uncontrolled ascending cholangitis or cyst rupture, it may be preferable to establish some form of temporary external drainage, prior to carrying out definitive surgery.\textsuperscript{4} This can be achieved by percutaneous transhepatic cholangiodrainage where appropriate\textsuperscript{3} or by open T-tube cholecystotomy. Formal cyst excision and hepaticojejunostomy should be carried out once the general condition of the patient has improved.

**Cyst excision and hepaticoduodenostomy**

This procedure is somewhat simpler than the conventional operation, as it avoids the need to create a roux loop. It also has the merit of producing a more physiologically ‘normal’ anatomical result.\textsuperscript{51} However, it is believed that these patients are more vulnerable to duodenohepatic reflux, stasis and cholangitis, particularly where the intrahepatic ducts are dilated,\textsuperscript{3} and for this reason most authors prefer the roux loop hepaticojejunostomy.

**Mucosectomy and hepaticojejunostomy**

In longstanding choledochal cysts, the cyst wall may be so thick and adherent that it is very difficult to separate it from adjacent structures such as the hepatic artery and portal vein. In these cases it may be preferable to open the cyst and excise the cyst lining from within, without attempting to excise the cyst itself. Complete removal of the cyst mucosa in this way diminishes the risk of malignancy and allows a hepaticojejunostomy to be carried out in the usual manner.

**Choledochocyst-enterostomy**

This operation is technically straightforward and may have a role in the acute situation where radical excision is hazardous.\textsuperscript{4} However, it is very unsatisfactory in the long run, because of the high incidence of stasis, calculus formation, cholangitis and malignancy. Indeed, most surgeons would suggest that such cases should go on to have a formal cyst excision and hepaticojejunostomy in due course.\textsuperscript{53}
‘Antireflux valves’

It has been suggested that there might be benefits in creating a drainage limb with an antireflux nipple valve. The reported cases have done satisfactorily, but such operations are considerably more complex, and appear to offer no clear advantages over the more conventional procedure.

Miscellaneous

A variety of other procedures have been described, which generally pertain to the management of specific anatomical variants. Thus:

- Type II cysts may be treated by cyst excision and primary ductal reconstruction. These are rare lesions, of which there are only a handful of reported cases.
- Type III cysts are also very rare and may be removed transduodenally. Small lesions may be treated by sphincteroplasty or possibly by endoscopic sphincterotomy.
- Type V cysts are more difficult to deal with, and may require intrahepatic cystoenterostomy or even hepatic segmentectomy/lobectomy. Unfortunately, cholangitis and calculus formation can continue to be a problem, even after surgery.

Prognosis

In contrast to choledochocyst-enterostomy, which carries a long-term complication rate in excess of 50%, the results of primary cyst excision and hepaticoenterostomy are very satisfactory. There are many reported series with a long-term survival rate close to 100%, and the incidence of complications varies between 0 and 10%. Possible complications include calculus formation, cholangitis, anastomotic stricture, pancreatitis, anastomotic leak, adhesion obstruction and cholangiocarcinoma in the residual ducts. There is a general consensus that a number of these complications may relate to the quality of the hepato—enteric anastomosis, and in particular to the presence of residual ductal strictures. Because of this, several authors stress the importance of adequate peroperative investigation, and the desirability of a wide anastomosis. A number of reported series show that cyst excision and hepaticoenterostomy is almost complication-free in children under 5 years of age, and it is increasingly clear that early diagnosis and cyst excision offers the best hope of trouble free longterm survival. By contrast, the incidence of complications is much higher in older patients in whom the disease process is more advanced.

Conclusions

Congenital choledochal cysts are uncommon anomalies, which have a poor prognosis if left untreated. Early diagnosis followed by cyst excision and hepaticoenterostomy is the management of choice. Patients treated in this way have an excellent chance of
complication-free, long-term survival.

Key points

- 60% present before the age of 10 (and may present antenatally on ultrasound).
- Presentation of choledochal cyst:
  - Obstructive jaundice (75%)
  - Abdominal pain (50%)
  - Abdominal mass (30%)
  (All three together in <50% of cases).
- Complications of untreated choledochal cyst:
  - Intrahepatic calculi and cholangitis
  - Cirrhosis and portal hypertension
  - Hepatic abscess
  - Haemobilia
  - Cholangiocarcinoma.

- Diagnosis:
  - Ultrasound
  - CT
  - Cholangiography:
    - ERCP
    - PTC
    - MRCP
  - Scintigraphy (IDA/HIDA).

- Aims of management:
  - To allow free hepatico—enteric bile flow
  - To remove all cyst mucosa and therefore associated malignant potential
  - To exclude any common pancreaticobiliary channel, thereby preventing pancreaticobiliary reflux
  - To minimize the subsequent risk of cholangitis.

- Presentation:
  - Antenatal ultrasound finding
  - Palpable right upper quadrant mass
  - Childhood obstructive jaundice
  - Cholangitis
  - Cholangiocarcinoma (adult).

- Objectives of treatment:
  - Facilitate free hepato-enteric bile flow
  - Remove all cystic mucosa
  - Exclude pancreaticobiliary reflux via common channel
  - Minimize subsequent risk of cholangitis.

- Treatment options:
  - Excision of cyst with hepaticojejunostomy
  - External drainage
Mucosectomy and hepaticojejunostomy.

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Management of hydatid disease of the liver

Sandro Tagliacozzo

Biological and pathological basis of modern surgery

The echinococcus or hydatid cyst represents the larval stage of *Echinococcus granulosus*, a 2–6 mm long tapeworm. In the adult stage the tapeworm lives in the gut of the dog, the definitive host. The intermediate animal hosts, where the parasite lives and develops at the larval stage, are sheep, cattle, pigs and man (considered an ‘accidental’ intermediate host). There are also ‘sylvatic cycles’ of echinococcus which occur in Canada, Alaska, Australia and other countries with different definitive and intermediate hosts according to the local prevalence of animal species.

Human infection is direct or indirect from the dog through the parasite eggs (size 20–25 µm). Once ingested, they hatch and liberate the hexacanth embryo (bearing six hooks). This penetrates the gut wall, enters a mesenteric venule and is transported to the liver, where in most cases it will lodge. However, it may cross the portal network and reach the lung, where it may stop or continue beyond the vascular network, towards the various organs by way of systemic arterial vessels. In the liver the embryo loses its hooks and develops a larval cystic form: the echinococcus cyst or hydatid cyst. If it survives leukocytic response, the cyst grows, reaching 250 µm in diameter after 3 weeks and 1 cm after 5 months.

**Structure of the cyst**

The echinococcus cyst is composed of the wall and contents. The wall consists of two separate parts: the inner endocyst, namely the wall of the true vesicular metacestode, and the outer connective pericyst or ectocyst, deriving from the host organ, in the case of man the liver, able to ensure nutritional exchanges for a long time (Fig. 13.1). The wall, in
Figure 13.1 Structure of the liver hydatid cyst. L: Liver; P: pericyst; C: chitinous layer; G: germinal layer; BC: brood capsules or vesicles; P: protoscoleces; DC: daughter cysts (similar to mother cyst).

turn, is composed of two layers. The outer layer consists of a cuticle up to, or over 1 mm thick, the chitinous layer, similar to the white of a boiled egg, composed of concentric hyaline laminae. The inner layer consists of a thin (10–25 μm) germinal or parenchymal layer, which represents the living tissue, composed of an outer basal syncitial layer and inner nucleated cells. Its vesiculation perpetuates the parasite life cycle. In a fertile adult cyst, the inner surface of the germinal layer is scattered with innumerable granules, brood vesicles or capsules, 250–500 μm in diameter. They are released into the cystic fluid and, together with the hooks, they form the so-called hydatid sand. Each granule contains 5–30 darker ovoid corpuscles. These are the cephalic ends of echinococcus or protoscoleces, invaginated and covered with an anhistic cuticle. Hundreds of thousands of them can be contained in 1 ml of sand! Protoscoleces can produce implantations of cysts in the viscera if there is cystic fluid dissemination.

For a long time, the cyst contents can be composed of hydatid fluid only, a colorless fluid, clear as rock crystal (univesicular cyst), while in the mature cyst there may be a number of cysts similar to the mother cyst, called daughter cysts (multivesicular cysts). The origin and cause of daughter cyst formation is not well known, apart from a non-specific stress of the germinal layer for impaired vital exchanges with the host and decreased endocyst pressure.1 Among the various causes, pericyst thickening and the penetration of bile between the pericyst and cyst wall and inside it are of concern for the surgeon.
The pericyst, initially composed of very thin connective lamina, subsequently tends to become thicker (up to 1 cm or more), sclerose and calcify. The process of cyst expansion causes compression of hepatic parenchymal structures, in turn engulfed into the pericyst. Large vessels are compressed and displaced while, however, remaining patent for a long time. Similarly, bile ducts remain patent and may open into the pericyst, between it and the parasite wall. This phenomenon is very frequent, unlike the rare frank rupture of the cyst with effusion of the cyst contents into a large duct and the main bile duct. This is of the utmost importance for surgery, since on the one hand its appearance causes major changes in the cyst and pericyst development, and on the other it is a factor in the development of postoperative complications such as biliary fistulas. Bile filtration in the virtual interstitium between the pericyst and chitinous membrane can form a perivesicular biloma with loss of direct contact of the cyst with the pericyst, a decrease in the mother cyst pressure and membrane rupture, all phenomena which from early on can cause endogenous vesiculation. At the same time, the appearance of bile is preliminary to cyst infection.

Endogenous vesiculation indicates an initial positive attempt at survival by the primary parasite, otherwise condemned to death and degeneration.
Figure 13.3 Exogenous vesiculation: microscopic appearance. (A) Brood capsules and protoscoleces contained in a protrusion of germinal layer within the cuticle; (B,C) intrapericyst exogenous vesiculation hydatid membranes within the pericyst of primary cyst; (D) extrapericyst exogenous vesiculation encircled by a new pericyst and protruding in the liver parenchyma adjacent to the mother cyst.

Subsequently the neoformed hydatid material packed into the cystic cavity tends to show signs of stress and to degenerate extensively with different aspects of: fruit jelly, putty, plaster, dry clay or pus (Fig. 13.2). At the same time, the fibrous pericyst becomes thicker and calcium deposits appear as increasingly extended and confluent granules and laminae, forming in some cases a continuous thick shell. Some authors consider these degenerative aspects as corresponding to the parasite’s death, however this is not so. Except for extreme cases, within the degenerate material, viable hydatids can be found.² It is to be stressed that in many cases, the parasite ensures its survival and even favors its expansion in the involved organ by exogenous vesiculation.

Protoscoleces and brood vesicles generated by the germinal layer can penetrate the chitinous membrane through fissures and then tend to advance into the pericyst.³ Alternatively, there may be germinal islets trapped between the lamellae of the cuticular layer. Once the germinal elements penetrate the pericyst, they may grow inside and then project towards the liver parenchyma as diverticular protrusions surrounded by their own thin pericyst (Fig. 13.3). In their cavity, they contain cysts that grow favored by easy exchanges through the thin neoformed pericyst and behave as the mother cyst. Because there is no connection with the inner surface of primary pericyst they cannot be detected.
or even suspected with the most careful examination after emptying (Fig. 13.4). The exogenous cyst, while growing, can pull away from the mother cyst and this results in the commonly observed pattern of two or more adjacent cysts, or ‘satellite cysts’, separated by a parenchymal septum usually rich in vascular and ductal structures already displaced by the mother cyst. In other frequently observed instances, the exogenous cyst remains in contact with the primary cyst separated by a thin residual septum (‘sand-glass-like cyst’), or with the collapse of separating septum, the two cavities communicate through a more or less wide operculum (‘sacculations’).

As for the presence and frequency of exogenous vesiculation, the phenomenon is either ignored or largely underestimated, most likely because of the preference for conservative operations which do not allow its identification. However, it is recognized in about 30% of radical operations for multivesicular cysts. This incidence is bound to markedly increase when we accept the hypothesis, mentioned above, that sand-glass-like cysts and dual and multiple adjacent cysts are also an expression of the same event. Once the phenomenon was identified and quantitatively assessed, its importance was recognized beyond biological and pathological interest. Consequently, in a large number of patients where

Figure 13.4 Intra- and extrapericyst exogenous vesiculation. Macroscopic appearance in four total pericystectomy specimens. (A,B) Within the pericyst of open cysts viable daughter cysts are observed, separated from the mother cyst cavity; (C,D) clusters of pedunculated pseudodiverticula, non-communicating with the mother cyst cavity, covered with a thin pericyst and containing daughter cysts.
the surgical procedure then performed (and still largely performed) included no removal of the pericyst, this could not be considered effective: actually, only the cyst was resected. Viable, vital parasite foci remained, bound to represent disease progression. This was incorrectly considered a recurrence attributed to implantation from accidental dissemination because of poor protection of the operating field or reinfection. The latter interpretations, already unconvincing, have lost credibility, based on the observation that the findings of exogenous vesiculation and the incidence of recurrence in series of conservative surgery, interestingly enough, were similar, at about 30%. This was confirmed by the fact that the so-called recurrences were practically absent in series of radical surgery.

Briefly, from the knowledge of the parasite’s biology and the pathological relationship between the cyst and liver, stem the criteria of a new, rational surgery of the hydatid disease of the liver. It tends to critically minimize or reduce to nil postoperative biliary complications and the most serious long-term failure, namely recurrence.

**Indications for surgery**

For the two types of cysts mentioned above, indications for surgery are as follows:

- **Univesicular**, clear cysts with a thin and elastic pericyst (20% of cases) should be treated by conservative surgery (there is no need for radical surgery);
- **Multivesicular**, yellow cysts at different developmental stage with fibrous, thick and/or calcific pericyst (80% of cases) should be treated by radical surgery.

For modern rational operative surgery, the choice is not optional but rigorously determined. With the concept of radicality, surgery of liver hydatidosis becomes demanding and therefore selective surgical experience is required as the only means of ensuring a good chance of recovery.

Among radical operations, the choice between anatomical liver resection and total pericystectomy is at the surgeon’s discretion; however, it is readily understood that the second operation is undoubtedly more advantageous. In fact, the growth of the cyst is characterized by compression of vascular and ductal structures that supply large, healthy hepatic regions worth preserving, therefore favoring careful pericyst dissection with preservation of structures.

During its development, the hydatid cysts of the liver may undergo a number of complications, some of them clinically dramatic.

Infection of the cavity and its contents is less frequent than was previously thought (2–20%), and was not always clinically manifest. Most likely, it is caused by the penetration of bile into the cavity. Together with the contents, the mother membrane can be destroyed and consequently the altered excavated pericystic wall loses its function of delimiting the infectious process.

**Ruptured cyst**

Frank rupture into the bile ducts has already been mentioned. This occurrence should be distinguished from biliary communication through ductal fissurations, much more
frequent in mature cysts (40–70%).\textsuperscript{2,13} Frank rupture, usually into a central bile duct (5–12\% of cases),\textsuperscript{12} is characterized by the penetration of endocyst material into intra- and extrahepatic bile ducts to the infarction of the common bile duct and gallbladder.\textsuperscript{14,15}

The pattern of symptoms usually includes colicky pain accompanied and preceded by jaundice and cholangitic fever.\textsuperscript{16} Stenosis of the papilla of Vater and consequent, complete or incomplete, septic or aseptic cholestasis, when lasting 4–6 months, may then cause secondary biliary cirrhosis. In cases with suspected penetration of hydatid material into the bile ducts, intraoperative cholangiography and concomitant surgery with bile duct clearing and external or internal biliary drainage, preferably papillosphincterostomy, is mandatory.

A severe risk in the presence of a huge cyst is its rupture into the peritoneal cavity (5–12\% incidence).\textsuperscript{17} In most cases, the determining cause is blunt trauma and in children it may occur during play. In children, the cysts may reach huge dimensions and high pressure. At times, rupture into a free cavity may be spontaneous. Another cause of peritoneal effusion of hydatid contents is iatrogenic from percutaneous puncture for diagnosis or emptying, or it may occur during surgery with bad technique and poor isolation of the peritoneal cavity. This complication is very serious. Symptoms are complex, with acute abdominal pain, local signs of peritoneal irritation and anaphylactic reactions of varying degree to severe shock, characterized by intense dyspnea, tachycardia, marked hypotension and urticaria.\textsuperscript{18–20} The reaction is due to the abrupt release of allergens reabsorbed from the peritoneal serosa and conveyed to the circulation in a sensitized subject. The cyst rupture may be followed by bile peritonitis with a well-defined or insidious clinical pattern.

Initially, in some cases, rupture may be overlooked and show only long-term manifestations. The most severe manifestation results from the dissemination and implantation of endocyst material on the peritoneal surface shown as innumerable cysts of varying dimensions, often in clusters.\textsuperscript{21} Consequences include occupancy, compression and displacement phenomena of organs and structures with extremely severe and complex clinical patterns and corresponding general impairment.

Benzoimidazole therapy has represented a marked improvement in the treatment of rupture of a cyst into the peritoneal cavity. It should be started immediately and given for a prolonged period of time.\textsuperscript{22} In cases of manifest, diffuse and inoperable peritoneal hydatidosis, ultrasonography-guided emptying of huge, packed cysts is useful to relieve the most severe clinical patterns of compression and dysfunction.

Rupture of the cyst into the thoracic cavity and bronchobiliary fistula (BBF) are other very severe complications of liver hydatidosis. They are often caused by huge multivesicular cysts of segments VII and VIII, protruding through the diaphragm. Necrosis of the latter from compression, wear and often infection results in cyst communication, exceptionally with the pleural cavity and usually, for previous adhesions, with the pulmonary parenchyma of the lung base, corresponding to the posterior and/or lateral basal segment or medial lobe. Pulmonary inflammation together with the necrotizing action of bile causes erosion into a peripheral bronchus with subsequent passage of hydatid material and bile into the bronchial tree, favored by the differential pressure gradient (Fig. 13.5). Rupture of the cyst into the bronchial tree may be dramatic with abundant expectoration of bile and hydatid material. Daily bile effusion is persistent
and increasing, resulting in an extremely severe clinical pattern characterized by cough, abundant expectoration up to 1000 ml of bile and hydatid contents, fever, and very poor general condition. Bronchopulmonary involvement tends to involve several segments (fatal necrotizing bronchitis) with necrosis and abscess cavities. Hydatid BBF is a very severe clinical and pathologic complication requiring early surgery, preferably simultaneously for both the lung and the liver cyst, and is associated with a high mortality.

Figure 13.5 Bronchobiliary fistula. Biliary rupture of hepatic cyst, common bile duct obstruction with hydatid material, communication between the cyst cavity and a basal bronchus through an area of attenuated diaphragm are represented.
Diagnosis

Hydatid cyst of the liver may be asymptomatic for years, at times for decades. Diagnosis may be accidental, based on an incidental clinical exam that detects swelling when the cyst is located in a palpable abdominal area or, in the case of a more or less relevant hepatomegaly, subsequently assessed with other exams. Liver hydatidosis may be an incidental finding in a radiograph of the hepatic region when the cyst is calcified, during a chest radiograph for a raised hemidiaphragm or during US exam performed for other reasons such as gallstones. In children, large hepatic swellings from hydatid cysts are accompanied by evident deformations of the chest involving the last ribs and arches. Apart from a sense of pressure, a cyst of the liver may cause boring pain at the basal chest for the diaphragmatic pleural or peritoneal reactive process. Dyspepsia, possibly from reflexes originating in the periductal nervous network, is not unusual. Cholestasis from major bile duct compression may be responsible for fever, also of high grade. Liver function tests remain normal for a long time.

Diagnosis is established using several investigations. Conventional radiology may show a raised hemidiaphragm. In calcific cysts, high density roundish shadows are readily visualized (Fig. 13.6).

Diagnostic imaging

Ultrasonography (US)

At present, this is the most common and useful examination. It is non-invasive, low-cost and reproducible, thus suitable for postoperative follow-up or during medical therapy. US supplies precise information on the size, number, location and vascular and biliary relationships of the cyst as well as on its structure. Images have been described and classified according to types and classes.27–30

- Univesicular cysts (type I) are represented by a round anechoic area with posterior enhancement and possible internal echoes due to hydatid sand.
- Images of partial or total detachment of the chitinous layer (type II) show the ‘dual wall’, ‘water-lily’, ‘water snake’ signs.
- Multivesicular cysts (type III) are represented by the typical images of daughter cysts identified by the ‘honeycomb’, ‘rosette’, ‘spoked-wheel’ and ‘cluster’ sign (Fig. 13.7).
- Semi-solid or pseudotumoral aspects (type IV) are characterized by hypo- and hyperechogenicity.
- Partially or totally calcific cysts (type V) are represented by echoic menisci with posterior shadowing. Calcification is considered pathognomonic especially in endemic areas.

US supplies significant information on biliary involvement of hydatid and parahydatid disease:
Figure 13.6 Plain radiographs. (A) Partial ‘en brioche’ image of diaphragm profile; (B) calcific image pathognomonic of hydatid cyst.

Figure 13.7 US image. (A) Total detachment of parasite membrane from pericyst; (B) multivesicular hydatid cyst: ‘rosette’ sign.

intra- and extrahepatic bile duct dilation, cholelithiasis or common bile duct lithiasis, and the condition of the hepatic veins, portal system and caval vein. US is also useful in postoperative follow-up.

**Computed tomography (CT)**

At present, CT is the procedure of choice on which radical surgery is based. Besides
precise information on the cyst features, similar to those acquired by US (Fig. 13.8), CT is fundamental in the identification of the vascular relationships, number, site and type of the cysts: dual, sand-glass like, with vesiculations (Fig. 13.9). CT is invaluable for the diagnosis of recurring patterns. Spiral CT is at present the gold standard investigation.

**Magnetic resonance imaging (MRI)**

This is complementary to CT, especially in the differential diagnosis with hepatocellular carcinoma, organizing hematoma and amebic abscesses.31–34 The introduction of fast sequences enables the acquisition of images during gadolinium infusion (DTPA). Multiple coronal scans evaluate non-invasively and accurately the relationships with vascular structures: portal vein and inferior caval vein, thus rendering invasive investigations such as venography and arteriography unnecessary (Fig. 13.10). Recently, with MR-cholangiography it has been possible to visualize the intra- and extrahepatic biliary tree with its bile contents.

**Figure 13.8** CT image. (A) Univesicular cyst; (B) ‘water-snake’ sign of membrane detachment.

**Figure 13.9** CT image. (A) Multivesicular cyst: ‘honeycomb’ or ‘rosette’ sign; (B) calcific cyst of segment VII in contact with the caval vein and causing intrahepatic duct dilation stasis.
**Angiography**

Arterial, parenchymal arteriography, inferior caval vein and hepatic vein venography now play a minor role after the introduction of US and CTangiography. They are used to detect the relationships with huge or central cysts and in the differential diagnosis with primary liver tumors or metastases.

Preoperative intravenous cholangiography is performed according to the clinical presentation. It may supply information on common bile duct anatomy, but it does not detect the biliary relationship of the cyst. Percutaneous cholangiography is contraindicated in liver hydatidosis for the risk of perforation and dissemination of hydatid contents. Endoscopic retrograde cholangiopancreatography (ERCP) can be considered the most suitable procedure for the characterization of the common bile duct and sometimes of the biliary relationships of the cyst. It allows pre- or postoperative papillotomy with associated bile duct clearing. During surgery and after emptying of the cyst in some cases peroperative cholangiography is very useful.

![Figure 13.10](image)

**Figure 13.10** (A) MRI coronal T1-weighted sequence after DTPA gadolinium injection with visualization of a cyst, about 2 cm in diameter, of segment IV at the level of portal vein bifurcation (in the same patient a bulky hydatid cyst of segment VII, VIII and V is present); (B) same technique in another patient. Inferior caval vein compression with marked stenosis caused by a bulky cyst of right hemiliver.

**Scintography**

A common procedure for many years, this has been practically abandoned as a preoperative exam. It is still valid to acquire postoperative anatomic and functional information.
Immunodiagnosis

Immunodiagnosis of hydatidosis now plays a minor role following the progress in diagnostic imaging. In fact, all serum tests are poorly sensitive and/or specific. The concomitant use of several tests is suggested to enhance the specificity when results are concordant and to enhance the sensitivity when there are discrepancies. False positives may lead to unnecessary chemotherapy or surgery. False negatives may lead to no treatment at all or to diagnostic puncture, with the consequent risk for anaphylactic shock and dissemination. Tests tend to become negative some time after removal of the cyst, thus they are useless for postoperative control of recurrence. In conclusion, positive and negative tests should be considered respectively reliable only when validated by concomitant findings of other exams. The most common immune tests are the Casoni skin test, the complement fixation test (CFT), the indirect hemagglutination assay (IHA), immunoelectrophoresis (IEP) and the enzyme-linked immunosorbent assay (ELISA). Finally, immunofluorescence (IF) of scoleces should be mentioned. It is a specific and sensitive reaction, but technically difficult to carry out.

Operation

According to location and size, cysts can be divided into parenchymal or superficial and vasculobiliary or deep. In turn the distinction may be based on the predominant vascular relationship. Obviously, the validity of the topographic definition according to hemilivers, sectors, segments or subsegments adopted by the most reliable classifications is confirmed. However, because hydatid cysts are spherical and often huge and because they can be removed sparing the healthy tissue then they do not fit properly into the usually adopted anatomical distribution, for cancer surgery in particular. While no intrahepatic expanding neoplasm can be free of vasculobiliary contacts, especially the hepatic veins, superficial cysts have vascular relationships limited to minor peripheral structures. Vasculobiliary or deep cysts represent about 75% of cysts that come to surgery and are those with relationships to first, second and third order branches of hilar elements, the hepatic veins and the inferior caval vein in both its supra-retro and subhepatic segments (Fig. 13.11). First and second order portal branches may be involved with deep cysts located close to the hilum. They are bulky, thus their dissection is difficult both in the case of hemihepatectomy or the more frequent total pericystectomy. Usually, the cysts of segment VII and VIII, on the right, and segment II on the left, have relationships with the major hepatic veins. In these cases dissection of the cyst from the cava and involved hepatic vein is mandatory. The latter should be ligated and sectioned or more frequently dissected and preserved with adjacent lateral sutures. As for bile ducts, their adhesion to the pericyst is very dense and dissection is difficult. If there is a communication, this requires very careful dissection for effective repair.
Residual surfaces after removal of deep or vasculobiliary cysts: dissected and preserved vascular and biliary elements are indispensable for the survival and function of parenchymal structures adjacent to the cyst. (A) The caval vein (c) and right hepatic vein with branchings are well visualized; (B) vasculobiliary network of hilar origin distribution.

With reference to the hepatic segments of the Couinaud classification, it is suitable to distinguish vasculobiliary or deep cysts according to the topographical denominations immediately indicative of their predominant relationship with hilar vascular and/or hepatic venous or caval vein structures:

- Hepatic venous cysts
- Right or caval intermediate cysts (segments VII, VIII, VI, V)
- Hilar cysts
- Central cysts (interportohepatic) (VIII, IV and V).  

In turn, hepatic venous cysts are divided into right (VII and VIII), median (IV), left (II); hilar cysts are divided into right (V), anterior median (IV) and posterior (I), left (II and/or III) (Fig. 13.12).

Evidently, there may be some overlap between locations. For example, right hepatic cysts may extend to the mid right lobe and left hepatic cysts may be located between the two hila. Obviously, these possibilities do not affect the principles on which the classification is based.

Access must be wide for two main reasons: first, because of the frequent presence of adhesions of the protruding cyst to adjacent structures and organs, in particular the diaphragm. Second, because of the need for extended liver mobilization to control the vessels and exploit the liver flexibility to reduce the cavities or residual surfaces after pericyst removal.

Bilateral subcostal incision and right thoracolaparotomy are most commonly performed. The former is definitely suitable for liver surgery, however in hydatidosis because of the very tight adhesions to the right hemidiaphragm in particular, more readily separable only by exposure of the two peritoneal and pleural surfaces, a thoracic approach should be considered. On the other hand, because surgery has become highly
specialized, thoracolaparotomy has fallen into disuse by most surgeons expert in liver surgery.

![Figure 13.12](image)

Figure 13.12 Topography of vasculobiliary hydatid cysts. 1, 4, 8: Right, median, left hepatic cysts; 3, 5, 6, 9: right, anterior median, posterior median, left hilar cysts; 2: intermediate cyst; 7: interportohepatic cyst.

However, thoracolaparotomy increases access during mobilization and dissection of the liver and reduces excessive liver torsion and compression that could cause intraoperative rupture of cysts into the peritoneal cavity or bile ducts. Major steps during right thoracolaparotomy, usually performed on the 8th intercostal space are the oblique patient’s position and the splitting of the operating table. The incision starts from the posterior axillary line, follows the space to the costal arch, crosses the abdomen to reach and advance over the median line, 2 cm above the umbilicus. Once the intercostal muscles, the costal arch and the abdominal wall are incised, the incision of the diaphragm follows the course of muscle fibers to the posterior angle of the cut. The incision edges are separated using Finochietto’s self-retaining retractor.

In reconstruction, after the retractor is removed and the table split is reduced, the diaphragm edges are sutured with slowly absorbable stitches and then the thoracic and abdominal wall are also sutured. Stitches in the thoracic wall are knotted when all are apposed and adequate resection of the costal arch cartilage is performed. This is mandatory for perfect costal approximation temporarily obtained using a Bernard forceps to grasp the ribs above and below the incision.

Protection of the operating field is mandatory before the planned operation on the cyst or before the cyst is emptied. A cautious approach is to apply protection before liver dissection and when the cyst is protruding from the liver surface and adhering to the adjacent structures and organs. Isolation of the peritoneal and/or pleural cavity to limit the access to the operative field is achieved with dry gauze, preferred by the author, or soaked in a parasiticidal solution or hypertonic saline, however not considered harmless by all. During prior emptying of the cyst the gauze pads should be placed around the site of puncture by the trocar.

Emptying of the cyst is performed with a large caliber trocar, connected with an aspirator by a similarly large non-collapsible tube. As soon as the cyst pressure is
relieved and the protruding pericyst tends to collapse, two of its plicae are grasped and raised with Allis or ovum forceps. The amount emptied depends on the contents: it will be practically complete in univesicular cysts, more or less partial if the hydatid material is abundant and dense. When the pericyst wall is opened with electric cautery, direct emptying is completed through a large tube with a frontal opening, connected to a powerful aspirator. If possible, two alternate, separate systems are more suitable because of the inevitable tube blockage. Now and then paraffin oil aspiration is useful to facilitate the flow of material in the tube. Aspiration is easier with a long ovum forceps to mobilize the material attached to the endocyst walls or break big daughter cysts. Clearing of possible communicating sacculations is also necessary. In case of adjacent cysts, separated by a relatively thin septum on indirect palpation, emptying should be performed with the trocar introduced into the cavity through the septum to minimize the risk of dissemination. The breach is widened to complete emptying.

For sterilization of the cyst, performed by injection before emptying, several parasiticidal substances have been used: 2–10% formalin solution, 33% hypertonic saline, 0.5% silver nitrate, 10 vol hydrogen dioxide, 1% iodide alcohol solution and 0.1% cetrimide. This method should not be followed for two reasons. First, it appears deceptive to pretend that the entire contents of a multivesicular cyst could be reached by the substance in a few minutes, undergoing the supposed parasiticidal effect. In any case, it would be ineffective against vital elements trapped into the pericyst or developed externally as exogenous vesiculations. Second, practically all solutions markedly damage bile ducts, the cause of severe sclerosing cholangitis, even if in the absence of an open communication. Consequently, apart from the actual efficacy, the injection of parasiticidal substances, leaving them in the cavity for some time, should be abandoned. Some, such as iodine solution, can be applied after emptying of the cyst. Benzoimidazole drugs have been used preoperatively for cyst sterilization, however surgery must be delayed and this is not attractive to patients and surgeons because the outcome is not definite.

Operations not involving the removal of pericyst adhering to the hepatic parenchyma are considered conservative or non-radical. They were devised many years ago and continued because there were no alternatives, with unsatisfactory results, high morbidity, biliary complications in particular, and a high incidence of recurrence. At present, most conservative operations should be abandoned and replaced by a single updated operation with indications limited to clear univesicular cysts. Their pericyst is thin and elastic, through which the underlying parenchyma is seen. Exogenous vesiculation or biliary fissurations cannot be missed; the latter evidenced by the color of cystic fluid. However, the large size and high pressure typical of these very viable cysts, may be responsible for biliary wall impairment which results, after the cyst is removed, in postoperative bile leakage. In these rare cases, bile is seen through the drainage tube in the residual cavity and is observed for 15–20 days, followed by recovery. Bile leakage following incorrect conservative operations on cysts with thick or calcific pericyst lasts much longer and sometimes causes persistent external biliary fistulas.
After emptying and clearing the cyst cavity, its size and penetration in the depth of liver, especially towards the hilum, the hepatic veins and the retrohepatic caval vein, is assessed. The possible relationships with the hepatic ducts and biliary communication should be carefully evaluated. In fact, it may become evident after emptying and removal of membrane. The extent of pericyst resection is based on how much of it is protruding or how close it is to the hilar and adjacent major vasculobiliary structures. A pericyst margin adequate for subsequent suturing should also be considered. Resection is performed with electric cautery and the help of Allis forceps on the residual margin; particular attention should be paid to adjacent structures at risk (Fig. 13.13). The analogy of the method with the ‘dome saillant’ resection proposed by Lagrot in the 1950s and still used is only apparent because here it is limited to clear cysts with a thin and soft pericyst after wide field exposure, complete liver mobilization, control of hilar and caval structures. All these measures enable the resection of ample pericyst surfaces up to two-thirds of it, while suturing of residual margins exploits the flexibility of the liver once free of its ligaments.

The control of bile loss is very important. Bile transudation may occur on the resection margins from small orifices, which must be sutured to prevent bile collection within the cavity. As for the search for major communications, the induction of biliary hypertension
by compression of the distal hepatic pedicle over the duodenum, squeezing the gallbladder at the same time, may be useful. The possible even minimal communication is evidenced by a drop or flow of bile. In practice, to identify biliary communications injection of dyes is useless since the bile is evident per se and does not soil the surfaces. Peroperative cholangiography is also useless because small dehiscences are not detected, while it is unnecessary in major ones. Cholangiography is useful in the true rupture of the cyst into the common bile duct with effusion of hydatid material. However, these are not typical patterns of univesicular cysts.

Once the residual cystic wall has been controlled, closure is performed by suturing the resection edges. Approximation can be longitudinal, transverse or oblique, but traction should be prevented and circulation in the adjacent parenchyma should not be jeopardized. A double, continuous inverting suture is made with atraumatic mid-sized needles and chromic catgut. In many cases the procedure corresponds to the canalization of the cavity on a rubber tube, advanced outside the cavity in the most suitable position through a counterincision at the level of the hypochondrium or flank. The progress of postoperative cyst collapse until complete obliteration of the cavity can be documented by contrast radiography. Drainage is preferred because in spite of the absence of obvious biliary communications, some days after surgery there may be significant bile leakage which, if drained, heals with no further consequences. In theory, a cavity, reduced as described above, or even left in its original size, could be closed without drainage and heal with no complications. However, the actual possibility of bile collection with the risk of infection and abscess formation, argues in favor of the placement of drains. The use of omentum to fill the cavity or cover the residual surface is also unacceptable. In fact, the omentum, an excellent barrier against infections, is not equally effective against bile and may even become necrotic. When packed into the cavity, it hinders the interpretation of US or CT images in long-term follow-up to monitor the behavior of the cavity and identify recurrence.

Radical operations include anatomical liver resections and total pericystectomy.

Liver resections have been performed for many years for the surgical treatment of liver hydatidosis, and in the majority of cases the indication was of necessity. Giant cysts that occupy an entire hemiliver and beyond; multiple cysts with exclusive or predominant distribution to a lobe; huge cysts occupying completely a hepatic duct so as to hinder its preservation; ‘recurring’ cysts previously treated with conservative surgery for a huge primary cyst are all rare indications representing approximately 10% in the various series. Technically, these anatomical resections are similar to those performed for other indications, except for the possible extension of the cyst beyond the anatomical limits of the hemiliver or sector to be removed and the biliary relationship on which the indication was probably based (Fig. 13.14). The first occurrence may involve difficult pericyst dissection from vasculobiliary structures supplying territories to be preserved. The techniques to be performed are those of pericystectomy. The biliary relationship may be a result of the rupture of the cyst into a first order duct or by marked displacements, deformations and mural alterations of one or more ducts. Left lateral resection, where parenchymal preservation is unlikely, is usually more frequently required.
Wedge resections should be mentioned in passing. They are still valid in minute marginal anterior cysts.

Total pericystectomy (or cystopericystectomy) is considered to be the ideal radical operation suitable for the requirements of radicality for the hydatid disease, with maximal preservation of hepatic tissue and complete early recovery. Its feasibility is similar to that of liver resections. The same basic training is required, enhanced by a specific experience. The operation was conceived and proposed by Napalkoff in 1927 and again described in 1936 by Melnikoff. However, in subsequent experiences, results were unsatisfactory and even disastrous due to hemorrhage; thus, following unanimous disapproval, it was practically abandoned. Costantini applied it again in 1950 and Yovanovitch in 1959, with indications for peripheral cysts, distant to porta hepatis. Bourgeon, the most convinced supporter, advocated it in 1961, 1964 and 1977, but in practice, in many cases, he favored partial pericystectomy.
Since the early 1970s it was understood that the persistence of pericyst with its close biliary relationships, more or less wide fissurations and true ruptures, represented the main cause of frequent postoperative complications: abundant, prolonged bile leakage, infections, residual cavities, biliary fistulas.\textsuperscript{72,73} The other major reason for the removal of pericyst, exogenous vesiculation and implantation of viable parasites in and out the pericyst, was still overlooked. The correlation of persistent hydatid material with the frequent recurrences with which surgery of hydatidosis seemed to be inevitably burdened, was noted in several series.\textsuperscript{11,74} At present, the operation has gained widespread acceptance.\textsuperscript{75,76} Pericystectomy can be performed with the cyst closed or open. In the first case, en bloc removal of the pericyst and its contents is a safe operation with respect to the risk of contamination. In the second case, emptying may favor dissemination, although protection measures make it quite improbable. However, protection measures are necessary also before dissection of a closed cyst. The latter procedure is more elegant, rapid and simpler, but in the case of bulky, deep cysts or those which have ruptured into the common bile duct, the procedure may be risky, thus operations on the open cyst are preferable and necessary. This enables the dissection of pericyst from vasculobiliary structures, even in the most difficult conditions.

When the cyst is protruding from the liver surface at any site, dissection is started in close contact with the pericyst and performed along the transition line between it and the

\textbf{Figure 13.15} Total pericystectomy. Dissection of pericyst from vasculobiliary structures should be along the presumed centriperipheral direction (following the direction of emerging and merging branches).
parenchyma sometimes delineated by a groove. This plane is very important, defined according to the features of the cyst and hepatic tissue. Concomitant, chronic, non-parasitic liver disease, or consequent to hepatic vein stasis caused by the cyst, a true Budd-Chiari syndrome, creates major difficulties. The smaller vascular branches entering the pericyst must be electrocoagulated or ligated and dissected. Caution is necessary because consequent bleeding would hinder the field of vision with unnecessary and even considerable blood loss during the procedure. Dissection of large vessels from the pericyst should be centripetal and along the course of vascular and biliary structures, following the direction of its emerging or confluent branches (Fig. 13.15). In other words, for the dissection around the hepatic veins the direction should be from the apical liver convexity towards the free margin and for hilar elements from the hilum to the periphery. Therefore, in vessel dissection, the surface corresponding to the obtuse angle the branches describe when emerging or merging should be preferred. The large vessel is more readily dissected and longitudinal lacerations are prevented when scissors are trapped into the acute angle between it and its branch. The tight adhesion of large vessels to the pericyst rules out the finger fracture procedure, which might result in pericystectomy as an incorrect, hazardous technique. The use of the ultrasound dissector, which favors the visualization of the vascular network, and hemostasis seems advantageous, while dissection of large vessels from pericyst is still feasible.\textsuperscript{51,77}

\textbf{Figure 13.16} Total open pericystectomy. Stripping of pericyst and traction on each strip by folding facilitates deep dissection of vasculobiliary structures also in case of calcific pericyst.
Dissection is circumferential, according to the cyst location. The dissected parenchyma tends to flatten its spherical hollow surface, leaving the still adhering pericyst area largely uncovered. In very deep cysts and in bulky cysts dissection may become hazardous because the field is no longer under control. For this reason, and to prevent excessive manipulation of the cyst, its emptying is suitable and then open cyst pericystectomy can be performed. The same procedure should be followed in cases of cysts with pedunculated protrusions from exogenous vesiculations. They have a very thin pericyst, which may cause possible lacerations at the level of the pedicle in particular. As a general rule, any risk of cyst rupture should prompt emptying and then operation on the open cyst with a number of advantages, including the possible exploration of the cavity and better handling of the pericyst wall. By folding the pericyst at the level of the dissection plane the procedure is facilitated, especially if the already dissected pericyst is sectioned in strips, subjecting each to tension independently (Fig. 13.16). If the pericyst is not very calcific, another very useful method is to carefully incise it with a scalpel on its internal surface to reach the adhering parenchyma. With a cross- or star-shaped incision, and by lifting backwards each strip with Allis or Kocher forceps and dissecting from different sides, apparently unfavorable situations are resolved and dissection can be completed (Fig. 13.17). Access to mid-sized cysts through a

**Figure 13.17** Total open pericystectomy. Cautious full depth incision of pericyst with a lancet on the cavity bottom allows access to vessel dissection from several directions, even in the case of very thick cysts.
fissure is another very effective and in some cases resolving technique. Once major vasculobiliary structures are reached with dissection, the corresponding fissure is identified, opened and extended to the cyst wall. The cyst is accessible from several sides and seems to become more superficial (Fig. 13.18). Retraction of intersectorial surfaces resolves the problem of the difficult access to the deep hemisphere of the cyst. Therefore, operations on the closed cyst are facilitated with relevant vascular relationships as the interportal liver becomes accessible (Fig. 13.19).

Despite all precautions, during pericystectomy, vascular lacerations may occur, especially the hepatic veins. It is possible to interrupt the dissection on that side of the cyst and compress the parenchyma against the pericyst while the operation is resumed on another side. Direct digital compression of lacerated vascular segment can also allow further dissection and achieve more adequate exposure. The laceration becomes more readily identified and its definitive hemostasis can be performed with a suture which should also maintain vessel patency.

During pericystectomy temporary clamping of the hilum and/or caval vein may be necessary. To prevent bleeding, clamping is limited to 10–15 minutes, a few minutes being usually enough. Pringle’s maneuver is not suitable for pericystectomy because of the relatively long time required for pericyst dissection. Clamping of hepatic veins is rarely necessary. Preventive isolation and application of a tape around the subhepatic caval vein and above the confluence of hepatic veins can be a safety precaution. The preparation of the right hepatic vein or the caval surface at the level of its confluence is a valid alternative, especially for cysts of segment VII and VIII. It should be kept in mind that a hepatic vein laceration proximal to the confluence is to be feared more for air embolism than for bleeding.
As for bleeding during total pericystectomy, the aversion shown for a long time by surgeons to this operation was directed against bleeding, at times dramatic, caused by it. This is a possible occurrence, but only when liver surgery is performed by inexperienced surgeons.

As for the amount of blood that should be available for transfusion, within wide variations, 2–4 units are required for peripheral cysts and 6–7 for central ones. Autotransfusion and intraoperative recovery, the latter obviously limited to the sterile phases of the operation, offer great advantage.

Among radical operations, in subtotal pericystectomy one or several areas of the pericyst are not excised; they adhere to vascular structures and their excision would be too hazardous. This fairly common solution is being abandoned because of the growing experience. It may be justified in some crucial areas such as the confluence of hepatic veins into the caval vein and hilar structures, in particular contralateral ones, and in case of cysts extending beyond the involved hemiliver. This is also the case for the retrohepatic caval vein, not rarely protruding in large cystic cavities of the right lobe. The decision whether to leave an area of pericyst in these sites is up to the surgeon alone.

During pericystectomy, a hepatic region may be ischemia because of impairment of blood supply. In this case, the extension of the involved region should be evaluated and identified. In some cases, its removal with pericyst resection is not a problem. Vascular impairment of a wider region is entirely different, but this should not occur.

After pericyst excision, the residual liver surfaces must be treated. They are characterized by a vascular profile of protruding hepatic veins or hilar structures. In general, closure of surfaces with suture of liver margins should not cause any vascular embarrassment. The procedure is simpler after the excision of deep cysts, although closure of external surfaces is very often feasible. In both cases the procedure does not correspond to the closure of a residual cavity but rather to the approximation of involved
liver surfaces which then grow and merge through the rapid process of liver regeneration. If approximation is complete and there is no reason to

**Figure 13.20** Exploration and cleansing of biliary tract. Through papillosphincterostomy the spoon for stones or a probe can be carefully advanced to identify the biliary breach and specify the type of communication, whether lateral or terminal, with the cyst cavity.

suggest bile loss, no drainage is necessary in the residual space. With the pericyst completely removed, an omental flap can be used on residual surfaces to prevent adhesion of displaced loops of bowel.

Because of the previously mentioned relationships of the cyst with the intrahepatic bile ducts, during operations on the cyst, complementary surgery on the bile ducts may be necessary. It may be required also for ‘parahydatid’ biliary pathology, dominated by cholelithiasis which is either consequent, incidental or pre-existing. En bloc cholecystectomy may be necessary for cysts of segments IV and V.

Surgical measures to be taken for intrahepatic bile ducts in case of communication or rupture have already been described. In rupture, peroperative cholangiography can detect bile duct obstruction with clear images of filling defects. Access to the common bile duct is through a choledochotomy or transduodenal papillosphincterostomy with complete clearing of the duct (Fig. 13.20). Bile duct drainage can be external with a T-tube or
internal following a papillosphincterostomy or, more rarely, biliary-enteric anastomosis. The author prefers papillosphincterostomy. This can be performed even when pressure increase in the bile ducts secondary to papillitis is suspected, to prevent the appearance or persistence of bile leakage. At present, prophylactic surgical biliary diversion can be replaced by endoscopic papillosphincterotomy, when necessary.

### Medical therapy

For over 20 years, benzoimidazole chemotherapy has been used in the treatment of hydatidosis. As for liver hydatidosis, it is to be anticipated that results are varying and unpredictable. Biological recovery is rare and limited to young adults affected by univesicular cysts, more often resulting in morphological changes of the cyst, visualized on US or CT exams. The primary parasite can be impaired or even dead, but all proliferation does not cease. This result is achieved after prolonged treatments and is not free of severe side effects due to drug toxicity, and poor absorption and difficult penetration into the cyst, which require high doses. For these reasons, medical therapy is clearly subordinate to surgery. Indications for medical management include inoperable patients, preparation for surgery, patients who could not undergo radical surgery and prophylaxis of postoperative recurrences. These indications have subsequently been extended.

Benzoimidazole compounds include mebendazole, a well-known antihelminthic used in the treatment of intestinal helminthiasis, followed by flubendazole and albendazole. Their mechanism of action involves their interference with the basic structures of the parasite, with the inhibition of absorption mechanisms of glucose in particular, and more generally of nutrition. Absorption following oral administration is low, liver metabolism rapid and clearance is through the urine. Fat intake favors absorption and increases plasma concentration, while it is low inside the cyst and the in vitro proven parasiticidal action is hindered. Doses administered in man are: for mebendazole 4–5 g/day corresponding to 50 mg/kg/day with administration during meals for 3–12 months and for albendazole 10 mg/kg/day in one or two daily administrations in four one-month cycles with 15 days rest, or 10–12 mg/kg/day continuously for 3-month cycles.

In the assessment of results of chemotherapy in man, the definition of death of the parasite and recovery from the disease poses big difficulties and relevant uncertainties. Viability tests on the surgical specimen cannot be considered conclusive as confirmed by the development of parasites from culture of cystic fluid shown to be negative on direct microscopy. More particularly, it is difficult to understand that the drug could overcome the barrier of a dense fibrotic or calcific pericyst, up to 0.5 cm thick, and kill the hydatid material packed into the cavity. It is difficult to believe that exogenous vesiculations within the pericyst can be reached. Recurrence following albendazole therapy occurs in at least 20–30% of responsive cases, to which a further 20% of patients, considered negative in whom no change was visualized, should be added.

PAIR (puncture, aspiration, introduction, reaspiration with 95% alcohol or 30% saline solution) is a non-surgical treatment of hydatid cysts of the liver based on an old method used in inoperable patients with diffuse peritoneal hydatidosis. At present,
puncture emptying is proposed again because of the lower risk achieved with benzoimidazole therapy, US guide and use of fine needles. However, the use of this method for all cysts of the liver of any site or type in place of surgery is not acceptable for the same reasons as exploratory punctures for diagnosis or control of the contents viability.

Key points

- Complications of hepatic hydatidosis include:
  - Metastatic hydatid
  - Secondary bacterial infection
  - Intrabiliary rupture
  - Intraperitoneal rupture
  - Bronchobiliary fistula.

- Diagnosis of hepatic hydatidosis:
  - Incidental finding (in patient from endemic region)
  - Abdominal mass
  - Calcified hepatic cyst on the plain abdominal photograph (AXR)
  - Ultrasound/CT/MRI
  - Hydatid serology/Casoni skin test.

- Preoperative management:
  - Systemic albendazole/mebendazole
  - ERCP (exclude cystobiliary fistula)
  - Protection of operative field before surgical emptying of cyst contents
  - Sterilization of cyst cavity.

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Further reading

Introduction

While practising in Hong Kong in 1930, Digby drew attention to a condition which was subsequently known as recurrent pyogenic cholangitis by reporting on eight cases of ‘common duct stones of liver origin’. The term recurrent pyogenic cholangitis or RFC was used by Cook et al. in 1954 when they reported their experience with the condition in a series of 90 patients. The synonyms associated with this condition include Asiatic cholangiohepatitis, oriental cholangiohepatitis, Hong Kong Disease, Chinese biliary obstruction syndrome and primary cholangitis. This condition is commonly seen in Chinese living in Canton and Hong Kong but is not restricted to the Chinese in the Orient since it also occurs in Chinese immigrants in Malaysia, Singapore, North America and Australia. RPC is also common in Japanese in Japan and Taiwanese in Taiwan. Although rare, RPC has also been reported to afflict occidentals.

Pathogenesis

In RFC the gallstones found within the biliary system are calcium bilirubinate stones or pigmented calcium stones. Calcium bilirubinate stones are prevalent in Asia and are very rare in Europe and the United States. In addition to the presence of these friable concretions of various shapes and sizes within the biliary tree, the bile is often muddy in consistency and contains numerous fine particles of calcium bilirubinate. Biochemical analysis of these stones revealed a bilirubin content of 40.2–57.1% and a cholesterol content of 2.9–25.6%. This differs greatly from cholesterol stones, which are common in Europe and the United States, which contain >96% of cholesterol in pure cholesterol stone, and >71.3% in mixed cholesterol stone but the bilirubin content is only 0.02–5.0%. The peculiarity of the formation of calcium bilirubinate stones in RPC has been ascribed to the high incidence of bile being infected with Escherichia coli (E. coli). In man, the major portion of bilirubin is excreted in bile as bilirubin glucuronide. In the presence of 3-glucuronidase, bilirubin glucuronide is hydrolysed into free bilirubin and glucuronic acid. Normally, calcium is secreted into bile and when it combines with the carboxyl radical of free bilirubin, insoluble calcium bilirubinate is formed. Normal bile is free of β-glucuronidase activity, whereas bile infected with E. coli has intense β-glucuronidase activity. Bile calcium content increases in the presence of biliary tract inflammation and this coupled with the increased hydrolysis of bilirubin glucuronide by the β-glucuronidase from E. coli gives rise to the multiple stones formation classically.
seen in RPC. There are two types of pigmented stones, black and brown. The infected type seen in RFC is the brown pigment stone.

The postulated port of entry for the micro-organisms of bowel origin is via the portal vein from an attack of enteric infection. In the acute stage of RPC, Ong reported that 39.5% of the studied cases had a positive portal blood culture while the positive supraduodenal lymph node culture rate was 38.1%. The rate of infected bile in patients with pigmented stone compared to those with cholesterol stone is correspondingly much higher in the former. In comparing patients with pigmented stones against those with cholesterol stones, Maki demonstrated that 88.3% of the bile in patients with pigmented stone was infected and *E. coli* was isolated from all cases. This compared to 43.5% in patients with cholesterol stone and of these only 70% of cases had *E. coli* isolated. However, bacteria excreted into the bile within a non-obstructed biliary system will not usually give rise to infection and an attack of

![Figure 14.1](image)

**Figure 14.1** (A) Magnified view of *Clonorchis sinensis* (×12.5). (B) Numerous *Clonorchis* removed from the CBD of one patient.

cholangitis. Thus obstruction by parasites such as *Clonorchis sinensis* (Fig. 14.1) and *Ascaris lumbricoides* can initiate the sequence of events which eventually lead to the formation of intrahepatic pigment stones. Furthermore, the egg or carcass of the parasite can act as a nidus for the deposition of calcium bilirubinate. However, only a proportion of patients with RFC have positive ova in stools indicating parasitic infestation, while in some patients the remains of parasites can be identified within the stones recovered. *Clonorchis* infection does not occur in the Sarawak state of West Malaysia due to the absence of the snail, Bithynia, which is the first intermediate host in the life cycle of *Clonorchis sinensis*. Yet RPC is common among the Chinese and the indigenous race, the Dyaks. Thus parasitic infestation is only one of the aetiological factors for RPC. Maki suggested that the migration of roundworms through the ampulla
of Vater leads to papillitis and secondary dyskinesia of the common bile duct (CBD). This leads to increased intral hepatic ductal pressure, dilatation of the CBD and poor drainage of the biliary system.\textsuperscript{13} A poorly draining biliary system contributing to the formation of intrahepatic stones and colonization of the bile by bacteria was experimentally shown in rabbits by Ong in 1962. Rabbits who had the CBD constricted by a linen thread prior to a single intraportal injection of an \textit{E. coli} suspension developed ductal dilatation and stone formation in the CBD and intrahepatic ducts. On culture, the bile from the gallbladder and bile ducts was positive for \textit{E. coli}.\textsuperscript{12}

In the mid 1950s in Japan, the proportion of pigmented to cholesterol stones found in professionals was almost equal. However, almost 90\% of the gallstones found in farmers were of pigmented calcium stone. As the farmers were economically less well off, they could only afford a diet which was deficient in fat and protein. It was postulated that the deficient diet may be a factor for the development of pigmented stone.\textsuperscript{13} Matsushiro et al. have demonstrated that a diet low in protein and fat leads to lower levels of glucaro-1:4-lactone, a powerful inhibitor of \textit{β}-glucuronidase, in bile.\textsuperscript{14} The reduced level of glucaro-1:4-lactone in bile thus permits increased hydrolysis of bilirubin glucuronide to free bilirubin and glucuronic acid by the bacterial \textit{β}-glucuronidase present in infected bile. The free bilirubin then conjugates with calcium in the bile to form the typical calcium bilirubinate stones of RPC. In Hong Kong, RPC is no longer seen in the younger generation born and bred in modern-day Hong Kong. Young patients, in their 30s, who present to our institution with RPC are invariably immigrants from China. We suspect that the much better social and economic conditions of modern-day Hong Kong have played a role in eradicating the condition.\textsuperscript{15} The reduced incidence of gastroenteritis, the inability of the enteric organism, which gained entry via the portal blood, to establish itself within the liver parenchyma due to better host defence from an improved high protein, low carbohydrate diet and possibly the fact that less Chinese herbal medicine is being consumed by the modern generation of youngsters may all have contributed to the demise of this condition.

\textbf{Figure 14.2} A totally destroyed left liver lobe consisting of a cavernous biliary sac with negligible liver parenchymal tissue, (f=falciform ligament).
Pathology

Macroscopically, due to the repeated attacks of biliary sepsis, it is common to find adhesions between the liver surface and the surrounding parietal peritoneum, especially the diaphragmatic surface, at operation. The liver surface is scarred and prominent dilated ducts may be obvious. The affected lobe of the liver, usually the left, is normally atrophic with compensatory hypertrophy of the remaining lobe. On palpation, the stones within the dilated biliary ducts are easily palpable. Occasionally, the underlying lobe can be so destroyed by the repeated attacks of cholangiohepatitis that what remains is a cavernous biliary sac with minimal surrounding liver parenchyma (Fig. 14.2). Within the sac is a soup of biliary mud and stones. The brown pigment stones are soft stones which crumble when squeezed between fingers or forceps. The size variation goes from fine grains to stones of 4–5 cm in diameter. The stones are irregular, can take up the shape of the biliary duct or become faceted when the stones are packed (Fig. 14.3). Apart from the stones, the bile duct is filled with biliary mud. This is a broth of mucus, altered bile products, microcalculi, desquamated epithelium, parasites and pus.

The pathological hallmark of RPC is the steadily progressive, recurrent cholangiohepatitis with periportal fibrosis. Histologically, in the the early acute stage of an attack of cholangiohepatitis, it is similar to that of bacterial cholangitis associated with cholecystitis and calculus obstruction seen in the Western world, while the histological picture of the acute, chronic and advanced stage of the disease is not dissimilar to that seen in sclerosing cholangitis. In the early lesions the lumen of the small biliary ducts is filled with pus, with rapid extension into the surrounding tissue. There is marked dissociation of the liver cells by polymorphonuclear infiltration of the sinusoids together with Kupffer cell hyperplasia. In the lobules around the affected duct there is a varying degree of cellular necrosis. Resolution of the underlying inflammation leads to dense
round-cell infiltration which is then replaced by fibrous tissue. In the larger intrahepatic ducts, the duct wall becomes inflamed, ulcerated and destroyed together with the formation of cholangitic abscesses. Resolution results in intense fibrosis which accounts for the undue prominence of the duct wall seen on sectioning a liver affected by RPC. During the acute episode, these larger ducts can become irregular in calibre and short segments of relative stricture can occur at intervals along the duct. The duct proximal to the stenosis dilates. Recurrent attacks of infection and resolution lead to permanent damage of the duct wall and the ducts remain dilated. The relative stricture then becomes a true localized stricture. These strictures are most frequently encountered at the site of ductal confluence. One of the main concerns of these inflammatory strictures is malignant transformation into cholangiocarcinoma. Ohta et al., from their autopsy studies, suggested that repeated inflammatory damage to the ductal epithelium from the attacks of cholangitis can lead to atypical epithelial hyperplasia, dysplasia and eventually cholangiocarcinoma.18

The left lobe of the liver is preferentially affected. The exact reason for this is unknown. One possible explanation may be the selective distribution of portal blood within the liver. Two studies suggested that the left lobe of the liver receives blood from the colon and the left lobe will be the first port of call for enteric organisms such as E. coli which have entered the portal venous system.19,20 Colonization of the bile with E. coli will lead to the production of β-glucuronidase in the biliary system. Another explanation is that the more oblique course of the left hepatic duct results in poorer drainage of the left ductal system as compared to the right hepatic duct, thus leading to increased incidence of stone formation. If stones are found in the right hepatic duct, almost invariably stones are found in the left duct. In one study of 115 patients with hepatolithiasis, the ratio of stones found in the left and right hepatic ducts was 6:1.5 The stones form in the dilated ducts proximal to the stricture site. These strictures can be multiple and bilobar in distribution and commonly occur at the origin of the right and left hepatic ducts. Stones within the common bile duct are usually lodged at the supraduodenal portion of the duct or at the ampulla. At ERCP, a patulous ampulla of Vater (probably a result of repeated passage of stones) is not an uncommon finding in patients with RPC.

The bile in patients with hepatolithiasis is usually infected with enteric organisms. The two most common organisms isolated are E. coli and Klebsiella species. The overall positive bile culture rate has been reported to be as high as 87% and the incidence of positive culture in patients requiring surgical intervention and those which settled on conservative measures is similar (90% versus 85%).21

The gallbladders in these patients are usually thinwalled, large and distended. The majority of them do not contain gallstones. While the incidence of CBD stones and biliary mud varied from 60 to 90%, the incidence of associated gallstones in the gallbladder was only 15 to 40%.4,7 Macroscopically, the gallbladder looks normal but histological examination invariably shows features compatible with low grade chronic cholecystitis. Along the gastrohepatic omentum gross lymphadenitis with enlarged lymph nodes is commonly encountered.
Clinical presentation

Patients with RFC tend to be younger (third and fourth decade) than those affected by cholesterol stone disease, which is much more prevalent in older women, in the Western world. Although the condition does not have a particular sex prevalence, those afflicted are almost invariably from the lower socio-economic classes. The usual presentation consists of the classical Charcot’s triad of abdominal pain, fever (with or without chills and rigors) and jaundice which signifies an attack of cholangitis. The patient may not notice the jaundice but a history of tea-coloured urine is usual. The jaundice is usually not severe since cholangitis secondary to a completely obstructed biliary system will rapidly progress to acute suppurative obstructive cholangitis with sepsicaemia. In addition to the triad of symptoms, these patients also develop mental confusion and shock, which is referred to as Reynaud’s pentad. The epigastric/right upper quadrant pain is usually described as a constant and gnawing/cutting pain, which may radiate to the back. Vomiting is not a constant feature. Patients have spiking fever, not unlike that seen with an underlying abscess or collection, which normally resolves rapidly when the conservative treatment has been effective.

On examination, the patient looks unwell and restless with a tinge of jaundice. The associated jaundice is typically mild and clinically can be just discernible. Abdominal examination may reveal the telltale signs of surgical scars from previous operations. Tenderness with varying degree of guarding is noted in the epigastrium or right upper quadrant. A tender hepatomegaly may be present. Marked tenderness may imply the presence of an underlying abscess. Deterioration in the abdominal signs (increasing and generalized tenderness) and/or the development of worsening haemodynamic parameters (persistent hypotension, tachycardia, poor urine output despite adequate resuscitation) argues for emergency surgical intervention to decompress the biliary system.

Those patients who present or develop shock have a flushed face, warm periphery, bounding peripheral pulse and hypotension. The massive vasodilatation and reduced cardiac contractility secondary to the endotoxaemia adequately explain the state of shock.

Investigations

Both the haematological and biochemical tests do not differentiate patients with RFC from those with other causes of biliary obstruction and infection. Full blood count will reveal an underlying leucocytosis with neutrophilia and mild thrombocytopaenia in some patients. A number of patients will also have a concomitant mild derangement of the clotting profile with a prolonged prothrombin time. The deranged liver function test is compatible with an obstructive picture with a moderately raised level of bilirubin and a high serum alkaline phosphatase level. The level of \( \gamma \)-glutamyltranspeptidase is elevated. The slightly elevated alanine transaminase level in some patients is a reflection of the parenchymal damage secondary to the underlying infection within the biliary system.

Other than showing the presence of pneumobilia in some cases, a plain abdominal radiograph is not helpful. The calcium bilirubinate stones are radiolucent because of the
low calcium and high bilirubin content. The least expensive and most helpful investigation is ultrasonography (USG). It can demonstrate the presence of stones within the dilated intrahepatic and common bile ducts, the presence or absence of an underlying liver abscess and occasionally the presence of a solid liver mass secondary to malignancy complicating a benign stricture. Also it can reveal the presence or absence of gallstone(s) within the gallbladder. Intra- and extrahepatic ductal stones are present in the majority of patients, but cholelithiasis is much less common and is seen in the minority of cases. Although intrahepatic stones normally cast sonic shadows on USG, the presence of air within the bile ducts (either spontaneously or secondary to previous biliary drainage procedures) can give rise to highly reflective echoes with posterior shadows, thus confusing and misleading the radiologist in diagnosing the presence of stones within the bile ducts. In about 3% of RPC, pneumobilia is present. In some cases the amorphous and small stones can form a cast of the biliary tree and, under such circumstances, highly reflective echoes and posterior acoustic shadowing on USG may be absent. It may then be difficult to identify dilated bile ducts and the ducts can appear as soft tissue masses on USG.

USG images and their interpretation are operator dependent. Computed tomography (CT) removes this bias and can provide images of the dilated intra- and extrahepatic ducts, even if they are filled with sludge or pus. On CT scanning these filling defects are of higher attenuation than bile, but have a lower attenuation than contrast-enhanced liver parenchyma. Although uncommon, the amorphous stones which completely fill the ducts and are isodense with the hepatic parenchyma could be missed on CT. Unlike USG, there is no difficulty in distinguishing pneumobilia from stones on CT and visualization of the extrahepatic ducts is not limited by overlying bowel gas.

USG and CT do not provide sufficient details of the ductal anatomy. Cholangiography, in the form of endoscopic retrograde cholangiopancreatography (ERCP) and/or percutaneous transhepatic cholangiography (PTC), is essential for the detail delineation of the entire biliary tract. Older methods of delineating the biliary tracts such as oral cholecystography and intravenous cholangiography are no longer used because they provide suboptimal visualization of the ductal system. In addition to the potential complication of allergic reaction to the contrast injected, there is no place for intravenous cholangiography in the presence of biliary obstruction or cholangitis. Our first line of investigation is ERCP since it is both diagnostic and therapeutic. The typical cholangiogram will show dilated extrahepatic ducts in more than half the cases. The intrahepatic ducts have the classical ‘truncated tree’ pattern where the ‘tree’ has been trimmed back to its ‘main branches’. The terminal end of these ‘branches’ are tapered, resembling an arrow or a spear head (Fig. 14.4). It is more common to see a dilated left ductal system containing calculi than an affected right system. There may be an accompanying relative or true stricture distal to the dilated ducts. When a stone or stricture prevents the filling of the intrahepatic ducts, or when it is technically impossible to perform an ERCP due to previous biliary-enteric bypass surgery, PTC under USG guidance is performed. As a result of the stones and stricture(s), the biliary anatomy can be very complicated. Once an obstructed biliary duct is punctured during PTC, the obstructed system must be drained to avoid cholangitis and/or bile leak. Underfilling during cholangiography can lead to missed segmental ducts. More importantly, the
paucity of intrahepatic ducts shown on cholangiograms should prompt the surgeon to count the number of segmental ducts present in order not to miss the diagnosis of undrained segment(s). Cholangiography complements USG and CT and their findings should be considered as a whole and not in isolation.

**Figure 14.5** MR cholangiogram demonstrating a stricture (arrow) at the confluence of the right and left hepatic ducts.

We have shown that magnetic resonance (MR) cholangiography is comparable to ERCP in diagnosing choledocholithiasis. Apart from being non-invasive, MR cholangiography can delineate biliary strictures which may be difficult to show or missed on ERCP due to technical reasons (Fig. 14.5). In a recent study by Park et al. MR cholangiography has been shown to be better than ERCP/PTC. Occasionally, a radioisotope scan is performed to demonstrate the presence of undrained or hypo-functioning liver segments.
Figure 14.4 Typical truncated biliary tree appearance together with the arrow or spear head sign (arrow) on ERCP. A large stone(s) in the left duct.

The radiographic features of certain conditions can simulate RPC. Sclerosing cholangitis can lead to biliary tract strictures. However, these are usually more peripherally located and there is a lack of the marked proximal dilatation and stones seen in RPC. Although the common bile duct is massively dilated in choledochal cysts, in most cases, there is an abrupt transition to normal or slightly dilated proximal ducts. Patients with Caroli disease (cavernous ectasia of the biliary tract) have dilated intrahepatic ducts and calculi but the extrahepatic ducts are disproportionately small. The condition is often associated with renal cystic disease which, on CT, helps to distinguish it from RPC.

In almost all cases, given the clinical and investigation findings, the diagnosis of RPC is seldom in doubt. The investigations merely help to define the extent and severity of the underlying disease and guide the management plan.
Acute management

RPC patients have repeated attacks of acute cholangitis which would settle on conservative measures in the majority of cases. The need for urgent therapeutic interventional procedures only applies to a minority of cases such as those with signs of peritonitis secondary to perforated gangrenous gallbladder, ruptured liver abscess or those with septicaemic shock despite conservative measures. The role of definitive procedures for most patients who settled on conservative measures depends on the frequency and severity of each attack, presence of biliary strictures (which may be malignant) and the presence of any existing co-morbid medical conditions.

The initial approach to any acute attack is to control the underlying infection with the commencement of intravenous fluid infusion, antibiotic treatment after blood culture, prescription of adequate analgesia and keeping the patient nil per oral. Our standard first line antibiotic regimen is cefuroxime. Metronidazole is sometimes prescribed to cover the anaerobe Bacteroides fragilis, which is present in a minor proportion of patients who have had previous biliary tract surgery and/or complicated anatomy due to stones and strictures. An urgent ultrasound scan of the liver is performed to identify the extent of lithiasis within the biliary tree, the presence of a liver mass which can be an abscess or an underlying cholangiocarcinoma. Those patients who fail to respond or have evidence of a severe attack of cholangitis with or without shock undergo an urgent ERCP. The smallest amount of contrast feasible is used during ERCP as increased biliary pressure from excessive contrast injection will result in cholangiovenous reflux, which can lead to septicaemia. No attempt is made to perform a full cholangiogram or to remove all calculi from the biliary system. In the procedure, the system is decompressed with a nasobiliary drain. Only when the patient’s condition has improved and stabilized would a check cholangiogram with endoscopic removal of stones be performed. If part of the biliary tree cannot be decompressed adequately because of an obstructing distal stone or stricture, then endoscopic drainage alone may not be adequate and successful. As such, percutaneous transhepatic biliary drainage of the obstructed biliary ducts will be of use. However, these drainage tubes are small and can be easily blocked by the tenacious biliary mud. If a liver abscess is present, the abscess is drained percutaneously under ultrasound guidance.

The patient is monitored closely after admission for signs of deterioration. Those responding to the conservative treatment will have a reduction in abdominal pain, a fall in temperature towards normal and the disappearance of tachycardia over the first 24–48 hours. If there is no obvious improvement after 48 hours, the possibility of undrained biliary system or individual liver segments due to impacted stones or underlying strictures must be considered and the need for urgent surgical intervention entertained. At any time during conservative management, the presence of increasing abdominal pain coupled with shock and peritoneal signs mandates urgent surgical treatment.

Those patients who present in shock must be actively resuscitated. Those who respond quickly can be treated conservatively, while those who fail must undergo therapeutic intervention. It is unclear why conservative measures work for some but not others. In a series of 88 RPC patients presenting with acute cholangitis, 17% required therapeutic
intervention for septic shock. A pulse rate greater than 100/min and a platelet count of more than $150 \times 10^9/\text{l}$ within 24 hours of presentation were the only two independent factors which predicted the need for therapeutic intervention.21

The sole aim of an urgent therapeutic intervention during an acute attack is to decompress the obstructed biliary system. Non-operative interventional procedures using the endoscopic or percutaneous routes are preferred to open surgical route.29 Occasionally, open surgery is required to deal with peritonitis as a result of gangrenous cholecystitis or ruptured liver abscess. The most expedient means to decompress the CBD is insertion of a large T-tube. No attempt is made to perform definitive surgery. When the usually enlarged and thick walled CBD is opened, thick infected biliary mud and bile will gushed out. The biliary mud and friable bilirubinate stones are scooped out. Following a gentle saline flush of the CBD, a bougie is passed down the CBD into the duodenum to check for patency of the lower end of the CBD. The way an impacted stone in the lower end, which cannot be removed during CBD exploration, is dealt with depends on whether there is a concomitant attack of pancreatitis. In the absence of acute pancreatitis, the stone can be dealt with percutaneously via the T-tube tract when the acute episode is over. In the presence of acute pancreatitis, a transduodenal sphincteroplasty is performed to remove the stone. An alternative is the use of electrohydraulic lithotripsy to fragment the impacted stone, thus avoiding a transduodenal sphincteroplasty.30

The patency of the right and left hepatic ducts is checked to ensure there is free flow of bile into the CHD and CBD. Any strictures found are dilated with graduated sounds to release the infected bile and mud dammed up behind the stricture(s). Gentle irrigation of the hepatic ducts with saline is performed. Irrigation or flushing at high pressure via a syringe must be resisted as this can initiate or aggravate a septic state. When bile flow from both hepatic ducts is established, a large bore T-tube is placed, the choledochotomy closed with catgut and the operation terminated. The T-tube not only decompresses the system but also affords a percutaneous route for endoscopic intervention when the patient has recovered.

Large palpable liver abscesses are drained intra-operatively. Multiple small abscesses will respond to appropriate antibiotics after the biliary system is decompressed. A cholecystectomy is performed only when it is grossly distended or there is evidence of cystic duct obstruction, empyema or gangrene of the gallbladder. During the emergency CBD exploration, an otherwise non-inflamed gallbladder, with or without stone(s) in situ, is left behind because of the added risk of performing a cholecystectomy in an ill patient.

Definitive management

The definitive management of RPC is to use a multidisciplinary approach,31 aiming to remove all biliary stones, to establish adequate drainage to the biliary system, and to resect non-functioning liver segments which harbour bacteria and serve as foci of infection. If properly performed, definitive interventional procedures decrease the episodes and the severity of future attacks of cholangitis. In some patients cure is possible.
Minimal access approach

Once the acute episode has settled, more definitive treatment via the endoscope or under radiological guidance can be performed. Those treated initially by nasobiliary drainage have a check cholangiogram to delineate the extent of lithiasis and the existence of ductal stricture(s). Stones within the CBD and CHD can be removed with a dormia basket and large stones can be crushed with the mechanical lithotripter or fragmented by laser prior to their removal. For those RPC patients with stones confined to the CBD, endoscopic sphincterotomy with stone extraction only is safe and effective. The medium-term result
of endoscopic sphincterotomy is comparable to surgical sphincteroplasty. In 118 patients who underwent endoscopic treatment, 95.8% remained symptom free after a median follow-up of 2.3 years, compared to 83.4% who had a good outcome after surgical sphincteroplasty at a mean follow-up of 7.3 years. In the absence of ductal strictures, small intrahepatic calculi not retrieved by ERCP can be shattered by extracorporeal shock wave lithotripsy (ESWL) and the fragments allowed to fall into the bowel through a widely patent sphincteroplasty.

Intrahepatic calculi within dilated biliary ducts usually lie proximal to a site of relative or true stricture. The stricture can be dilated sufficiently to allow complete removal of the stones endoscopically (Fig. 14.6). When the stricture is confined to one lobe of the liver which is atrophic, and the contralateral liver lobe is normal or relatively unaffected, hepatic resection should be performed unless the patient is medically unfit to undergo liver resection. In the presence of multiple strictures, a more conservative approach with repeated dilatation can be successful in achieving stone clearance and control of disease. Balloon dilatation of intrahepatic biliary strictures prior to stone removal has been reported to be highly successful. The immediate overall success rate of complete stone clearance with balloon dilatation in 57 patients was 94.5%. Long segmental strictures which are likely to restenose can be stented successfully. The main complications of dilatation therapy include septicaemia, haemobilia, mild diarrhoea and restenosis. The cumulative probability of stricture recurrence after dilatation is 4% at 2 years and 8% at 3 years. The true long term patency rate following dilatation alone is still unknown since benign strictures treated surgically can recur 10 or more years later, as partial obstructions can remain completely asymptomatic for long periods. Apart from the problem of restenosing, it is difficult to rule out the presence of a malignant stricture with certainty.

In patients with a percutaneous transhepatic biliary drainage (PTBD) catheter in situ, the tract can be dilated to allow dormia basket stone retrieval under fluoroscopic screening or to allow passage of a flexible twin channel choledochoscope. Under direct vision the stone(s) can be fragmented with the electrohydraulic lithotripter and the fragments removed with a basket. Intrahepatic strictures can be dilated or stented. Instillation of stone dissolving agents directly into the affected biliary duct has been advocated by some, but we do not practise this approach as it is often painful, time-consuming, ineffective and can lead to ascending cholangitis and sepsis. In patients where the initial endoscopic approach has failed, the established percutaneous route can be combined with endoscopy subsequently to achieve stone clearance or stricture dilatation.

In those patients who received acute surgical intervention and T-tube decompression of the biliary system, the tract is allowed to mature. After 6 weeks, any stones present can be removed through the tract with a choledochoscope or under radiological control.
Figure 14.7 (A) Longitudinal incision for the exploration of CBD only, (B) separate incisions for exploration of the CBD and the hepatic ducts, (C) incision for the combined exploration of the CBD and one of the hepatic ducts (left side is shown), (D) horizontal incision over the CHD for CBD exploration and subsequent formation of hepaticojejunostomy (--- = incision).

**Definitive surgery**

Since RFC can and does affect the biliary tract at different sites with varying degrees of severity, the aim of the surgery is to provide adequate biliary drainage for bile and debris. This encompasses stone extraction, stricturoplasty or excision of stricture, resecting non-functioning liver segments and creating a bilio-enteric bypass with a permanent percutaneous access loop to the biliary tract to allow subsequent access to the biliary system for stone extraction and dilatation of stricture(s). Before embarking on definitive surgery, it is mandatory to have a complete knowledge of the location of calculi and stricture(s), and the uni- or bilobar extent of disease with or without concomitant liver atrophy.

In the presence of predominantly extrahepatic disease, simple exploration of the common bile duct with intraoperative choledochoscopy will suffice, In the absence of extrahepatic ductal stricture, the incisions used for the exploration of the CBD and hepatic ducts will depend on the location of the stones (Fig. 14.7A-D).

We routinely remove the gallbladder in these patients since, histologically, it shows
underlying evidence of low grade inflammation. Furthermore, if the sphincter of Oddi has been previously destroyed, the gallbladder will be permanently in a collapsed state. The placement of a large T-tube following the exploration will allow post-operative imaging of the biliary tracts and any residual stones found can be easily removed under radiological control or with a flexible choledochoscope. When there is stenosis of the ampulla of Vater or distal CBD, or impacted stone(s) in the lower CBD, a transduodenal sphincteroplasty is performed. In patients who have had multiple operations on the CBD, the standard approach can be difficult. Under such circumstances, Ong et al. have described an extraperitoneal approach to the duodenum, which is located by its anterior position to the right kidney. A transduodenal sphincteroplasty is performed and the CBD explored from below. However, this approach is seldom necessary as the result of endoscopic sphincterotomy has been shown to be comparable.

In the presence of extra- and intrahepatic calculi, stone extraction can be difficult if they are impacted, situated behind relative or true ductal strictures or present within angulated ducts such as the right posterior or left medial segmental ducts. Although direct hepatotorny can be performed to remove the stones, it can be very bloody if the stones are deepseated. Following the removal of all the stones within the CBD and CHD, after a choledochoscopic examination to rule out any strictures in the right and left hepatic ducts, the right and left ducts are flushed with saline. The right and left lobes of the liver are gently massaged in between the flushing. This manoeuvre normally helps to discharge more biliary mud and small stones from the intrahepatic ducts. Once the effluent is relatively clear, a repeat choledochoscopy is performed. Any residual stones can be retrieved with a dormia basket. Segmental ductal stricture is dilated prior to stone retrieval. Any impacted or large stones can be shattered with the electrohydraulic lithotripter introduced through the working channel of the flexible choledochoscope. It is not always possible to clear the intrahepatic ducts of stones completely. Once the large stones and strictures are dealt with, small stones or fragments can be left to ‘fall out’, provided an adequate biliary drainage procedure has been performed.

The thick, dilated CBD/CHD with an inelastic wall behaves more like a cavernous sac which does not drain adequately, even in the presence of a sphinteroplasty. Although it is reasonable to perform a supraduodenal cholecodochoduodenostomy as a biliary drainage procedure, this has the disadvantage that patients may develop ‘sump syndrome’, developing symptoms of pain and fever, which is thought to be a result of debris being lodged in the diseased distal CBD. While the sump syndrome can be treated by performing an endoscopic sphincterotomy, supraduodenal choledochoduodenostomy is contraindicated in the presence of a proximal biliary tract stricture or when the CBD is not wide enough. Under such circumstances, we routinely perform an end to side hepaticojejunostomy with a retrocolic Roux-en-Y loop. This provides a widely patent anastomosis for biliary drainage and for small stones to fall freely into the loop of bowel. Furthermore, the closed end of the Roux loop can provide a permanent access route to the biliary tract.

With the hepaticojejunostomy it is crucial that the access loop is short and has a straight course from the anterolateral abdominal wall to the anastomosis. A poorly constructed jejunal loop with redundant length makes subsequent choledochoscopy and access to the intrahepatic ducts difficult. The access loop can either be placed
intraperitoneally, to be accessed percutaneously under ultrasound guidance, or it can be placed under the skin as a hepaticocutaneous jejunostomy. We prefer to leave the loop intraperitoneally. In those cases where immediate access to the biliary tract is not necessary, the end of the loop is tacked to the peritoneal surface of the anterolateral abdominal wall with catgut. The staples from the GIA stapler used to transect the jejunum during Roux loop formation or the ligaclips placed around the blind end of the loop at the end of the operation allow the interventional radiologist subsequently to identify and access the loop percutaneously. Once the loop is punctured, the tract can be gradually dilated to admit a twin channel choledochoscope for endoscopic manipulation.\(^{15}\) For those cases where access to the biliary tract is required soon after the operation, a 24 Fr catheter is introduced through the anterolateral abdominal wall into the access loop at the end of the operation. The tract is allowed to mature for 4–6 weeks before instrumentation.

Hepaticocutaneous jejunostomy has been used by others.\(^{36}\) Although the biliary tract can be accessed sooner through the cutaneous stoma compared to our technique, the cutaneous stoma is not without its complication. Fifteen per cent of patients with hepaticocutaneous jejunostomy, performed either with the cutaneous stoma formed at the initial operation or subsequently created from its subcutaneous site, did experience complications. These complications include wound infection of the closed stoma wound, development of cutaneous fistula after stoma closure, difficulty in reconstructing the stoma for subsequent use and development of parajejunostomy hernia. Repeated therapeutic intervention of the biliary tract is inevitable due to the chronic relapsing nature of the condition. The formation of a hepaticojejunostomy with an access loop is a satisfactory and adequate way to manage further attacks of stones, strictures and cholangitic attacks. On a median follow-up time of 27 months, symptoms recurred only in 12 patients (29%). Only one patient required a reoperation for stricture while the others were adequately treated through the access jejunal loop.\(^{36}\)

RPC predisposes to the formation of inflammatory, non-iatrogenic strictures in the biliary tract. Strictures in the subsegmental and peripheral ducts are difficult to treat. Fortunately, obstruction of these minor ducts does not produce jaundice and the cholangitic attacks may pass unnoticed and the infection subsides without any intervention. However, strictures in the major bile ducts do lead to unremitting cholangitis, stones and liver abscess formation, septicaemic episodes and death. Over a 10-year period, we treated 57 patients with major bile duct strictures.\(^{37}\) Forty-four of the 60 strictures involved the left hepatic duct (23) or the left lateral segmental ducts (21). Strictures in the CBD/CHD can be treated by the formation of a choledochojejunostomy or a hepaticojejunostomy. Stricture involving the confluence of the hepatic ducts can be treated by hepatotomy and Y-V plasty, but the procedure is technically difficult and bleeding, bile leakage and restenosis are potential serious complications.\(^{5,38}\) We have stopped performing Y-V plasty for such strictures due to our poor results. Instead, we treat such strictures by performing bilateral hepaticojejunostomy. In a relatively normal left lobe of the liver with a left duct stricture at its origin, a left duct approach as described by Hepp and Couinaud\(^ {39}\) for a side-to-side anastomosis between the left duct and a Roux loop can be performed without the need for a left hepatectomy. The biliary drainage procedures performed for these inflammatory strictures are occasionally
combined with liver resection, or liver resection alone is performed to deal with these strictures.

Before embarking on hepatic resection, the severity of symptoms, status of the remaining biliary tract, parenchymal functional reserve and alternative procedures have to be considered. Hepatic resection is only performed for those with recurrent, troublesome and localized severe disease. Disease can be confined to the left lateral segment which is atrophic and contains large number of calculi within cavernous bile ducts. In more extensive disease, the medial segment of the left lobe can also be affected due to a tight stricture in the left hepatic duct. Hepatectomy is performed not only to remove the source of symptoms and sepsis, but also to remove the underlying stricture which has the potential to turn malignant. Liver resection for right-sided disease is unusual. By the time resection is necessary, the right lobe is usually destroyed, with compensatory left lobe hypertrophy. Consequently, a right hepatectomy should lead to little functional disturbance. In one series of 172 patients with hepatolithiasis, liver resection was necessary in 37% of patients, of which left lateral segmentectomy and left hepatectomy accounted for most of the resections (90.5%). Right hepatectomy was only performed in one patient. Troublesome adhesions between the diseased liver and the diaphragm and adjacent viscera can make liver resection difficult. Severe adhesions and fibrosis around the left hepatic vein and the inferior vena cava can make dissection in the region difficult and severe bleeding from these structures due to injudicious dissection can be a problem. The overall operative mortality in hepatic resection for hepatolithiasis is low (≤2%), but the morbidity, such as wound infection, subphrenic collections and biliary fistulae, from operating on an underlying septic condition is correspondingly high (approximately 30%).

Complications

In RPC the biliary mud and stones within the common bile duct can lead to acute pancreatitis. In 1971, Ong et al. reported that approximately half of all patients with acute pancreatitis, in Hong Kong, were associated with RPC. Another report claims that about 20% of RPC patients had high serum amylase levels but were clinically asymptomatic. In some patients, the big common bile duct stones can lead to the formation of a choledochoduodenal fistula.

Liver abscesses complicating RPC can present with rupture into the peritoneal cavity or adjacent viscera. A left lobe liver abscess can rupture into the pericardial cavity and cause cardiac tamponade, while a right lobe abscess can lead to the formation of a pleurobiliary or bronchobiliary fistula. A chronic abscess can, on clinical and radiological grounds, be indistinguishable from an underlying cholangiocarcinoma. The final diagnosis can only be certain after histological examination of the resected specimen.

Cholangiocarcinoma complicating RPC has been reported. The higher incidence of cholangiocarcinoma in areas where RPC is also prevalent has been attributed to the presence of *Clonorchis sinensis* infestation. In a necropsy study of 50 cases of cholangiocarcinoma, 92% of the cases were associated with clonorchiasis and...
intrahepatic stones were found in 20% of the cases. In a huge series of 1105 cases of hepatolithiasis studied over the period 1978–90, Chen et al. reported that the incidence of cholangiocarcinoma in these patients increased from 2.4% (between 1978 and 1987) to 13.7% (between 1988 and 1990), despite a decreasing incidence of clonorchiasis in the population.

Thrombophlebitis of the branches of the portal vein due to the underlying periductal inflammation can lead to portal venous thrombosis with an enlarged spleen. Occasionally, septic emboli to the pulmonary tree can lead to the development of lung abscesses and significant pulmonary hypertension.

Despite multiple operations, RPC patients with longstanding severe disease can develop secondary biliary cirrhosis and liver failure. When cirrhosis sets in, portal hypertension and bleeding oesophageal varices ensue, thus making further corrective surgery for the underlying stricture(s) more hazardous. In these patients the only available option is liver transplantation.

Conclusions

As the name implies, RPC runs a recurrent and unrelenting course with variable frequencies of attacks of cholangitis. Medical therapy is ineffective and surgical treatment is not entirely satisfactory. Despite surgery, stones and strictures can return. In Hong Kong and Taiwan, the peak age incidence of RPC has changed over the years from the third to the fifth decade in the 1950s and 1970s to the seventh decade in the early 1990s. This is due to an increasing proportion of patients who have survived previous surgery, only to have RPC recur again in later life. In Hong Kong, young patients in their third and fourth decade of life who present to us with RPC are invariably immigrants from mainland China. RPC is a dying disease in Hong Kong, but is still common in China. Although there are various theories on the pathogenesis of RPC, we believe the condition is closely linked to the level of social and economic conditions of a community. Surgery merely deals with the consequences of the condition, but does not address its roots. With better living conditions and public hygiene, perhaps RPC can be eradicated in this millennium. Until then, a judicious choice of a mixture of treatment, both medical and surgical, is necessary to achieve a satisfactory and long-lasting solution to a recurrent inflammatory condition.

Key points

• Calculi are predominantly calcium bilirubinate.
• Probably secondary to *E. coli* infection of bile.
• Presentation:
  Third and fourth decade
  Recurrent attacks of cholangitis
  Obstructive jaundice
  Preferentially affects left lobe.
• Investigations:
  Plain abdominal radiography (AXR)
  CT
  ERCP ± PTC.
• Complications:
  Acute pancreatitis
  Liver abscess
  Cholangiocarcinoma
  Portal thrombophlebitis
  Secondary biliary cirrhosis.

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Management of liver abscess

Justin Geoghegan, Dermot Malone and Oscar Traynor

Introduction

Liver abscess was recognized in the time of Hippocrates, but was first recorded in modern medical literature during the first part of the nineteenth century. These early observations noted that this condition was almost invariably fatal, a viewpoint supported by several reports that appeared around the beginning of the 1900s. The landmark description by Oschner in 1938 of a 62% survival rate in a patient series treated by surgical drainage was the first report to demonstrate any real progress in the treatment of liver abscess. Combined with the rapid developments in antibiotic therapy, surgical drainage remained the mainstay of treatment for the next two decades. Percutaneous drainage was first reported in 1953. More recently, in parallel with other developments in minimal access techniques, radiologically-guided non-operative drainage has effectively replaced surgical drainage in all but a few circumstances.

Improvements in diagnostic imaging, antibiotic therapy and the adoption of percutaneous drainage techniques have all contributed to improved outcomes in the management of liver abscess. Nevertheless, this condition still frequently results in severe illness with an associated mortality in some series as high as 35%. The reasons for this lie in important changes which have occurred in the demographics and aetiology of liver abscess. Increasingly, this disease occurs in an older population, many of whom have serious underlying disease, so that usually it is the underlying condition which determines the outcome rather than the liver abscess itself.

Successful management requires a multidisciplinary team approach. Patients remain under the primary care of the surgical service but, in most cases, the majority of interventions are performed by the radiologist. Therefore, close communication between these two teams is essential if good outcomes are to be achieved. Major input from gastroenterology, microbiology and intensive care specialists may also be needed. Radiology training authorities in both the United Kingdom and United States recommend that catheter drainage of easily accessible intra-abdominal abscesses, including liver abscesses, should be within the capability of a fully trained general radiologist. However, for liver abscesses that are not easily accessible the patient should be referred to a specialist hepatobiliary team which includes an interventional radiologist. Delay in
referring appropriate patients may result in unnecessarily prolonged hospitalization and jeopardize outcome.

Liver abscess may be categorized as being pyogenic or amoebic depending on the causative organism. Pyogenic abscess is due to bacterial or occasionally fungal infection, whereas amoebic abscess is due to infection with the protozoon *Entamoeba histolytica*. These two entities can overlap considerably in their clinical presentation and appearances on imaging. However, because there are major differences in pathogenesis, clinical course, complications and management they are considered separately in this chapter.

Pyogenic liver abscess

Aetiology and pathogenesis

The incidence of liver abscess in autopsy series has remained fairly constant over the last 50 years at between 0.01% and 0.59%. However, there have been important shifts in aetiological patterns with an increasing proportion occurring as complications of other hepatobiliary disorders or of their treatment (Fig. 15.1). Ascending cholangitis has replaced portal pyaemia due to intra-abdominal infection as the commonest cause of liver abscess. An increasing percentage of patients with liver abscess due to ascending cholangitis have underlying malignant disease, with the remainder due to choledocholithiasis or biliary stricture. Endoscopic or percutaneous stenting or instrumentation of the obstructed biliary tree is an important progenitor of biliary sepsis. Eventual stent occlusion sets the scene for cholangitis and possibly liver abscess formation. Portal pyaemia is classically associated with appendicitis or other colonic conditions such as complicated diverticulitis or perforated carcinoma, but may also be

![Figure 15.1 Aetiology of liver abscess.](image-url)
caused by necrotizing pancreatitis. Complication of these conditions by liver abscess has become increasingly unusual because of earlier presentation and diagnosis, and improvements in management of the primary pathology. Around 15–25% of cases are classified as cryptogenic with no underlying cause identifiable. Liver abscess may also occur due to direct extension into the liver parenchyma of a localized perforation of an adjacent viscus, particularly the gallbladder, colon, stomach or duodenum.

Haematogenous spread from non-gastrointestinal sources accounts for 10–20% of liver abscesses and has been reported most typically in association with bacterial endocarditis and in intravenous drug abusers. This scenario is also being seen with increasing frequency in immunocompromised patients, many of whom have underlying haematological or other malignancy, or AIDS. Opportunistic pathogens, such as Pseudomonas species or Candida, are more frequently isolated in these patients.

An increasing proportion of liver abscesses occur as complications of therapy of other hepatobiliary disorders. Liver abscess formation may occur as a complication of arterial chemoembolization of hepatocellular carcinoma. Risk factors for abscess formation include advanced age, tumour size greater than 5 cm, and gas forming in the embolized tumour. Interstitial tumour therapy by cryoablation or percutaneous injection of alcohol have also been reported to be associated with liver abscess formation in a small percentage of patients. A high index of suspicion with early recourse to diagnostic aspiration is needed in patients with liver tumours who develop clinical evidence of sepsis following interstitial lytic therapy.

Immunosuppression following liver transplantation may also predispose to liver abscess formation. Biliary reconstruction by Roux-en-Y hepaticojejunostomy is cited as a predisposing factor in some case reports. A range of causative organisms have been reported including Haemophilus parainfluenzae, Pseudomonas and Candida.

**Morphology and microbiology**

The site, distribution and bacteriology may give important clues about the underlying aetiology. Liver abscess may be single or multiple. The majority of cases of single abscess occur in the right liver and isolated left-sided abscess occurs in 10% or less. Multiple abscesses usually involve both sides or the right side alone, and the left side is rarely affected in isolation. Whether or not this apparent predilection for the right side simply reflects the greater parenchymal mass of the right liver remains unclear. It has been postulated that it reflects preferential distribution of portal inflow from the superior mesenteric vein territory to the right liver. However, this theory is difficult to sustain given that appendicitis is now rarely the primary septic source yet the right-sided preponderance of liver abscesses persists. Single abscesses are more likely to be cryptogenic, in contrast to multiple abscesses. The latter are more likely to be due to uncontrolled sepsis in the biliary tree or haematogenous dissemination from a remote septic focus and are more frequently associated with a profound systemic septic response.

The commonest organisms responsible for pyogenic liver abscess are Gram-negative aerobes with E. coli and Klebsiella being the commonest isolates, reflecting the gastrointestinal origin of these infections in the majority of cases. In one large series from
Taiwan, *Klebsiella* species were found more frequently in single abscesses and *E. coli* was more commonly isolated from multiple abscesses, although most other series are too small to reproduce this finding. Abscesses arising from a gastrointestinal source are usually polymicrobial.

Table 15.1 **Clinical features of liver abscess**

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<td>Fever</td>
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<td>Abdominal pain</td>
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<td>Jaundice</td>
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<td>Anorexia</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>Hepatomegaly</td>
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<td>Septic shock</td>
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<td>Diabetes</td>
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The proportion of cases in which anaerobic organisms are identified has increased as a result of improvements in culture techniques, so that in recent series these organisms account for up to 30% of isolates. Liver abscess occurring as a consequence of bacteraemia arising from a non-gastrointestinal focus is more likely to be monomicrobial, most frequently due to staphylococci or streptococci.

**Clinical features**

The average age of affected patients has increased over the last 30 years and, in recent series, the mean age of patients with liver abscess lies within the sixth decade, with approximately equal incidence in both sexes. The clinical features may be relatively non-specific. The commonest symptoms are fever, abdominal pain and jaundice (Table 15.1). Nausea, anorexia and vomiting are common. Localized tenderness and hepatomegaly may also be present. Septic shock requiring aggressive intensive care management is present in up to 20% of patients. The proportion of patients with diabetes mellitus varies in reported series from 15 to 45%. Approximately 10% of patients present with signs of generalized peritonitis due to intraperitoneal rupture of the abscess.

**Laboratory findings**

In most instances the white cell count is elevated. Up to two-thirds of patients are anaemic, reflecting the chronicity of the clinical presentation. More than 50% of patients have abnormal liver function tests. Alkaline phosphatase and transaminases are elevated
in 60–80% of patients, while serum bilirubin is increased in 30%. Serum albumin may be lowered as a non-specific response to inflammation.

Similarly, prothrombin time and other coagulation parameters may be grossly abnormal in patients with severe sepsis. Blood cultures are positive in 30–50% of all patients. The causative organism can be grown from aspirated pus in approximately 85–90% of cases. Sterile culture may be due to improper handling of specimens or prior antibiotic administration.

**Diagnosis**

Improvements in imaging techniques have led to earlier diagnosis of liver abscess and more accurate differentiation from other conditions.

Chest radiograph shows an elevated right hemidiaphragm or pleural effusion in 50% of cases (Fig. 15.2A). This is typically so non-specific as to be unhelpful. The plain film of the abdomen has no significant role in diagnosis. Angiography and especially scintigraphy were previously widely used diagnostic tools in this situation. Indium-labelled leucocyte scanning has a sensitivity greater than 95%, but the additional information given by crosssectional imaging has meant that isotope scanning and angiography have become redundant in diagnosis of liver abscess.

Initial evaluation of the liver is usually by ultrasound, which has a sensitivity of 75–90%. The sonographic appearances of liver abscess varies as the disease progresses. Early on, the lesion tends to be less distinct and hyperechoic (Fig. 15.3B). This is a non-specific finding which may also be produced by unrelated conditions such as focal fatty change. As the abscess matures, the margins become better demarcated and the contents typically become hypoechoic (Fig. 15.3A). There are usually some internal echoes and, because fluid attenuates ultrasound less than the surrounding solid liver, increased through-transmission of sound is usually seen. This shows as a hyperechoic (bright) shadow behind the lesion. This sign is very useful in differentiating solid from fluid-containing liver lesions. It may occasionally be absent when pus is very thick—its absence does not exclude the diagnosis of liver abscess. Ultrasound may fail to detect multiple small abscesses or a single abscess high in the right liver.

CT scanning has a sensitivity of 97% or greater and is more accurate than ultrasound in differentiating liver abscess from other lesions. A typical protocol would be to scan the liver in 8–10 mm slices with helical CT, beginning the scan 60–70 s after a pump injection of iodinated contrast medium. The aim is to scan the liver during the portal venous phase of enhancement, which provides maximum liver-to-lesion attenuation differences. Typically, the lesion itself does not enhance on contrast injection (Fig. 15.3D,E). It may be surrounded by a peripheral rim of contrast enhancement (Fig. 15.3E). The outline may be highly variable. Some appear round or oval but many have an irregular or lobulated margin (Fig. 15.3A). Gas bubbles or an air-fluid level are diagnostic of liver abscess, but are present in only 20% of cases.
Figure 15.2 Management of liver abscess. Case history: A 56-year-old woman underwent a laparoscopic division of pelvic adhesions and re-presented one week later with abdominal pain and peritonitis due to a distal ileal laceration. She underwent a modified right hemicolecctomy. Postoperatively she remained febrile. An abdominal ultrasound (not shown) demonstrated a liver abscess. She was referred to a hepatobiliary unit for percutaneous drainage. (A) Chest radiograph on admission: the right hemidiaphragm is slightly elevated. (B) CT liver on admission: the liver abscess is shown as a large hypodense (dark) lesion in the right liver. The patient proceeded to have the abscess drained by a low intercostal access route under ultrasound and screening guidance. The initial clinical improvement was less than expected. Anaerobic streptococci and *Candida albicans* were cultured from the pus. Further clinical improvement followed the optimization of antimicrobial therapy. A low-grade fever persisted and she complained of pain around the catheter entry site. (C,D) CT thorax and abdomen one week after drainage: there is now a moderate-sized right pleural effusion and basal pulmonary atelectasis. The liver abscess has been adequately drained. The catheter is well shown in the subcapsular right lobe of the liver. There is a little subphrenic fluid. (E) Chest radiograph one week after drainage: the pleural effusion and right basal atelectasis are evident and were not present predrainage. The low-grade pyrexia was considered either due to right basal pneumonia or pleural contamination from the catheter access tract. (F) Ultrasound of chest: the pleural effusion has been identified and marked for aspiration.
Twenty ml of turbid serous fluid were aspirated and sent for microbiological examination. There were no pus cells or micro-organisms. The effusion was considered most likely reactive. (G) Tractogram’ 10 days after catheter insertion: the catheter has been removed over a guidewire. A vascular sheath, with a side-port, is being used to inject the (dark) contrast along the tract as the sheath is withdrawn. There is no evidence of any pleural or peritoneal connection along the tract. Pleural transgression had been excluded. The patient’s condition had improved. The abscess drainage tube was uneventfully removed.

In its current state of development, magnetic resonance imaging does not appear to offer any great advantage over CT in the characterization of infective focal lesions in the liver.\textsuperscript{35,37} It may have a role if associated biliary pathology is suspected as MR cholangiography can non-invasively confirm or exclude this and facilitate planning of subsequent intervention.\textsuperscript{38}

Differential diagnosis of pyogenic liver abscess includes amoebic abscess and other parasitic liver cysts, particularly hydatid disease, necrotic or infected primary or metastatic tumour, and coincidental simple liver cysts and other benign solid liver lesions (Table 15.2).

Amoebic abscess is considered separately later in this chapter. Hydatid disease should be suspected in endemic areas or in immigrants from or travellers to
the classical radiological findings include calcification in the cyst wall in 20–30% of instances, the presence of daughter cysts which may float freely within the lumen of the primary cyst and a floating detached inner membrane. Identification of hydatid disease is critical as it has generally been considered that percutaneous puncture should be avoided because it may lead to widespread intraperitoneal dissemination of the infection. Some authors, however, suggest that this may be overcautious and that percutaneous drainage of hydatid cysts can be performed safely provided a sufficiently long track through normal hepatic parenchyma is used. Percutaneous sclerotherapy of hydatid cysts has also been reported.40 Hydatid cyst disease is dealt with in more detail in Chapter 13.

Management

The fundamental aims of management are the complete drainage of pus, treatment with antibiotics and identification and elimination of the primary source of infection (if any). The introduction of percutaneous drainage techniques marked the beginning of the shift in management from major open surgery to minimally invasive therapy involving close teamwork between the surgeon, gastroenterologist and interventional radiologist. Percutaneous drainage has, combined with appropriate antibiotic therapy, become the mainstay of treatment.8–10,17,18,41–44 Once the diagnosis is likely based on clinical and/or radiological information, management comprises planning, performing and following-up a percutaneous drainage procedure.
Figure 15.3 Management of liver abscess. Case history: A 37-year-old male presented to a general hospital for investigation of fever and abdominal pain. A diagnosis of liver abscess was made after an ultrasound of the abdomen. He was admitted and commenced on antibiotic therapy. (A) Ultrasound on admission: the abscess in the right liver shows as a lobulated, hypoechoic lesion. The margins of the abscess are very sharply delineated. The right kidney is shown behind the right liver. (B) Ultrasound on admission: there is a second lesion in the left lobe of the liver (cursors). This is more echogenic and less well-defined than the large right lobe lesion. (C) Ultrasound on admission: the gallbladder is contracted and contains many stones. These cast a dense, dark acoustic shadow. (D) CT on admission: axial enhanced scan. At this axial level, the lobulated abscess deep in the right lobe of the liver appears as three separate, moderately hypodense cavities. The left lobe lesion is less clearly shown. The patient’s condition had not improved significantly after 10 days of
antibiotic therapy. The local radiologists did not consider the abscess suitable for percutaneous drainage. He was transferred to a hepatobiliary unit. (E) CT after 10 days of antibiotic therapy: the abscess deep in the right lobe now contains less fluid and has a very thick rim of inflammatory tissue. The left lobe abscess has a more homogeneous inflammatory appearance—there is no evidence of any cavity or fluid in the left lobe of the liver. (F) Ultrasound after 10 days of antibiotic therapy: a thick inflammatory rim of moderately hypoechoic (dark) tissue can now be seen around the the more hypoechoic (darker) central cavity deep in the right lobe of the liver. The pus contains more echoes than on the scan performed 10 days earlier.

Percutaneous drainage was requested as the patient’s clinical condition had not improved significantly. (G) Abscess drainage—ultrasound-guided needle puncture: this oblique intercostal scan shows the hyperechoic (bright) needle entering the hypoechoic (dark) inflammatory area deep in the right lobe of the liver. The bevelled tip of the 22 g needle shows as a bright terminal echo. (H) Abscess drainage—cavity opacification under fluoroscopic guidance: after withdrawal of some pus to confirm needle tip position and obtain a sample for culture and sensitivity a few ml of contrast were injected to identify the dependent portion of the cavity. (I) Abscess drainage—guidewire placement under fluoroscopic guidance: a stiff interventional guidewire with a floppy ‘J’ tip, which will coil in the cavity (and not penetrate the back wall), is introduced. (J) Abscess drainage—guidewire visualization with ultrasound: the guidewire is very hyperechoic (bright) and its introduction and position can be monitored with ultrasound also. (K) Abscess drainage—tract dilatation under fluoroscopic guidance: serial dilators (8, 10, 12 Fr) are passed over the guidewire to prepare the tract for catheter placement. This is an important step of the procedure which reduces the risk of unwanted hepatic trauma. (L) Abscess drainage—catheter placement under fluoroscopic guidance: a 12 Fr catheter with an end-hole, multiple distal side-holes and a separate ‘sump’ lumen to improve drainage and allow irrigation (Ring-McLean catheter, Cook, Bloomington, Indiana, USA) has been placed over the guidewire. (M) Ultrasound scan after catheter placement: there is no evidence of any haematoma/complication despite the long catheter tract. The two walls of the catheter are seen as hyperechoic (bright) ‘tram tracks’, (N) Sinogram 10 days postdrainage: the patient's pyrexia has resolved, he feels better, the white cell count has fallen and there is no drainage from the catheter. The sinogram shows a small cavity at the tip of the lateral view. The catheter tract communicates with the biliary tree. There is no evidence of any stones in the extrahepatic bile ducts, which drain freely. This communication was presumably iatrogenic and was of no clinical importance in the absence of stones, strictures etc. The catheter was uneventfully removed.