### NCCN Guidelines Version 1.2013 Panel Members

**Neuroendocrine Tumors**

<table>
<thead>
<tr>
<th>Member Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthew H. Kulke, MD/Chair</td>
<td>Dana-Farber/Brigham and Women’s Cancer Center</td>
</tr>
<tr>
<td>Al B. Benson, III, MD</td>
<td>Robert H. Lurie Comprehensive Cancer Center of Northwestern University</td>
</tr>
<tr>
<td>Emily Bergsland, MD</td>
<td>UCSF Helen Diller Family Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Jordan D. Berlin, MD</td>
<td>Vanderbilt-Ingram Cancer Center</td>
</tr>
<tr>
<td>Lawrence S. Blaszkowsky, MD</td>
<td>Massachusetts General Hospital Cancer Center</td>
</tr>
<tr>
<td>Michael A. Choti, MD, MBA</td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
</tr>
<tr>
<td>Orlo H. Clark, MD</td>
<td>UCSF Helen Diller Family Comprehensive Cancer Center</td>
</tr>
<tr>
<td>James Eason, MD</td>
<td>St. Jude Children's Research Hospital/The University of Tennessee Health Science Center</td>
</tr>
<tr>
<td>Lyska Emerson, MD</td>
<td>Huntsman Cancer Institute at the University of Utah</td>
</tr>
<tr>
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<td>Fox Chase Cancer Center</td>
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<td>City of Hope Comprehensive Cancer Center</td>
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<td>Stanford Cancer Institute</td>
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<td>Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine</td>
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<tr>
<td>Venu G. Pillarisetty, MD</td>
<td>University of Washington Medical Center/Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>Leonard Saltz, MD</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>David E. Schteingart, MD</td>
<td>University of Michigan Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Manisha H. Shah, MD</td>
<td>The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute</td>
</tr>
<tr>
<td>Jonathan R. Strosberg, MD</td>
<td>Moffitt Cancer Center</td>
</tr>
<tr>
<td>Jean-Nicolas Vauthey, MD</td>
<td>The University of Texas MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Rebekah White, MD</td>
<td>Duke Cancer Institute</td>
</tr>
<tr>
<td>James C. Yao, MD</td>
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**NCCN Guidelines Panel Disclosures**

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NCCN Neuroendocrine Tumors Panel Members
Summary of the Guidelines Updates

Neuroendocrine Tumors, Clinical Presentations and Diagnosis (NE-1)
Carcinoid Tumors (CARC-1)
Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors) (PanNET-1)
Neuroendocrine Tumors of Unknown Primary (NUP-1)
Adrenal Gland Tumors (AGT-1)
Pheochromocytoma/Paraganglioma (PHEO-1)
Poorly Differentiated (High Grade)/Large or Small Cell (HGNET-1)
Multiple Endocrine Neoplasia, Type 1 (MEN1-1)
Multiple Endocrine Neoplasia, Type 2 (MEN2-1)

Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A)
Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B)
Surgical Principles for Management of Neuroendocrine Tumors (NE-C)

Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

Staging (ST-1)
NCCN Guidelines Version 1.2013 Updates
Neuroendocrine Tumors

Updates in Version 1.2013 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2012 include:

**Carcinoid Tumors**

**Global**
- Evaluation, “chest CT” was added “as appropriate.”
- Surveillance
  - “>1 y postresection” was modified by adding a time frame of “up to 10 y” for when surveillance can be stopped.
  - 1st bullet was modified: “Every 6-12 mo thereafter.”
  - Bullet, “Consider CT or MRI” replaced “Imaging studies as clinically indicated.”

**CARC-1**
- Duodenal
  - Footnote “f” was added: “If endoscopic resection performed, follow-up EGD as appropriate.”

**CARC-3**
- Rectal
  - Evaluation
    - EUS was moved from “as appropriate” to “recommended” and “endorectal MRI” was added with EUS.
  - Surveillance
    - For tumors ≤2 cm, the surveillance was modified: “1≤2 cm: Proctoscopy Endoscopy with rectal MRI or EUS at 6 and 12 mo, then as clinically indicated.”

**CARC-4**
- Gastric
  - For locoregional disease, patients with normal gastrin, a treatment option was added, “Consider endoscopic or wedge resection for tumors ≤2 cm.”
  - For hypergastrinemic patients, the surveillance was modified: “Years 4+: Annually with EGD.”
- Footnotes
  - Footnote “n” was modified: “For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks...”
  - Footnote “o” was added: “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”

**CARC-6**
- Footnotes
  - Footnote “n” was modified by adding: “For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks...” and removing “See PROMID study: J Clin Oncol 2009;27:4656-4663.” A separate footnote “s” was added: “For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.”
  - Footnote “o” was added: “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”
  - Footnote “w” was modified by adding “oxaliplatin” and “See Discussion for details.”

Continued on next page
Updates in Version 1.2013 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2012 include:

**PanNET-4**
- Glucagonoma
  - Evaluation, “EUS” was added to “as appropriate.”
- Footnotes
  - Footnote “k” was modified: “For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks...”
  - Footnote “l” was added: “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”

**PanNET-5**
- VIPoma
  - Evaluation, “EUS” was added to “as appropriate.”
- Footnotes
  - Footnote “k” was modified: “For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks...”
  - Footnote “l” was added: “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”

**PanNET-6**
- Surveillance
  - “>1 y postresection” was modified by adding a time frame of “up to 10 y” for when surveillance can be stopped.
  - 1st bullet was modified: “Every 6-12 mo thereafter.”
  - Bullet, “Consider CT or MRI” replaced “Imaging studies as clinically indicated.”

**PanNET-7**
- Footnote was removed: “Octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. Octreotide can be used alone or in combination with other agents.”

Continued on next page
Updates in Version 1.2013 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2012 include:

**Neuroendocrine Tumors of Unknown Primary**

- **NUP-1**
  - Neuroendocrine tumors of unknown primary was clarified by adding: “Biopsy-proven.”
  - Initial workup, “Consider EGD and/or colonoscopy” was added.
  - “Additional workup following primary not discovered” was removed from the page.
  - Footnote “d” was added: “Consider small bowel primary tumor based on symptoms and associated radiologic findings.”

**Adrenal Gland Tumors**

- **AGT-2**
  - History of prior or current malignancy
    - Additional evaluation was modified by adding: “Consider image-guided needle biopsy” with a corresponding footnote, “False negatives are possible, may consider proceeding directly to surgery in selected cases.”
  - Footnote “j” was revised: “Adrenal vein sampling can be considered is considered the standard for distinguishing single unilateral adenomas from bilateral hyperplasia.”

- **AGT-3**
  - ACTH- independent Cushing’s syndrome tumor descriptors were modified:
    - Tumor <5 cm, contralateral gland normal, circumscribed tumor and other benign imaging characteristics
    - Tumor <5 cm, benign imaging characteristics, contralateral gland abnormal
    - Tumor >5 cm or inhomogeneous, irregular margins, local invasion or other malignant imaging characteristics

- **AGT-4**
  - Footnote “o” was revised by adding, “The decision for open versus laparoscopic surgery is based on tumor size and degree of concern regarding potential malignancy.”

- **AGT-5**
  - For both locoregional and metastatic disease, the separation of “low-grade tumor” and “high-grade tumor” was removed.
  - **Localized disease**
    - Treatment after resection:
      - Bullet was added, “if high risk for local recurrence”
      - Follow-up was modified: “Every 3–6–12 mo up to 5 y, consider imaging and biomarkers, if tumor initially functional.”
  - **Metastatic disease**
    - 1st bullet was modified: “Consider observation with imaging for clinically indolent disease every 3 mo and biomarkers (if tumor initially functional).”
  - Footnotes
    - Footnote “t” was added: “Mitotane may have more benefit for control of hormone symptoms than control of tumor.”
    - Footnote “u” was added: High-risk local recurrence features include: positive margins, rupture of capsule, large size, and high grade.

Continued on next page
Updates in Version 1.2013 of the NCCN Guidelines from Version 1.2012 include:

**Pheochromocytoma**

<table>
<thead>
<tr>
<th>PHEO-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>• Bullet was modified: “Alpha blockade (phenoxybenzamine) with aggressive volume repletion ± alpha-methyltyrosine ± beta blockade 40-days preoperative (beta blockade only after alpha blockade)” and “forced hydration and sodium loading” was removed.</td>
</tr>
<tr>
<td>• Footnotes</td>
</tr>
<tr>
<td>• Footnote “d” was modified: “Genetic counseling and genetic testing is recommended should be offered with genetic testing when appropriate (See Discussion).”</td>
</tr>
<tr>
<td>• Footnote “e” was revised: “Phenoxybenzamine or doxazosin can be considered. Phenoxybenzamine initial dose of 10 mg PO twice daily, titrated up to control hypertension and starting therapy at least 7 days prior to planned procedure. Side effects include postural hypotension and dry mucous membranes. Please refer to the FDA prescribing information at <a href="http://www.fda.gov">www.fda.gov</a>.”</td>
</tr>
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<table>
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<tr>
<th>PHEO-2</th>
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<tbody>
<tr>
<td><strong>Surveillance</strong></td>
</tr>
<tr>
<td>• Resectable was revised:</td>
</tr>
<tr>
<td>• For 3-12 mo postresection, 2nd bullet was added: “Consider CT or MRI or PET scan.”</td>
</tr>
<tr>
<td>• “Long term &gt;1 y postresection up to 10 y” and for “Years 1-3: every 6-12 mo” and “Years 4+ up to 10 y: annually.” and 2nd bullet, “Consider CT or MRI or PET scan” replaced “Imaging studies as clinically indicated.”</td>
</tr>
<tr>
<td>• “Genetic counseling and testing as clinically indicated” was added.</td>
</tr>
<tr>
<td>• Locally unresectable and metastatic disease was revised:</td>
</tr>
<tr>
<td>• “Every 3-4 12 mo.” and 2nd bullet, “Consider CT or MRI or PET scan” replaced “Imaging studies as clinically indicated.”</td>
</tr>
<tr>
<td>• “Genetic counseling and testing as clinically indicated” was added.</td>
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</tbody>
</table>

**Poorly Differentiated (High Grade)/Large or Small Cell**

<table>
<thead>
<tr>
<th>HGNET-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor type</strong></td>
</tr>
<tr>
<td>• “Anaplastic” was removed.</td>
</tr>
<tr>
<td>• “Large” was added to “small cell carcinoma other than lung.”</td>
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<tr>
<td><strong>Evaluation</strong></td>
</tr>
<tr>
<td>• “FDG PET scan” was added to “as appropriate.”</td>
</tr>
<tr>
<td><strong>Primary treatment</strong></td>
</tr>
<tr>
<td>• Resectable, “Consider definitive chemoradiation (see NCCN Guidelines for Small Cell Lung Cancer)” was added.</td>
</tr>
<tr>
<td>• Footnotes</td>
</tr>
<tr>
<td>• Footnote “b” was added: “Evolving data suggest that patients with intermediate Ki-67 level in 20%-50% range may not respond as well to platinum/etoposide as patients with small cell histology or extremely high Ki-67. Clinical judgement should be used.”</td>
</tr>
<tr>
<td>• Footnote “c” was modified: “For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks...”</td>
</tr>
<tr>
<td>• Footnote “d” was added: “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”</td>
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</table>

**Multiple Endocrine Neoplasia, Type 1**

<table>
<thead>
<tr>
<th>MEN1</th>
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<tbody>
<tr>
<td>• The MEN1 section was extensively revised with:</td>
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<tr>
<td>• New sections titled</td>
</tr>
<tr>
<td>• Diagnosis of or Clinical Suspicion of MEN1 (MEN1-1)</td>
</tr>
<tr>
<td>• Table, “Tumors in Patients with MEN1” (MEN1-A)</td>
</tr>
<tr>
<td>• Treatment of PanNETs Specific to MEN1 Patients (MEN1-B)</td>
</tr>
<tr>
<td>• Algorithms</td>
</tr>
<tr>
<td>• Clinical evaluation, treatment, and surveillance recommendations for MEN1-related tumors were reorganized and revised for parathyroid, PanNET, and pituitary tumors. (MEN1-2)</td>
</tr>
<tr>
<td>• Specific algorithms were removed for: gastrinoma, glucagonoma, insulinoma, VIPoma, pancreatic polypeptidoma, somatostatinoma, and nonfunctioning tumor and were directed to treatment for sporadic PanNET tumors. Under pituitary tumors, the recommendations for prolactinoma, Cushing’s disease, acromegaly, TSH-producing adenomas, and nonfunctioning adenomas were removed from the guidelines.</td>
</tr>
</tbody>
</table>

*Continued on next page*
Updates in Version 1.2013 of the NCCN Guidelines from Version 1.2012 include:

**Multiple Endocrine Neoplasia, Type 2**
- The MEN2 section was extensively revised with:
  - New sections titled
    - Diagnosis of or Clinical Suspicion of MEN2 (MEN2-1)
    - Table, “Tumors in Patients with MEN2” (MEN2-A)
  - Algorithms
    - Clinical evaluation, treatment, and surveillance recommendations for MEN2-related tumors were reorganized and revised for medullary thyroid cancer, parathyroid, and pheochromocytoma. (MEN2-2)

**Principles of Pathology For Diagnosis and Reporting of Neuroendocrine Tumors**

**NE-A 1 of 4**
- Required information, 4th bullet was modified by adding: “Mitotic rate and/or Ki-67.” Ki-67 labeling index was removed from optional information.
- Table 1, differentiation column was modified by removing: “NET” from well-differentiated and “neuroendocrine carcinoma” from poorly differentiated.
- Footnote “a” was added: “Table 1 should be used as a general guide. Some tumors may not fall into a single category. Clinical judgment should be used. Definitions vary between lung, thymus and GEP-NETs in some classification systems.”

**NE-A 2 of 4**
- Functional status
  - Last sentence was modified: “However, a note may be added with additional information of the immunoreactivity of specific peptide hormone functional status of a tumor.”
- Immunohistochemistry and other ancillary techniques
  - Last sentence was revised: “...intestinal or pancreatic origin by CDX2; and pancreatic and rectal NETs by Isl1 and PAX8” and a corresponding reference was added.

**NE-A 3 of 4**
- Mitotic rate
  - Last sentence was revised: “Note that in cases where an accurate mitotic rate is precluded by inadequate tissue, such as in small biopsy samples including a FNA...”
- KI67 index
  - 4th sentence was added: “The pathologist should report the actual parameters used to assign grade (ie, mitotic rate and proliferation index)...The Ki-67 index cutpoints are not currently well-defined but tend to parallel those proposed in GEP-NETs, and generally the data suggests that Ki-67 proliferation rates of <20% excludes small cell lung carcinoma.

**Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors**

**NE-B**
- Title was revised, “Serum Hormone Evaluation: Immunohistochemical and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors.”
- Immunohistochemical studies section was removed.
- Pheochromocytoma/paraganglioma, “dopamine (urine)” was revised by removing “optional” and adding a footnote, “Should be considered with cervical paraganglioma.”
- Footnote “1” was modified by adding to gastrin: “False elevations may occur especially in patients on proton pump inhibitors”.

**Surgical Principles for Management of Neuroendocrine Tumors**

**NE-C**
- 2nd bullet was revised by adding: “Generally surgery will include splenectomy but with benign insulinoma, spleen preservation should be considered.”
- The following bullets were removed and replaced with “For MEN1-related surgical principles, see MEN1-B.”
  - “Surgical treatment of PanNETs in patients with MEN1 is not well-defined...Resection of dominant tumors (>2-2.5 cm) helps symptom management (insulinoma) and may decrease the risk of developing metastatic disease (gastrinoma).”
  - “Distal pancreatectomy with enucleation of tumors from the head of the pancreas is recommended for MEN1 insulinoma patients...Enucleation or a Whipple procedure is recommended for gastrinomas in the head of the pancreas.”

**Staging**

**ST-5**
- AJCC staging for adrenal cortical cancers was added.
Carcinoid tumors

Clinical presentations:
- Jejunal, ileal, colon (See CARC-1)
- Duodenal (See CARC-1)
- Appendix (See CARC-2)
- Rectal (See CARC-3)
- Gastric (See CARC-4)
- Bronchopulmonary, thymus (See CARC-5)
- Atypical lung carcinoid
- Locoregional unresectable disease and/or distant metastases (See CARC-6)

Neuroendocrine tumors of the pancreas (islet cell tumors)

Clinical presentations:
- Nonfunctioning pancreatic tumors (See PanNET-1)
- Gastrinoma (See PanNET-2)
- Insulinoma (See PanNET-3)
- Glucagonoma (See PanNET-4)
- VIPoma (See PanNET-5)
- Recurrent disease (See PanNET-6)
- Locoregional unresectable disease and/or distant metastases (See PanNET-7)

Neuroendocrine tumors of unknown primary

(See NUP-1)

Adrenal gland tumors (See AGT-1)

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated (high grade)/Large or small cell (See HGNET-1)

Multiple endocrine neoplasia, type 1 (See MEN1-1)

Clinical presentations:
- Hyperparathyroidism (See MEN1-2)
- Gastrinoma
- Glucagonoma
- Insulinoma
- VIPoma, pancreatic polypeptidoma, somatostatinoma, nonfunctioning tumor
- Pituitary tumor (See MEN1-2)
  - Prolactinoma
  - Cushing's disease
  - Acromegaly
  - TSH-producing adenomas
  - Nonfunctioning adenoma
- Adrenal gland tumor (See AGT-1)
- Bronchopulmonary carcinoid, thymus carcinoid (See CARC-5)
- Lipomas, skin angiomas

Multiple endocrine neoplasia, type 2 (See MEN2-1)

Clinical presentations:
- Medullary thyroid carcinoma (See MEN2-2 and See NCCN Thyroid Carcinoma Guidelines)
- Pheochromocytoma (See MEN2-2)
- Hyperparathyroidism (MEN2A)
- Marfanoid habitus (MEN2B)
- Mucosal neuromas (MEN2B)
- Lichen planus amyloidosis (MEN2A)

Merkel cell carcinoma

(See Merkel Cell Carcinoma Guidelines)

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### NCCN Guidelines Version 1.2013

**Carcinoid Tumors**

#### CLINICAL LOCATION

<table>
<thead>
<tr>
<th>Jejunal/ileal/colon</th>
<th>Duodenal</th>
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</table>

#### EVALUATION\(^a,^b\)

- **Recommended:**
  - Abdominal/pelvic multiphasic CT or MRI
  - Septum scan
  - Colonoscopy
  - Small-bowel imaging
  - Chest CT

- **As appropriate:**
  - Octreoscan
  - Colonoscopy
  - Small-bowel imaging
  - Chest CT

#### PRIMARY TREATMENT OF NON-METASTATIC DISEASE\(^c\)

- **Locoregional disease**
  - Bowel resection with regional lymphadenectomy\(^d\)
  - Consider prophylactic cholecystectomy\(^e\) when appropriate

- **Metastatic disease**
  - Endoscopic resection\(^f\)
  - Local excision (transduodenal) ± lymph node sampling
  - Pancreatoduodenectomy

#### SURVEILLANCE\(^g,^h\)

- **3-12 mo postresection:**
  - H&P
  - Consider 5-HIAA
  - Consider chromogranin A (category 3)
  - Consider abdominal/pelvic multiphasic CT or MRI

- **Metastatic Disease (CARC-6)**

- **Locoregional disease**
  - Endoscopic resection\(^f\)
  - Local excision (transduodenal) ± lymph node sampling
  - Pancreatoduodenectomy

- **Metastatic disease**
  - Endoscopic resection\(^f\)
  - Local excision (transduodenal) ± lymph node sampling
  - Pancreatoduodenectomy

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\(^a\) See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

\(^b\) See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

\(^c\) See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

\(^d\) Should include careful examination of the entire bowel, as multiple synchronous lesions may be present.

\(^e\) If possible future need for octreotide.

\(^f\) If endoscopic resection performed, follow-up EGD as appropriate.

\(^g\) Earlier, if symptoms.

\(^h\) Octreoscan and PET scan are not recommended for routine surveillance.

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
<table>
<thead>
<tr>
<th>CLINICAL LOCATION</th>
<th>EVALUATION&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>PRIMARY TREATMENT OF NON-METASTATIC DISEASE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>SURVEILLANCE&lt;sup&gt;g,h&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix&lt;sup&gt;i&lt;/sup&gt;</td>
<td>≤2 cm and confined to the appendix</td>
<td>Simple appendectomy&lt;sup&gt;j&lt;/sup&gt;</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>
| | >2 cm or incomplete resection (nodes, margins) | Recommended:  
  • Abdominal/pelvic multiphasic CT or MRI  
  As appropriate:  
  • Chest CT | 3-12 mo postresection:  
  • H&P  
  • Consider 5-HIAA  
  • Consider chromogranin A (category 3)  
  • Consider abdominal multiphasic CT/MRI |
| | | | >1 y postresection up to 10 y:  
  • Every 6-12 mo  
  > H&P  
  > Consider 5-HIAA  
  > Consider chromogranin A (category 3)  
  > Consider CT or MRI |
| | Metastatic disease | Metastatic Disease (CARC-6) | |

<sup>a</sup>See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

<sup>b</sup>See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

<sup>c</sup>See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

<sup>g</sup>Earlier, if symptoms.

<sup>h</sup>Octreoscan and PET scan are not recommended for routine surveillance.

<sup>i</sup>Some appendiceal carcinoids will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. See NCCN Guidelines for Colon Cancer.

<sup>j</sup>Some institutions will consider more aggressive treatments for 1- to 2-cm tumors with poor prognostic features. See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CLINICAL LOCATION | EVALUATION<sup>a,b</sup> | PRIMARY TREATMENT OF NON-METASTATIC DISEASE<sup>c</sup> | SURVEILLANCE<sup>g,h</sup>

| Rectal | Recommended: | Resection (transanal or endoscopic excision, if possible) | <1 cm: No follow-up required
1-2 cm: Endoscopy with rectal MRI or EUS at 6 and 12 mo, then as clinically indicated

3-12 mo postresection:
• H&P
• Consider chromogranin A (category 3)
• Consider abdominal/pelvic multiphasic CT or MRI
>1 y postresection up to 10 y:
• Every 6-12 mo
  ▶ H&P
  ▶ Consider chromogranin A (category 3)
  ▶ Consider CT or MRI

| ≤2 cm<sup>k</sup> | Colonoscopy | ≤2 cm<sup>k</sup> | ≥2 cm | Low anterior resection or Abdominoperineal resection (APR) | >2 cm |

For 1-2 cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.

<sup>a</sup>See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

<sup>b</sup>See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

<sup>c</sup>See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

<sup>g</sup>Earlier, if symptoms.

<sup>h</sup>Octreoscan and PET scan are not recommended for routine surveillance.

<sup>k</sup>For 1-2 cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.
**Carcinoid Tumors**

**Gastric**

**Recommended:**
- EGD
- Gastrin level
- Multiphasic CT or MRI for patients with normal gastrin
- B12 level if hypergastrinemia

**As appropriate:**
- EUS
- Chest CT
- Octreoscan for patients with normal gastrin

**Hypergastrinemic patients**

**Locoregional disease**

- Tumor ≤2 cm
- Solitary or multiple

**Patients with normal gastrin**

- Tumor >2 cm
- Solitary or multiple

**Metastatic disease**

**Metastatic Disease (CARC-6)**

- Radical gastric resection + lymph node removal
- Consider endoscopic or wedge resection for tumors ≤2 cm

**PRIMARY TREATMENT OF NON-METASTATIC DISEASE**

- Observe or
- Endoscopic resection + biopsy of tumor(s) and adjacent mucosa or
  - Octreotide for Zollinger-Ellison patients (category 2B)

**SURVEILLANCE**

- H&P every 6-12 mo up to 10 y

- New lesion(s) or increasing tumors, consider antrectomy

- 3-12 mo postresection:
  - H&P
  - Consider chromogranin A (category 3)
  - Multiphasic CT or MRI

- >1 y postresection up to 10 y:
  - Every 6-12 mo
  - H&P
  - Consider chromogranin A (category 3)
  - Consider CT or MRI

**CLINICAL LOCATION**

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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1. Gastrin levels need to be completed while fasting and off protein pump inhibitors for 1 week.

2. If gastric pH is low or clinical or radiographic evidence, see gastrinoma on PanNET-2.

3. For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

4. Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.
**Carcinoid Tumors**

**CLINICAL LOCATION**

- **Bronchopulmonary**
  - Recommended: Chest CT and abdominal multiphasic CT or MRI
  - As appropriate: Octreoscan, Bronchoscopy, ACTH/cortisol

- **Thymus**
  - Recommended: Chest mediastinal CT and abdominal multiphasic CT or MRI
  - As appropriate: Octreoscan, Bronchoscopy, ACTH/cortisol

**EVALUATION**

- **Localized disease**
  - Recommended: Chest/mediastinal CT or MRI
  - As appropriate: Octreoscan, Bronchoscopy, ACTH/cortisol

- **Locoregional disease**
  - Recommended: Chest CT and abdominal CT or MRI
  - As appropriate: Octreoscan, Bronchoscopy, ACTH/cortisol

- **Metastatic disease**
  - Recommended: Chest CT and abdominal CT or MRI
  - As appropriate: Octreoscan, Bronchoscopy, ACTH/cortisol

**PRIMARY TREATMENT OF NON-METASTATIC DISEASE**

- **Localized disease**
  - Resect
- **Locoregional disease**
  - Resect
- **Metastatic disease**
  - Complete resection
  - Incomplete resection
    - RT ± chemotherapy

**SURVEILLANCE**

- **3-12 mo postresection:**
  - H&P
  - Consider chromogranin A (category 3)
  - Chest mediastinal multiphasic CT or MRI
  - >1 y postresection up to 10 y:
    - Every 6-12 mo
      - H&P
      - Consider chromogranin A (category 3)
      - Consider CT or MRI

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

a. See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
b. See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).
c. See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
d. Earlier, if symptoms.

---

h. Octreoscan and PET scan are not recommended for routine surveillance.

p. Thymic carcinoids are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

q. Consider 5-FU or capecitabine at radiosensitizing doses. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

If complete resection possible → Resect primary + metastases

Locoregional unresectable disease and/or distant metastases
- Imaging:
  - Multiphasic CT or MRI
  - Consider octreoscan
- Consider 5-HIAA
- Consider chromogranin A (category 3)

Asymptomatic, low tumor burden
- Observe with markers and scans every 3-12 mo or Octreotide

Locally symptomatic from primary tumor
- Consider resection of primary tumor

Clinically significant tumor burden
- Octreotide

Carcinoid syndrome
- Octreotide
- Echocardiogram

Octreotide, if not already receiving and:
- Consider hepatic regional therapy (arterial embolization, chemoembolization, radioembolization [category 2B]) or
- Consider cytoreductive surgery/ablative therapy (category 2B)
- Consider everolimus (10 mg/d) (category 3)
- Consider cytotoxic chemotherapy (category 3), if no other options feasible

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Clinical Diagnosis**

**Evaluation**
- Nonfunctioning pancreatic tumors
  - Recommended: Multiphasic CT or MRI
  - As appropriate: OctreoScan
  - Pancreatic polypeptide (category 3)
  - Chromogranin A (category 3)

**Management of Primary Non-Metastatic Disease**
- Small (<2 cm)
  - Enucleation ± regional nodes
  - or Distal pancreatectomy ± regional nodes/splenectomy
  - or Pancreatoduodenectomy ± regional nodes
  - or Consider observation in selected cases
- Larger (≥2 cm), or invasive tumors
  - Pancreatoduodenectomy + regional nodes
  - or Distal pancreatectomy + splenectomy + regional nodes

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

*a* For rare tumors such as somatostatinoma, ACTHoma, PTHrP-secreting tumors, and PPoma, follow the nonfunctioning pancreatic tumor pathway.

*b* See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

*c* See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

*d* For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

*e* Risks and benefits of surgical resection should be carefully weighed in patients with small lesions.

*f* See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

*g* Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

*h* Neuroendocrine tumors of the pancreas that are 1-2 cm have a small, but real risk of lymph node metastases. Therefore, lymph node resection should be considered.

*i* Selected cases: tumors <1 cm, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities.
PanNET-2

NCCN Guidelines Version 1.2013
Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors)

CLINICAL DIAGNOSIS

EVALUATIONb,c,d

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASEf,g

Occult
No primary tumor or metastases on imaging

Observe or
Exploratory surgery including duodenotomy and intraoperative ultrasound; local resection/enucleation of tumor(s) + periduodenal node dissection

Duodenotomy and intraoperative ultrasound; local resection/enucleation of tumor(s) + periduodenal node dissection

Duodenum

Exophytic or peripheral tumors by imagingm

Distal pancreatectomy ± splenectomyg

For deeper or invasive tumors and those in proximity to the main pancreatic duct

Pancreateo-duodenectomy

Distal

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Insulinoma**

**EVALUATION**

- **Locoregional disease**
  - Recommended: Multiphasic CT or MRI
  - As appropriate: EUS
  - 48-72-hr observed fast, insulin/glucose ratio, if diagnosis uncertain
  - Chromogranin A (category 3)

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

- Exophytic or peripheral tumors by imaging
  - Head or Distal
  - Pancreate-duodenectomy

- Deeper or invasive tumors and those in proximity to the main pancreatic duct
  - Head
  - Distal pancreatic resection (spleen-preserving), consider laparoscopic resection

**Metastatic disease**

- As appropriate: Octreoscan
  - See Metastases (PanNET-7)

---

**Note:** All recommendations are category 2A unless otherwise indicated.

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**NCCN Guidelines Version 1.2013**

**Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors)**

**CLINICAL DIAGNOSIS**

---

**EVALUATION**

- **Recommended:**
  - Glucagon/blood glucose
  - Multiphasic contrast-enhanced CT or MRI
  - As appropriate:
    - Octreoscan
    - EUS
    - Chromogranin A (category 3)

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

- **Head (rare)**
  - Pancreatoduodenectomy + peripancreatic lymph nodes

- **Distal**
  - Distal pancreatectomy + peripancreatic lymph node dissection + splenectomy

---

- **Stabilize with IV fluids and octreotide**
  - Glucose levels

- **Locoregional disease**
  - See Metastases (PanNET-7)

---

- **Metastatic disease**
  - See Metastases (PanNET-7)

---

**Note:** All recommendations are category 2A unless otherwise indicated.

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---

b See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

c See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

d For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

f See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

k For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

l Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

p Small (<2 cm), peripheral glucagonomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.

q Consider perioperative anticoagulation.
**Clinical Diagnosis**

**Evaluation**

**Management of Primary Non-Metastatic Disease**

**VIPoma**

- **Recommended:**
  - Electrolytes
  - VIP levels
  - Multiphasic CT or MRI
- **As appropriate:**
  - Octreoscan
  - EUS
  - Chromogranin A (category 3)

**Locoregional Disease**

- Stabilize with IV fluids and octreotide
- Correct electrolyte imbalance (K^+, Mg^2+, HCO_3^-)

**Head**

- Pancreatoduodenectomy + peripancreatic lymph nodes

**Distal**

- Distal pancreatectomy + peripancreatic lymph node dissection + splenectomy

**See Surveillance (PanNET-6)**

**Metastatic Disease**

- See Metastases (PanNET-7)

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**References:**

b See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

c See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

d For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

f See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

g Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

k For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

l See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

m Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

n Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.
**NCCN Guidelines Version 1.2013**  
Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors)

### SURVEILLANCE

#### Locoregional disease

- **3-12 mo postresection:**
  - H&P and consider markers from preoperative evaluation as indicated
  - Multiphasic CT or MRI
  - >1 y postresection up to 10 y:
    - Every 6-12 mo
      - H&P
      - Consider markers
      - Consider CT or MRI

#### Distant metastases

- 3-12 mo postresection:
  - See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)

### RECURRENT DISEASE

- **Resectable** → Resection

### MANAGEMENT OF RECURRENT DISEASE

- **Unresectable**
  - See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)

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See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

Earlier, if symptoms.

Octreoscan and PET scan are not recommended for routine surveillance.

Note: All recommendations are category 2A unless otherwise indicated.

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**NCCN Guidelines Version 1.2013**

**Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors)**

**MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES**

- **Locoregional unresectable disease and/or Distant metastases**
  - If complete resection possible
    - Resect metastases + primary
    - Clinically significant progressive disease, see below
  - Asymptomatic, low tumor burden, and stable disease
    - Observe with markers and scans every 3-12 mo
    - Clinically significant progressive disease, see below
  - Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease
    - Manage clinically significant symptoms as appropriate
    - Hepatic regional therapy (ie, arterial embolization, chemoembolization, radioembolization [category 2B]) or Cytoreductive surgery/ablative therapy (category 2B)
    - Consider octreotide if not already receiving (category 2B)

- **Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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† *See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).*


§ The following agents have been used: capecitabine, dacarbazine, doxorubicin, 5-FU, streptozocin, and temozolomide.

‖ Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited, but data on their use are emerging.

Χ Octreotide should be used with caution in patients with insulinoma as it may transiently worsen hypoglycemia (See Discussion for details).
INITIAL WORKUP

- Tumor-directed localizing studies:
  - Multiphasic CT or MRI
  - Consider octreoscan, ultrasound, EUS
  - Bone scan, if symptoms
  - Consider FDG-PET scan in poorly differentiated tumors only
  - Consider EGD and/or colonoscopy

- Biopsy-proven neuroendocrine tumors (NET) of unknown primary

  - Primary not discovered
    - Well-differentiated
      - See Carcinoid Tumors (CARC-6)
    - Poorly differentiated
      - See Primary Treatment for poorly differentiated (high-grade) neuroendocrine tumor (HGNET-1)

- Primary found
  - See specific tumor type (NE-1)

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

*a* Consider possibility of functioning adrenal neoplasms and suspected carcinoid tumor syndrome prior to biopsy. Alpha blockade is required prior to biopsy or manipulation for suspected pheochromocytoma or paraganglioma (*See PHEO-1*). Octreotide premedication is required before biopsy in a suspected functioning carcinoid tumor.

*b* Sequence of initial workup may vary.

*c* See *Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).*

*d* Consider small bowel primary tumor based on symptoms and associated radiologic findings.


*f* See *Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).*
## NCCN Guidelines Version 1.2013
### Adrenal Gland Tumors

### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Adrenal gland tumor on imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of prior or current malignancy with risk of or suspicion of adrenal metastasis</td>
</tr>
<tr>
<td>No history of prior or current malignancy</td>
</tr>
</tbody>
</table>

### EVALUATION\(^a,b\)

| Adrenal protocol (CT\(^c\) scan or MRI\(^d\) to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics |
| Morphologic evaluation |
| Functional evaluation |

### CLINICAL DIAGNOSIS

- **Hyperaldosteronism**
  - See Primary Treatment (AGT-2)

- **Cushing’s syndrome**
  - See Primary Treatment (AGT-3)

- **Non-functioning tumor**
  - See Primary Treatment (AGT-4)

- **Pheochromocytoma**
  - Elevated plasma-free metanephrines\(^f\) or confirmed elevation of urine metanephrines and catecholamines
  - See Pheochromocytoma Guidelines (PHEO-1)

### Notes

- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^a\) See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

\(^b\) See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

\(^c\) If unenhanced is < +10 HU, then the tumor is probably benign. If unenhanced is > +10 HU, then use enhanced and wash-out. If >60% wash-out in 15 min, the tumor is likely to be benign; if >60%, the tumor is possibly malignant. (Caoili E, Korobkin M, Francis I, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629-633.)

\(^d\) Chemical shift imaging demonstrating signal drop out.


\(^f\) Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation. Elevations that are 4 times above the upper limit of normal are diagnostic.
# NCCN Guidelines Version 1.2013
## Adrenal Gland Tumors

### CLINICAL DIAGNOSIS

<table>
<thead>
<tr>
<th>History of prior or current malignancy with risk of or suspicion of adrenal metastasis</th>
<th>Rule out pheochromocytoma</th>
<th>Consider image-guided needle biopsy</th>
<th>Adrenal cortical tissue</th>
<th>Primarily treat primary aldosteronism (see NCCN disease-specific treatment guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperaldosteronism, suspect benign</td>
<td>Not a surgical candidate</td>
<td>Surgical candidate</td>
<td>Consider adrenal vein sampling for aldosterone</td>
<td>Bilateral aldosterone production</td>
</tr>
<tr>
<td>Hyperaldosteronism, suspect malignant</td>
<td>Open adrenalectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ADDITIONAL EVALUATION

- Not a surgical candidate
- Surgical candidate
- Consider adrenal vein sampling for aldosterone
- Bilateral aldosterone production
- Unilateral aldosterone production
- Metastasis from other site discovered

### PRIMARY TREATMENT

- Unilateral aldosterone production
  - Adrenalectomy, laparoscopic preferred
- Bilateral aldosterone production
  - Medical management of hypertension and hypokalemia with spironolactone or eplerenone
- Metastasis from other site discovered
  - See NCCN disease-specific treatment guidelines

### Note

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**g** Suspect malignancies with irregular/inhomogeneous morphology, lipid-poor, do not wash-out, tumor >3 cm, or secretion of more than one hormone.

**h** Can proceed with adrenal biopsy if the clinical suspicion for pheochromocytoma is low and if plasma metanephrines are less than 2 times the upper limit of normal.

**i** False negatives are possible, may consider proceeding directly to surgery in selected cases.

**j** Adrenal vein sampling can be considered for distinguishing single unilateral adenomas from bilateral hyperplasia. CT imaging is not always reliable. Some NCCN Member Institutions recommend sampling in all cases of primary aldosteronism. However, it may be reasonable to exclude adrenal vein sampling in patients <40 y. Cortisol measurement in the catheterization samples is used to confirm proper catheter placement.

**k** See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
**ACTH-independent Cushing’s syndrome**

- **Tumor <5 cm, contralateral gland normal, circumscribed tumor and other benign imaging characteristics**
  - Adrenal vein sampling for cortisol
  - Asymmetric cortisol production

- **Tumor <5 cm, benign imaging characteristics, contralateral gland abnormal**
  - Adrenal vein sampling for cortisol
  - Symmetric cortisol production

- **Tumor >5 cm or inhomogeneous, irregular margins, local invasion or other malignant imaging characteristics**
  - Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion

**ACTH-dependent Cushing’s syndrome**

- **Tumor <5 cm, contralateral gland normal, circumscribed tumor and other benign imaging characteristics**
  - Assess and treat for pituitary ACTH production or ectopic sources of ACTH production

- **Tumor >5 cm or inhomogeneous, irregular margins, local invasion or other malignant imaging characteristics**
  - Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion

**Primary Treatment**

- Adrenalectomy, laparoscopic preferred
- Postoperative corticosteroid supplementation until hypothalamic-pituitary-adrenal (HPA) axis recovery
- Unilateral adrenalectomy with removal of most active side, laparoscopic preferred
- Postoperative corticosteroid supplementation until HPA axis recovery
- Medical management of hypercortisolism from presumed multinodular hyperplasia of the adrenal with ketoconazole, mitotane

**Notes:**

- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

- *See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).*
- Consider octreotide if Octreoscan is positive.
- May require removal of adjacent structures (i.e., liver, kidney, pancreas, spleen, diaphragm) for complete resection.
NCCN Guidelines Version 1.2013
Adrenal Gland Tumors

**CLINICAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>Non-functioning tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign-appearing adenoma (≤4 cm) by CT or MRI criteria or Myelolipoma by radiographic features (any size) without symptoms</td>
</tr>
<tr>
<td>Benign-appearing adenoma of intermediate size (4-6 cm) by CT or MRI criteria</td>
</tr>
<tr>
<td>Intermediate size tumor (4-6 cm) with aggressive features</td>
</tr>
<tr>
<td>Large tumor (&gt;6 cm) with aggressive features</td>
</tr>
<tr>
<td>Suspected carcinoma</td>
</tr>
</tbody>
</table>

**ADDITIONAL EVALUATION**

| Benign-appearing adenoma (≤4 cm) by CT or MRI criteria or Myelolipoma by radiographic features (any size) without symptoms |
| Benign-appearing adenoma of intermediate size (4-6 cm) by CT or MRI criteria |
| Intermediate size tumor (4-6 cm) with aggressive features |
| Large tumor (>6 cm) with aggressive features |

| Unchanged |
| Enlarging (≥1 cm in 1 year) |
| Repeat imaging in 6-12 months |
| Repeat imaging in 3-6 months |
| Repeat imaging in 6-12 months |

**PRIMARY TREATMENT**

| Benign-appearing adenoma (≤4 cm) by CT or MRI criteria or Myelolipoma by radiographic features (any size) without symptoms |
| Benign-appearing adenoma of intermediate size (4-6 cm) by CT or MRI criteria |
| Intermediate size tumor (4-6 cm) with aggressive features |
| Large tumor (>6 cm) with aggressive features |

| No further follow-up |
| Consider adrenalectomy or Short-interval follow-up |
| Repeat imaging in 6-12 months |
| Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion |

**Additional Notes:**

- If unenhanced is <+10 HU, then the tumor is probably benign. If unenhanced is >+10 HU, then use enhanced and wash-out. If >60% wash-out in 15 min, the tumor is likely to be benign; if <60%, the tumor is possibly malignant. (Caoili E, Korobkin M, Francis I, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629-633.)
- Chemical shift imaging demonstrating signal drop out.
- See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
- Aggressive features such as inhomogeneous, irregular margins, and local invasion.
- If size is resectable by laparoscopy, may explore laparoscopically with planned conversion for evidence of local invasion. The decision for open versus laparoscopic surgery is based on tumor size and degree of concern regarding potential malignancy.

**Discussion:**

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ADRENAL CARCINOMA

Localized disease

Resect tumor and adjacent lymph nodes
  - Open adrenalectomy recommended\textsuperscript{m,q}

If high risk for local recurrence:\textsuperscript{u}
  - Consider external-beam RT to tumor bed
  - Consider adjuvant mitotane therapy (category 3)

Follow-Up

Every 3-12 mo up to 5 y
  - Consider imaging and biomarkers, if tumor initially functional

Metastatic disease

Consider observation with imaging for clinically indolent disease every 3 mo and biomarkers (if tumor initially functional)

Consider resection of primary tumor and metastases if >90% removable, particularly if functional

Consider systemic therapy,\textsuperscript{r,s}
  - Cisplatin or carboplatin + etoposide ± doxorubicin ± mitotane\textsuperscript{t}
  - or
  - Streptozocin ± mitotane\textsuperscript{t}
  - or
  - Mitotane\textsuperscript{t} monotherapy

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

\textsuperscript{m}May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.

\textsuperscript{q}Cross-sectional imaging to stage disease.

\textsuperscript{r}Increased risk for local recurrence and peritoneal spread when done laparoscopically.

\textsuperscript{s}Monitor mitotane blood levels. Some institutions recommend target levels of 14-20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Mitotane therapy requires steroid replacement therapy.


\textsuperscript{u}Mitotane may have more benefit for control of hormone symptoms than control of tumor.

\textsuperscript{u}High-risk local recurrence features include: positive margins, rupture of capsule, large size, and high grade.

\textsuperscript{k}Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# NCCN Guidelines Version 1.2013
## Pheochromocytoma/Paraganglioma

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EVALUATION(^a,b)</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma/paraganglioma</td>
<td><strong>Recommended:</strong></td>
<td><strong>See Primary Treatment (PHEO-2)</strong></td>
</tr>
<tr>
<td></td>
<td>• Fractionated plasma-free metanephrine(^c) and normetanephrine or urine metanephrine</td>
<td><strong>Alpha blockade(^e) with aggressive volume repletion</strong></td>
</tr>
<tr>
<td></td>
<td>• Chest/abdominal multiphasic CT or MRI</td>
<td>± alpha-methyltyrosine</td>
</tr>
<tr>
<td></td>
<td>• Genetic counseling(^d)</td>
<td>± beta blockade preoperative (beta blockade only after alpha blockade)(^f)</td>
</tr>
<tr>
<td></td>
<td>As appropriate:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone scan, if bone symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MIBG scan/octreoscan, if suspect multiple tumors or CT negative</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).

\(^b\) See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

\(^c\) Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation. Elevations that are 4 times above the upper limit of normal are diagnostic.

\(^d\) Genetic counseling and genetic testing is recommended when appropriate (See Discussion).

\(^e\) Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room. Selective alpha\(_1\)-blocking agents, such as prazosin, terazosin, and doxazosin, are alternative medications when long-term therapy is required for metastatic pheochromocytoma. Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers.

\(^f\) Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room. Selective alpha\(_1\)-blocking agents, such as prazosin, terazosin, and doxazosin, are alternative medications when long-term therapy is required for metastatic pheochromocytoma. Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## NCCN Guidelines Version 1.2013
### Pheochromocytoma/Paraganglioma

#### PRIMARY TREATMENT

- **Resectable**
  - Resect (laparoscopic preferred when safe and feasible)

- **Locally unresectable**
  - Cytoreductive (R2) resection, if possible ± RT + alpha blockade ± alpha-methyltyrosine ± beta blockade

- **Distant metastases**
  - Cytoreductive (R2) resection when possible + continuous alpha blockade ± alpha-methyltyrosine ± beta blockade (optional)
  - Clinical trial or Systemic chemotherapy (eg, dacarbazine, cyclophosphamide, vincristine) or 131I MIBG (requires prior positive MIBG scan with dosimetry)

#### SURVEILLANCE

- **3-12 mo postresection:**
  - H&P, blood pressure, and markers
  - Consider CT or MRI or PET scan

- **≥1 y postresection up to 10 y:**
  - H&P, blood pressure, and markers
    - Years 1-3: every 6-12 mo
    - Years 4+ up to 10 y: annually
  - Consider CT or MRI or PET scan
  - Genetic counseling and testing as clinically indicated

- **Every 3-12 mo**
  - H&P, blood pressure, and markers
  - Consider CT or MRI or PET scan
  - Genetic counseling and testing as clinically indicated

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

*b* See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

*g* See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

*h* Earlier, if symptoms.
**NCCN Guidelines Version 1.2013**  
**Poorly Differentiated (High Grade)/ Large or Small Cell**

### TUMOR TYPE

#### Poorly differentiated (high-grade) NET or Large or small cell carcinoma other than lung

#### EVALUATION

- Recommended:
  - Chest/abdominal/pelvic CT
  - As appropriate:
    - Brain MRI or CT
    - FDG PET scan
    - Other scans as indicated
    - Plasma ACTH or other biochemical markers

#### PRIMARY TREATMENT\(^a\)

- Resectable
  - Resection + chemotherapy with small cell lung cancer regimen  
    (See NCCN Guidelines for Small Cell Lung Cancer)\(^b\) ± RT or
  - Consider definitive chemoradiation  
    (See NCCN Guidelines for Small Cell Lung Cancer)\(^b\)

- Locoregional, unresectable
  - RT + chemotherapy with small cell lung cancer regimen  
    (See NCCN Guidelines for Small Cell Lung Cancer)\(^b\)
  - Consider octreotide therapy\(^c,d\)
    if hormone secreting

- Metastatic
  - Chemotherapy with small cell lung cancer regimen  
    (See NCCN Guidelines for Small Cell Lung Cancer)\(^b\)
  - Consider octreotide therapy\(^c,d\)
    if hormone secreting

#### SURVEILLANCE\(^e\)

<table>
<thead>
<tr>
<th>H&amp;P + appropriate imaging studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Every 3 mo for 1 y, then every 6 mo</td>
</tr>
</tbody>
</table>

---

\(^a\) See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

\(^b\) Evolving data suggest that patients with intermediate Ki-67 level in 20%-50% range may not respond as well to platinum/etoposide as patients with small cell histology or extremely high Ki-67. Clinical judgement should be used.

\(^c\) For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

\(^d\) Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

\(^e\) Earlier, if symptoms.

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors: multi-gland parathyroid hyperplasia; pancreatic NET; or pituitary tumors.\(^a,b\) See Tumors in Patients with MEN1 (MEN1-A)

- MEN1 may also be associated with carcinoid tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas.\(^a,b\)
- Patients with MEN1 are more likely to have multiple PanNET’s than those with sporadic tumors.

For patients known or suspected to have MEN1, a clinical evaluation includes: See MEN1 Clinical Evaluation and Primary Treatment (MEN1-2)

1. Biochemical tests evaluating hormone levels;
2. Imaging tests needed to localize the site of the tumor or hyperplasia; and
3. Genetic counseling and testing

Genetic counseling and MEN1 genetic testing should be offered to the following:

- An individual with a clinical diagnosis or suspicion of MEN1\(^a,b,c,d\)
- An at-risk relative of an individual with a known germline MEN1 mutation\(^a\)

MEN1 clinical evaluation should be offered to the following:

- Individuals with a clinical diagnosis or suspicion of MEN1 even with negative MEN1 genetic test
- At-risk relatives even if MEN1 mutation has not been identified in the affected family member or if MEN1 genetic testing has not been performed in the affected or at-risk family member

---


\(^c\)A germline MEN1 mutation is seldom found in individuals with a single MEN1-associated tumor and no family history. (Ellard S, Hattersley AT, Brewer CM, Vaidya B. Detection of an MEN1 gene mutation depends on clinical features and supports current referral criteria for diagnostic molecular genetic testing. Clin Endocrinol (Oxf). 2005;62:169-175.)

\(^d\)10% of cases have de novo MEN1 mutations.
# NCCN Guidelines Version 1.2013
## Multiple Endocrine Neoplasia, Type 1

### CLINICAL EVALUATION\(^e\)

<table>
<thead>
<tr>
<th>Parathyroid:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended</td>
</tr>
<tr>
<td>▶ Serum calcium</td>
</tr>
<tr>
<td>▶ PTH</td>
</tr>
<tr>
<td>• As appropriate</td>
</tr>
<tr>
<td>▶ 24-hour urine calcium</td>
</tr>
<tr>
<td>▶ Neck ultrasound</td>
</tr>
<tr>
<td>▶ Parathyroid sestamibi scan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pancreatic neuroendocrine tumors (PanNET):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended</td>
</tr>
<tr>
<td>▶ Gastrin levels(^f) (basal, stimulated as indicated)</td>
</tr>
<tr>
<td>▶ Pancreatic polypeptide (category 3)</td>
</tr>
<tr>
<td>▶ Chromogranin A (category 3)</td>
</tr>
<tr>
<td>▶ Multiphasic CT or MRI</td>
</tr>
<tr>
<td>• As appropriate</td>
</tr>
<tr>
<td>▶ Glucagon, VIP, insulin, fasting glucose depending on symptoms</td>
</tr>
<tr>
<td>▶ EUS</td>
</tr>
<tr>
<td>▶ Octreoscan</td>
</tr>
</tbody>
</table>

### TREATMENT

<table>
<thead>
<tr>
<th>Subtotal parathyroidectomy ± cryopreservation of parathyroids ± thymectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>or Total parathyroidectomy with autotransplantation ± cryopreservation of parathyroids ± thymectomy</td>
</tr>
</tbody>
</table>

#### Diagnosis of or clinical suspicion of MEN1 (See MEN1-1)

- See MEN1 Surveillance (MEN1-3)

#### Pituitary:

- See Treatment of PanNETs Specific to MEN1 Patients (MEN1-B) and See appropriate sporadic PanNET workup and treatment (PanNET-1 through PanNET-5)

- See MEN1 Surveillance (MEN1-3)

- Consider referral to endocrinology for further workup

- See MEN1 Surveillance (MEN1-3)

---

\(^e\)For MEN1 genetic testing recommendations, see MEN1-1.

\(^f\)Gastrin levels need to be completed while fasting and off proton pump inhibitors for 1 week.

\(^g\)Potential hormones secreted include ACTH, FSH, LH, TSH, GH, and prolactin.

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MEN1 SURVEILLANCE\textsuperscript{h}

**Parathyroid:**
- Calcium annually → If calcium rises:
  - Serum PTH
  - Reimage with neck ultrasound and/or parathyroid sestamibi
  - Consider MRI neck

→ Consider referral to endocrinology

**PanNET:**
- Serum gastrin annually\textsuperscript{i}
- Serum chromogranin A\textsuperscript{i} and/or pancreatic polypeptide annually (category 3)
- Follow other previously elevated serum hormones or as symptoms indicate
- Consider imaging with multiphasic abdominal CT, MRI scan every 1-3 y
- Consider serial EUS

→ See appropriate sporadic PanNET workup and treatment (PanNET-1 through PanNET-5)

**Pituitary:**
- MRI of pituitary every 3-5 y
- Repeat prolactin, IGF-1, and other previously abnormal pituitary hormones annually or as symptoms indicate

→ If tumor grows or hormones increase, consider referral to endocrinology

\textsuperscript{h}Surveillance is indicated for all MEN tumors regardless of patient’s tumor type.

\textsuperscript{i}Serum gastrin and chromogranin A will be elevated in patients using proton pump inhibitors.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## TUMORS IN PATIENTS WITH MEN1

<table>
<thead>
<tr>
<th>Organ</th>
<th>Neoplasm</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid</td>
<td>Hyperplasia</td>
<td>98%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Islet cell</td>
<td>50%</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Adenoma</td>
<td>35%</td>
</tr>
<tr>
<td>Lung</td>
<td>Carcinoid</td>
<td>10%(^b)</td>
</tr>
<tr>
<td>Thymus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric (type 2)</td>
<td>Carcinoid</td>
<td>Occurs frequently in patients with gastrinoma</td>
</tr>
</tbody>
</table>

\(^a\)Higher incidence of adrenal tumors is also observed in MEN1.


---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
In general, surgical management of patients with MEN1 is similar to those with sporadic tumors. Refer to the relevant site-specific recommendations earlier in these guidelines. (See PanNET-1 through PanNET-5)

However, one notable exception is the multi-focality of pancreaticoduodenal NETs in patients with MEN1.

Decision to resect a pancreatic or duodenal NET in the setting of multifocal disease is complex. If surgery is performed to resect hormonally functional tumor(s), attempts should be made to preoperatively localize the site of the functional tumor. Surgical resection can be considered in the following scenarios:

- Insulinoma causing symptomatic hypoglycemia
- Tumor larger than 1-2 cm in size
- Tumor with relatively rapid rate of growth over 6-12 months
- Endoscopy with EUS is recommended prior to pancreatic surgery in order to preoperatively assess and localize tumors.

MEN1-associated metastatic pancreatic NETs are often slower growing than metastatic sporadic tumors. Observation can be considered for non-functioning indolent tumors.

A consultation with an endocrinologist for all patients with MEN1 should be considered.
**DIAGNOSIS OF OR CLINICAL SUSPICION OF MEN2**

- **MEN2 is subdivided into MEN2A and MEN2B.** Medullary thyroid cancer (MTC) occurs in ~100% of MEN2A and MEN2B and is often the first manifestation of the syndrome. See Tumors in Patients with MEN2 (MEN2-A)
  - A clinical diagnosis of MEN2A includes two or more MEN2A-associated cancers (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives\(^a,b\)
  - A clinical diagnosis of MEN2B includes the presence of MTC, pheochromocytoma, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, or 'marfanoid' body habitus, inability to cry tears\(^a,b\)
- For patients known or suspected to have MEN2, a clinical evaluation includes: See MEN2 Clinical Evaluation and Primary Treatment (MEN2-2)
  1. Biochemical tests evaluating hormone levels;
  2. Imaging tests needed to localize MEN2-associated tumors; and
  3. Genetic counseling and testing
- Genetic counseling and RET genetic testing should be offered to the following:
  - An individual with a diagnosis of MTC or clinical diagnosis of MEN2 or primary C-cell hyperplasia\(^a,b,c\)
  - An at-risk relative of an individual with a known germline RET mutation\(^a,b\)
    - Genetic testing of at-risk family members at a very early age.\(^a,b\) See NCCN Guidelines for Thyroid Carcinoma: Medullary Thyroid Cancer section.
- MEN2 clinical evaluation should be offered to the following:
  - Individuals with a clinical diagnosis or suspicion of MEN2 even with negative RET genetic test
  - At-risk relatives even if RET mutation has not been identified in the affected family member\(^b\) or if RET genetic testing has not been performed in the affected or at-risk family member

---
\(^c\) 50% of cases have de novo RET mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for RET mutations should still be performed on the affected individual.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### NCCN Guidelines Version 1.2013

#### Multiple Endocrine Neoplasia, Type 2

#### CLINICAL EVALUATION

**Medullary thyroid cancer:**
- Calcitonin, CEA
- Neck ultrasound of both thyroid and cervical lymph nodes

**Parathyroid:**
- Recommended
  - Serum calcium
  - PTH
- As appropriate
  - 24-hour urine calcium
  - Neck ultrasound
  - Parathyroid sestamibi

**Pheochromocytoma:**
- Recommended:
  - Fractionated plasma-free metanephrine and normetanephrine or urine metanephrine
  - MRI or multiphasic CT of abdomen
- As appropriate:
  - MIBG scan/octreoscan

#### TREATMENT

- **See NCCN Guidelines for Thyroid Carcinoma**
- **Four-gland identification:**
  - Selective parathyroid resection
- **Refer to endocrinology for medical preparation for adrenalectomy and Adrenalectomy**
  - Involved side only, laparoscopic procedure preferred as appropriate

#### SURVEILLANCE

3-6 mo postresection:
- H&P, blood pressure, and markers

> 6 mo postresection up to 10 y:
- H&P, blood pressure, and markers
  - Years 1-3: every 6 mo
  - Years 4+: annually
- Consider CT or MRI

---

### Note:

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**For RET genetic testing recommendations, see MEN2-1.**

**Evaluation of pheochromocytoma should be done before the administration of any anesthetic or invasive procedure.**

**More likely to be multifocal.**

**Subtotal parathyroidectomy is recommended when all the parathyroid glands are abnormal. Some thyroid surgeons recommend total parathyroidectomy with parathyroid autotransplantation, but others believe the risk of hypoparathyroidism (~6%) is too high to warrant this procedure.**

**Earlier, if symptoms.**

**See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).**
### TUMORS IN PATIENTS WITH MEN2<sup>a</sup>

<table>
<thead>
<tr>
<th>Organ</th>
<th>Neoplasm</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td></td>
<td>Adrenal</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Parathyroid</td>
<td>Hyperplasia</td>
</tr>
<tr>
<td>MEN2B</td>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td></td>
<td>Neuroma</td>
<td>Mucosal neuroma or intestine ganglioneuroma</td>
</tr>
<tr>
<td></td>
<td>Adrenal</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Parathyroid</td>
<td>Hyperplasia</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other physical exam findings include:
- Ectopic lenses (type 2B)
- Marfanoid features (type 2B)
- Lichen planus amyloidosis (type 2A)
- Hirschsprung’s disease (megacolon)

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Required information:
- Anatomic site of tumor
- Diagnosis
- Grade (See Table 1)
- Mitotic rate and/or Ki-67
- Size of tumor
- Presence of multicentric disease
- Presence of vascular invasion
- Presence of perineural invasion
- Presence of other pathologic components (eg, non-neuroendocrine components)
- Lymph node metastases to include the number of positive nodes and total number of nodes examined
- Margin status (report as positive or negative)
- Assign TNM stage per the AJCC TNM system (See Staging)

Optional information:
- Immunohistochemical staining for general neuroendocrine markers
- Immunohistochemical staining for specific peptide markers
- Presence of nonischemic tumor necrosis
- Presence of unusual histologic features (eg, oncocytic, clear cell, gland forming)
- Exact distance of tumor to margin(s) if less than 0.5 cm
- Background pathology of organ (ie, PanIN, ECL cell hyperplasia)

Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Count (per 10 HPF)</th>
<th>Ki-67 Index (%)</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade (G1)</td>
<td>&lt;2</td>
<td>&lt;3</td>
<td>Well-differentiated</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 to 20</td>
<td>3 to 20</td>
<td>Well-differentiated</td>
</tr>
<tr>
<td>grade (G2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade (G3)</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

Table 1 should be used as a general guide. Some tumors may not fall into a single category. Clinical judgment should be used. Definitions vary between lung, thymus and GEP-NETs in some classification systems.

See additional information on next page

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Functional status

- Functional status of a NET need not be included in the pathology report. However, if a specific clinical situation suggests that correlation with histologic evidence of peptide hormone may be helpful, then histochemical or immunohistochemical studies may be performed and included in the report. Functioning NETs should have the same pathologic diagnosis as the non-functioning NETs at the same anatomic site, since the functional status is based upon clinical findings and should not alter the pathologic diagnosis. However, a note may be added with additional information of the immunoreactivity of specific peptide hormone.

Immunohistochemistry and other ancillary techniques

- Immunohistochemistry and other ancillary techniques may not be required to diagnose well-differentiated NETs when sufficient tumor material is available for histologic review. Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, and CD56, although the last marker has recently proven to be less specific. In less well-differentiated tumors or tumors of unknown origin, it may be helpful (or required in the case of poorly differentiated neuroendocrine carcinomas) to utilize immunohistochemistry panels. Although not entirely specific, lung origin is favored by thyroid transcription factor 1 (TTF-1); intestinal or pancreatic origin by CDX2; and pancreatic and rectal NETs by Isl1 and PAX8.1,2

Classification and grade

- Many classification schemes have been proposed for NETs.3-9 The most recent WHO classification system is suggested and represents an attempt to unify European and American approaches.8 Multiple site-specific grading systems also exist; therefore, the specific classification and grading scheme being utilized should be reported in parentheses after the diagnosis to avoid confusion with overlapping terminology and criteria used in other systems. The raw data used to derive the grade should be reported. Regardless of the system used, it is most important to realize that the term “neuroendocrine tumor” or “neuroendocrine carcinoma” without any further qualification as to grade is inadequate for prognostication and therapy and is inappropriate for pathology reporting.1,10

Continued on next page

See References on NE-A 4 of 4
Mitotic rate

- Mitotic count should be based upon counting mitoses in at least 40 fields at 40x magnification in the areas of highest mitotic density, and should be reported as the number of mitoses per 10 HPF or per 2 mm². Ten HPF is equivalent to 2 mm² on many microscopes, although the field size may vary slightly.\(^4\) Note that in cases where an accurate mitotic rate is precluded by inadequate tissue, such as in small biopsy samples including a FNA, the Ki-67 index is the preferred method of establishing the proliferative rate.

Ki-67 index

- Ki-67 index is reported as the percentage of positive tumor cells in the area of highest nuclear labeling. Although recommendations have been to count 2000 tumor cells in order to determine the Ki-67 index, this is not practical in routine clinical practice. It is therefore currently acceptable to estimate the labeling index, despite the recognition that estimation is subject to limitations in reproducibility.\(^10\) If both mitotic rate and Ki-67 index are used and these are discordant, it is currently recommended that the higher grade be assigned.\(^11\) The pathologist should report the actual parameters used to assign grade (i.e., mitotic rate and proliferation index) so that retrospective reviews may be done and clinicians have the necessary information to make informed treatment decisions. Clinical judgment must be applied in these circumstances. Although the 2004 WHO does not utilize Ki-67 as part of its grading system for thymus and lung NETs, it may be quite useful in the setting of small biopsies and cytology specimens when there is insufficient tissue for an accurate mitotic count. The Ki-67 index cut-points are not currently well-defined but tend to parallel those proposed in GEP-NETs, and generally the data suggests that Ki-67 proliferation rates of <20% excludes small cell lung carcinoma.\(^12\)

See References on NE-A 4 of 4

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

REFERENCES

NCCN Guidelines Version 1.2013
Neuroendocrine Tumors

SERUM HORMONE EVALUATION POTENTIALLY INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS

HORMONE-RELATED STUDIES (blood markers)

- Carcinoid tumors
  - 5-HIAA (24-h urine)
  - Chromogranin A (category 3)
- PanNET
  - Chromogranin A (category 3)
- Gastrinoma
  - Gastrin
- Insulinoma
  - Proinsulin
  - Insulin/glucose ratio
  - C-peptide
- VIPoma
  - VIP
- Glucagonoma
  - Glucagon
  - Blood glucose
  - CBC
- Other pancreas
  - Somatostatin
  - Pancreatic polypeptide
  - Calcitonin
  - PTH-related peptide
- Pheochromocytoma/paraganglioma
  - Metanephrines (plasma and urine)
  - Catecholamines (urine)
  - Dopamine (urine)²
- Pituitary
  - Growth hormone/IGF-1
  - Prolactin
  - LH/FSH
  - TSH
  - Alpha subunits
  - ACTH
- Ectopic hormones
  - ACTH
  - GRH
  - GHRH

¹For most of the blood studies, an 8-hour fast is generally recommended in addition to certain dietary adjustments depending on the test ordered. Ordering physicians should be aware that some medications can also affect the results, but medications do not necessarily need to be discontinued if they are medically necessary. Below are examples:
  Chromogranin A: Impaired renal or hepatic function or treatment with proton pump inhibitors may result in artifactual elevations.
  Urine 5-HIAA: Patients should not eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, plantains, kiwi, dates, grapefruit, honeydew, or walnuts for a 48-hour period prior to start of urine collection. Additionally, patients should avoid coffee, alcohol, and smoking for this time period.
  Gastrin: ≥8 hour fast. False elevations may occur especially in patients on proton pump inhibitors.
  VIP: 8-hour fast.

²Should be considered with cervical paraganglioma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SURGICAL PRINCIPLES FOR MANAGEMENT OF NEUROENDOCRINE TUMORS

- Patients with localized PanNETs should be resected. Exceptions include patients with other life-limiting comorbidities, high surgical risk, or widely metastatic disease. Peripheral insulinomas and small (<2 cm), non-functional tumors are candidates for open or laparoscopic enucleation/local resection or spleen-preserving distal pancreatectomy. Virtually all insulinomas should be resected regardless of size because of the metabolic (hypoglycemic) complications. Non-functional PanNETs 1-2 cm in size have a small (7%-26%), but measurable risk of lymph node metastases; therefore, lymph node resection should be considered.
- Resection for larger (>2 cm) or malignant-appearing non-functional and functional PanNETs (ie, glucagonoma, VIPoma, somatostatinoma) should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes. Tumors of the head are generally treated with pancreaticoduodenectomy (Whipple procedure); tumors of the body and tail are treated with distal pancreatectomy and splenectomy or spleen-preserving surgery. Generally surgery will include splenectomy but with benign insulinoma, spleen preservation should be considered.
- Resection of gastrointestinal carcinoid should include both adequate regional lymph node resection (including all palpable disease where feasible) and thorough exploration of synchronous primary tumors (15%-30% incidence).
- Resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumor that has regressed should be considered for selected patients with adequate performance status.
- Patients with symptomatic recurrence from local effects or hormone hypersecretion can be effectively palliated by subtotal resection of a large proportion of the tumor (typically more than 90%); however, experienced judgment is required for management of patients with an unresectable tumor and/or distant metastases. Planned cytoreductive, incomplete (R2) resection of advanced disease in patients with asymptomatic or non-functional disease is controversial.
- Cholecystectomy is recommended when performing surgery for advanced NETs in patients anticipated to receive long-term octreotide therapy, as these patients are at higher risk of developing biliary symptoms and cholecystitis.
- Liver-directed therapies (eg, liver resection, thermal ablation, chemoembolization) for hepatic metastases from NETs following pancreaticoduodenectomy are associated with increased risk for perihepatic sepsis and liver abscess.
- Octreotide therapy should be administered parenterally prior to induction of anesthesia in patients with functional carcinoid tumors to prevent carcinoid crisis.
- All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C).
- In general, laparoscopic resection is preferable for patients suspected to have small (<6 cm), clinically benign, functional adrenal tumors. An open exploration is recommended for tumors that have a high risk of being malignant.
- For MEN1-related surgical principles, see MEN1-B.
# Staging

American Joint Committee on Cancer (AJCC)

TNM Staging System for Neuroendocrine Tumors (gastric, small bowel, colonic, rectal, and ampulla of Vater carcinoid tumors [well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas]) (7th ed., 2010)

### Stomach

**TNM**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ/dysplasia (tumor size less than 0.5 mm), confined to mucosa</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa and 1 cm or less in size</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or more than 1 cm in size</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor penetrates subserosa</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures</td>
</tr>
</tbody>
</table>

For any T, add (m) for multiple tumors

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

**Distant Metastases (M)**

|M0| No distant metastases |
|M1| Distant metastasis |

### Duodenum/Ampulla/Jejunum/Ileum

**TNM**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa and size 1 cm or less* (small intestinal tumors); tumor 1 cm or less (ampullary tumors)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or size &gt; 1 cm (small intestinal tumors); tumor &gt; 1 cm (ampullary tumors)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into non-peritonealized tissues</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades visceral peritoneum (serosa) or invades other organs</td>
</tr>
</tbody>
</table>

For any T, add (m) for multiple tumors

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

**Distant Metastases (M)**

|M0| No distant metastases |
|M1| Distant metastasis |

* Note: Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma.

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* Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science + Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit [www.springer.com](http://www.springer.com).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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## Staging

**American Joint Committee on Cancer (AJCC)**

TNM Staging System for Neuroendocrine Tumors (gastric, small bowel, colonic, rectal, and ampulla of Vater carcinoid tumors [well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas]) (7th ed., 2010)

### Colon or Rectum

<table>
<thead>
<tr>
<th>TNM</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td><strong>Stage 0</strong></td>
</tr>
<tr>
<td>TX</td>
<td>Tis</td>
</tr>
<tr>
<td>T0</td>
<td>N0 M0</td>
</tr>
<tr>
<td>T1</td>
<td>T1a</td>
</tr>
<tr>
<td>T1a</td>
<td>T1b</td>
</tr>
<tr>
<td>T2</td>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
<td>T4</td>
</tr>
<tr>
<td><strong>Regional Lymph Nodes (N)</strong></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>Distant Metastases (M)</strong></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Continued on next page
## Staging

**American Joint Committee on Cancer (AJCC)**

**TNM Staging System for Neuroendocrine Tumors (pancreatic) (7th ed., 2010)**

All pancreatic neuroendocrine tumors should be staged using this staging system.

### Pancreatic

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX  Primary tumor cannot be assessed</td>
<td>Stage 0  Tis  N0  M0</td>
</tr>
<tr>
<td>T0  No evidence of primary tumor</td>
<td>Stage IA  T1  N0  M0</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>Stage IB  T2  N0  M0</td>
</tr>
<tr>
<td>T1  Tumor limited to the pancreas, 2 cm or less in greatest dimension</td>
<td>Stage IIA  T3  N0  M0</td>
</tr>
<tr>
<td>T2  Tumor limited to the pancreas, more than 2 cm in greatest dimension</td>
<td>Stage IIB  T1  N1  M0</td>
</tr>
<tr>
<td>T3  Tumor extends beyond the pancreas but without involvement of the celiac</td>
<td>Stage III  T4  Any N  M0</td>
</tr>
<tr>
<td>axis or the superior mesenteric artery</td>
<td>Stage IV  Any T  Any N  M1</td>
</tr>
<tr>
<td>T4  Tumor involves the celiac axis or the superior mesenteric artery</td>
<td></td>
</tr>
<tr>
<td>(unresectable primary tumor)</td>
<td></td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>N</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX  Regional lymph nodes cannot be assessed</td>
<td>Stage 0  Tis  N0  M0</td>
</tr>
<tr>
<td>N0  No regional lymph node metastasis</td>
<td>Stage IA  T1  N0  M0</td>
</tr>
<tr>
<td>N1  Regional lymph node metastasis</td>
<td>Stage IB  T2  N0  M0</td>
</tr>
</tbody>
</table>

### Distant Metastases (M)

<table>
<thead>
<tr>
<th>M</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0  No distant metastases</td>
<td>Stage 0  Tis  N0  M0</td>
</tr>
<tr>
<td>M1  Distant metastasis</td>
<td>Stage IA  T1  N0  M0</td>
</tr>
</tbody>
</table>

* This also includes the “PanInIII” classification.
# Staging

**American Joint Committee on Cancer (AJCC)**

TNM Staging System for Neuroendocrine Tumors (appendiceal carcinoid) (7th ed., 2010)

## Appendiceal Carcinoid

<table>
<thead>
<tr>
<th>TNM</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>T0</td>
<td>T2, T3 N0 M0</td>
</tr>
<tr>
<td>T1</td>
<td>T4 N0 M0</td>
</tr>
<tr>
<td>T1a</td>
<td>Any T N1 M0</td>
</tr>
<tr>
<td>T1b</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>pN0</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph node cannot be assessed</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Penetration of the mesoappendix does not seem to be as important a prognostic factor as the size of the primary tumor and is not separately categorized.

Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4. However, if no tumor is present in the adhesion, microscopically, the classification should be classified pT1-3 depending on the anatomical depth of wall invasion.

pTNM Pathologic Classification. The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 does not exist as a category.

pN0. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Continued on next page
NCCN Guidelines Version 1.2013 Staging Neuroendocrine Tumors

Staging
American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors (adrenal) (7th ed., 2010)

Adrenal

TNM

Primary Tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion
- T2: Tumor greater than 5 cm, no extra-adrenal invasion
- T3: Tumor of any size with local invasion, but not invading adjacent organs*
- T4: Tumor of any size with invasion of adjacent organs*

Regional Lymph Nodes (N)
- NX: Nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in regional lymph node(s)

Distant Metastases (M)
- M0: No distant metastases
- M1: Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I
| T1 | N0 | M0 |

Stage II
| T2 | N0 | M0 |

Stage III
| T1 | N1 | M0 |
| T2 | N1 | M0 |
| T3 | N0 | M0 |

Stage IV
| T3 | N1 | M0 |
| T4 | N0 | M0 |
| T4 | N1 | M0 |
| Any T | Any N | M1 |

* Note: Adjacent organs include kidney, diaphragm, great vessels, pancreas, spleen, and liver.

pTNM Pathologic Classification. The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 does not exist as a category.

pN0. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

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Discussion
This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/20/12

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Neuroendocrine tumors are thought to arise from cells throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are carcinoid and pancreatic neuroendocrine tumors. Other neuroendocrine tumors include those arising in the parathyroid, adrenal, and pituitary glands, and in calcitonin-producing cells of the thyroid (causing medullary thyroid carcinoma [MTC]).

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database estimated that the incidence of neuroendocrine tumors in the United States was 5.25 cases per 100,000 people in the year 2004. This analysis suggested that the diagnosed incidence of neuroendocrine tumors is increasing, and that the prevalence of individuals with neuroendocrine tumors in the United States may exceed 100,000.

The majority of neuroendocrine tumors appear to be sporadic; risk factors for sporadic neuroendocrine tumors are poorly understood. Neuroendocrine tumors may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia types 1 and 2. Multiple endocrine neoplasia type 1 (MEN 1), associated with mutations in the menin gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands. Multiple endocrine neoplasia type 2 (MEN 2), associated with mutations in the RET proto-oncogene, is characterized by the development of medullary thyroid cancer, pheochromocytoma (often bilateral), and hyperparathyroidism. Neuroendocrine tumors have also been associated with Von-Hippel Lindau disease, tuberous sclerosis complex, and neurofibromatosis.

Patients with neuroendocrine tumors may or may not have symptoms attributable to hormonal hypersecretion. Such symptoms include intermittent flushing and diarrhea in patients with carcinoid syndrome, hypertension in patients with pheochromocytoma, and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic neuroendocrine tumors. Patients with hormonal symptoms are considered to have “functional” tumors, and those without symptoms are considered to have “nonfunctional” tumors.

The appropriate diagnosis and treatment of neuroendocrine tumors often involves collaboration between specialists in multiple disciplines, using specific biochemical, radiologic, and surgical methods. Specialists include pathologists, endocrinologists, radiologists (including nuclear medicine specialists), as well as medical, radiation, and surgical oncologists.

These NCCN Neuroendocrine Tumor guidelines discuss the diagnosis and management of both sporadic and hereditary neuroendocrine tumors and are intended to assist with clinical decision making. Most of the guideline sections pertain to well-differentiated, low to intermediate grade tumors; for poorly differentiated/high-grade/anaplastic or small cell carcinomas, please refer to the section entitled, ‘Poorly Differentiated (High Grade or Anaplastic)/Small Cell’ in the guidelines and ‘Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors,’ below. Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these NCCN guidelines.

Histologic Classification and Staging of Neuroendocrine Tumors

Neuroendocrine tumors are generally subclassified by site of origin and by histologic characteristics. Pancreatic neuroendocrine tumors arise in endocrine tissues of the pancreas; carcinoid tumors most commonly arise in the lungs and bronchi, small intestine, appendix, rectum, or thymus.
Neuroendocrine tumors are classified histologically based on tumor differentiation (well or poorly differentiated) and tumor grade (Grade 1-3). The majority of tumors fall into three broad histologic categories: well-differentiated, low-grade (G1) neuroendocrine tumors; well-differentiated, intermediate-grade (G2) neuroendocrine tumors; and poorly-differentiated, high-grade (G3) neuroendocrine tumors. The latter are also sometimes referred to as high grade neuroendocrine carcinomas or small cell carcinoma. These tumors are characterized by a high mitotic rate and an aggressive clinical course.

Tumor differentiation and tumor grade often correlate with mitotic count and Ki-67 proliferation index. In most cases, well differentiated, low-grade tumors have a mitotic count of <2/10 HPF and a Ki-67 index of <3%. Well differentiated, intermediate grade tumors usually have a mitotic count of 2-20/10 HPF and a Ki-67 index of 3-20%. In high grade tumors, the mitotic count usually exceeds 20/10 HPF and the Ki-67 index exceeds 20%. Most commonly used histologic classification schemes, including both the ENETS and WHO systems, incorporate mitotic rate and Ki-67 index. Numerous studies have confirmed that increased mitotic rate and high Ki-67 index are associated with a more aggressive clinical course and worse prognosis.

Neuroendocrine tumors are staged according to the American Joint Committee on Cancer (AJCC) tumor (T), node (N), metastasis (M) staging system. The AJCC introduced its first TNM staging system for the classification of neuroendocrine tumors in its 7th edition of the AJCC Cancer Staging Manual. There are separate staging systems for carcinoids of the stomach, duodenum/ampulla/jejunum/ileum, colon/rectum, and appendix. The association of tumor stage with prognosis has been confirmed in analyses of the SEER database.

Carcinoids of the lungs and bronchi are staged in the same manner as more common lung carcinomas. As in lung carcinoma, more advanced tumor stage for carcinoid tumors of the lungs and bronchi is associated with worse prognosis.

The TNM staging system for the classification of pancreatic neuroendocrine tumors in the 7th edition of the AJCC Cancer Staging Manual is the same as for exocrine pancreatic carcinoma. The primary tumor (T) is differentiated based on size and involvement of major vessels or other organs (see ‘Staging’ in the guidelines). A recent retrospective analysis of 425 patients with pancreatic neuroendocrine tumors treated at the H. Lee Moffitt Cancer Center and Research Institute between 1999 and 2010 validated this system, with 5-year overall survival rates of 92%, 84%, 81%, and 57% for stages I-IV, respectively (P<0.001). While the trends of this analysis are consistent with population-based studies, the survival rates from this analysis were significantly higher than those seen in population-based studies.

For example, in the SEER database analysis of pancreatic neuroendocrine tumors, the 5-year survival rate for patients with metastatic disease was only 19.5%.

In addition to information on histologic classification and stage, the margin status (positive or negative) and the presence of vascular or perineural invasion should be indicated on the pathology report, as they may also have prognostic significance.

Sporadic Neuroendocrine Tumors

Carcinoid Tumors

Approximately one-third of carcinoid tumors arise in the lungs or thymus and two-thirds arise in the gastrointestinal tract. Sites of origin within the gastrointestinal tract include the stomach, small intestine, appendix, and
The prognosis for patients with carcinoid tumors varies according to the stage at diagnosis, histologic classification, and primary site of the tumor (see ‘Histologic Classification and Staging of Neuroendocrine Tumors,’ above).

Carcinoid tumors may secrete various hormones and vasoactive peptides. Bronchial carcinoids have been associated with adrenocorticotropic hormone (ACTH) production, and are a cause of Cushing’s syndrome. Carcinoid tumors arising in the small intestine or appendix are more commonly associated with carcinoid syndrome, related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation causing episodic flushing and diarrhea. Additionally, about 10-30% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.

The metabolic products released by intestinal carcinoid tumors are rapidly destroyed by liver enzymes in the portal circulation, thus the classical syndrome, occurring in approximately 8% of patients with carcinoid tumors, is not usually observed unless liver metastases or rarely retroperitoneal disease have occurred, in which case hepatic metastases release metabolic products directly into the systemic circulation via the hepatic veins.

The NCCN guidelines address 7 major subtypes of carcinoid tumors: (1) jejunal/ileal/colon, (2) duodenal, (3) appendix, (4) rectal, (5) gastric, (6) bronchopulmonary, and (7) thymus.

**Evaluation of Carcinoid Tumors**

Patients who present with suspected carcinoid tumors should be evaluated with imaging studies to assess disease burden and possible primary location. Commonly used techniques include computed tomography (CT) and magnetic resonance imaging (MRI). Carcinoid tumors are highly vascular and can appear isodense with liver on CT scan, depending on contrast phase. Multi-phase CT or MRI scans should therefore be used for evaluation of liver metastasis. Since the majority of carcinoid tumors express high-affinity receptors for somatostatin, radiolabeled somatostatin receptor scintigraphy, performed using the radiolabeled somatostatin analog [111In-DTPA]-octreotide (OctreoScan), may also be used in the initial evaluation of carcinoid tumor patients. Additional recommendations vary by disease site and include colonoscopy and small bowel imaging as appropriate for jejunal, ileal, and colon carcinoids; endoscopic ultrasound (EUS) and/or esophagogastroduodenoscopy (EGD) as appropriate for duodenal and gastric carcinoids; proctoscopic examination for rectal carcinoids; and bronchoscopy as appropriate for bronchopulmonary and thymic carcinoids.

**Management of Locoregional Disease**

The management of locoregional carcinoid tumors depends on tumor size and primary site, as well as the general condition of the patient. Resection is the primary treatment approach for most localized carcinoid tumors. Specific recommendations for management of carcinoid tumor subtypes are described below.

**Gastric carcinoid tumors**

Three types of gastric carcinoid tumors are generally recognized: type 1 gastric carcinoids (associated with chronic atrophic gastritis), type 2 gastric carcinoids (associated with Zollinger-Ellison syndrome), and type 3 gastric carcinoids (sporadic). Type 1 and type 2 gastric carcinoids are both associated with hypergastrinemia; the major difference between them is that patients with type 1 gastric carcinoids generally have atrophic gastritis and absent acid secretion, whereas patients with type 2 gastric carcinoids have evidence of acid hypersecretion secondary to gastrinoma (Zollinger-Ellison syndrome).
For hypergastrinemic patients whose tumors are ≤2 cm and either solitary or multiple, options include (1) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa; (2) observation; or (3) octreotide for patients with gastrinoma and Zollinger-Ellison syndrome (category 2B recommendation). For hypergastrinemic patients with tumors >2 cm either solitary or multiple, endoscopic resection (if possible) or surgical resection is indicated. Patients with nonmetastatic gastric carcinoid and normal gastrin levels (type 3) have more aggressive tumors and are usually treated with radical resection of the tumor with regional lymphadenectomy.

**Thymic carcinoid tumors**
Localized and locoregional carcinoid tumors in the thymus are treated with surgical resection, generally without adjuvant therapy. Following incomplete resection of locoregional disease, however, radiation therapy (RT) alone is recommended; the addition of chemotherapy can also be considered (category 3). If chemotherapy is offered, capecitabine or 5-fluorouracil at radiosensitizing doses may be considered. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.

**Bronchopulmonary carcinoid tumors**
For localized or locoregional bronchopulmonary tumors, please refer to the Lung Neuroendocrine Tumors algorithm, which is part of the NCCN Small Cell Lung Cancer Guidelines.

**Carcinoid tumors of the duodenum, small intestine, and colon**
For localized lesions arising in the duodenum, endoscopic resection is recommended if feasible. Transduodenal local excision with or without lymph node sampling and panreatoduodenectomy are other options for primary treatment of nonmetastatic duodenal carcinoid tumors.

For patients presenting with tumors in the jejunum, ileum, or colon, surgical resection of the bowel with regional lymphadenectomy is recommended. The surgical procedure should include careful examination of the entire bowel, because multiple synchronous lesions may be present. If future treatment with octreotide is anticipated, a prophylactic cholecystectomy should be considered given the association between long-term treatment with somatostatin analogs and the development of biliary symptoms and gallstones.¹⁰

**Appendiceal carcinoid tumors**
Most appendiceal carcinoid tumors are identified incidentally, during appendectomy performed for appendicitis. The majority of appendiceal carcinoid tumors have well-differentiated histology, and for most appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient, as metastases are uncommon.³¹,³² It should be noted, however, that there is some controversy regarding the management of appendiceal carcinoids measuring <2 cm with more aggressive histologic features. A recent population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal carcinoids 2 cm or smaller.³³ Some NCCN institutions thus consider more aggressive treatment for 1-2 cm tumors with poor prognostic features such as lymphovascular or mesoappendiceal invasion or atypical histologic features.

Patients with an incomplete resection or with tumors >2 cm are at risk for locoregional or distant metastases. Such patients should be staged with abdominal/pelvic CT or MRI scans. If no distant disease is identified, they should undergo re-exploration with a right hemicolectomy. Additionally, a small proportion of appendiceal carcinoids may also contain evidence of adenocarcinoma (ie,
“adenocarcinoid” or “goblet cell carcinoma”). These tumors should be managed according to the NCCN Colon Cancer guidelines.

Carcinoid tumors of the rectum
The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumors, examination under anesthesia (EUA) and/or endoscopic ultrasound (EUS) prior to the procedure should be considered for tumors 1-2 cm in size. Tumors larger than 2 cm, tumors with invasion of the muscularis propria, or tumors associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection (APR).^34^ Surveillance
Surveillance of carcinoid tumors should include complete patient history and physical examination (H&P) and consideration of imaging studies such as CT (abdominal and/or pelvic triple-phase) and MRI. Most patients with carcinoid tumors of the jejunum/ileum/colon, duodenum, rectum, and thymus as well as type 3 gastric carcinoid lesions with normal gastrin levels should be re-evaluated 3 to 12 months after resection (earlier if the patient is symptomatic) and every 6 to 12 months thereafter.

Chromogranin A may be used as a tumor marker (category 3); while not diagnostic, elevated levels have been associated with recurrence.^35^ Chromogranin A levels can be elevated in a number of concurrent medical conditions, including renal or hepatic insufficiency, and are also commonly elevated in the setting of concurrent proton pump inhibitors. Several panelists therefore caution that rising chromogranin A levels in an asymptomatic patient with a tumor that appears stable by imaging does not necessarily indicate that a patient should be initiated on a new therapy.

5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, in a 24-hour urine sample may also be considered as a biochemical marker in some cases, particularly in patients with small-intestinal carcinoid tumors. While monitoring patients following treatment for a carcinoid tumor, decreasing levels of 5-HIAA indicates a response to treatment, while increasing or excessive concentration indicates that the treatment has not been successful. However, a patient with symptoms may still have a carcinoid tumor even if the concentration of 5-HIAA is normal. Diet and a variety of drugs can affect the 5-HIAA test. Therefore, patients should be advised not to eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, plantain, kiwi, dates, grapefruit, honeydew, or walnuts for a 48-hour period prior to start of urine collection. Additionally patients should avoid coffee, alcohol, and smoking for this time period. Medications that can increase 5-HIAA include acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (an ingredient found in some cough medicines), and phenobarbital.

Somatostatin receptor scintigraphy (OctreoScan) is not routinely recommended for surveillance following definitive resection, but may be indicated to assess disease location and disease burden for comparison in cases of subsequent possible recurrence.

In specific cases, follow-up recommendations for patients with resected carcinoid tumors differ from the above general recommendations. For rectal tumors (smaller than 1 cm), prognosis is excellent and no follow-up is usually required. Follow-up endoscopies are recommended for rectal tumors that are between 1 and 2 cm, 6 and 12 months after primary therapy, and then as clinically indicated^15^ for appendiceal...
tumors (2 cm or smaller, without aggressive features), follow-up examinations are done as clinically indicated. Some institutions recommend a follow-up examination 1 year after simple appendectomy and then with decreasing frequency.

Follow-up recommendations also differ to some extent for patients with gastric carcinoid tumors. Hypergastrinemic (type 1 or type 2) patients with small gastric carcinoid tumors who did not require endoscopic resection or treatment should be evaluated with H&P every 6 to 12 months. Imaging studies or surveillance may be performed on these patients as clinically indicated. Follow-up endoscopies are recommended for patients with type 1 and type 2 gastric carcinoid tumors. Surveillance every 6 to 12 months for the first 3 years and annually thereafter is appropriate if no evidence of recurrence or progression is seen. If clinically indicated, imaging studies should also be performed. Antrectomy to remove the source of gastrin production can be considered in patients with type 1 gastric carcinoids if new lesions or increasing tumor burden is observed.

**Management of Locoregional Unresectable and/or Metastatic Carcinoid Tumors**

Baseline imaging recommendations for patients suspected to have distant metastatic disease include multi-phase technique CT or MRI. Baseline levels of chromogranin A (category 3) or 5-HIAA may also be considered to monitor subsequent progression (discussed above). OctreoScan can also be considered both to assess sites of metastases and to assess somatostatin receptor status if treatment with octreotide is being considered. The most common sites of metastases from intestinal carcinoids include regional/mesenteric lymph nodes, liver, and bones.

In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection. In these patients, resection of the primary tumor and metastases should be performed. A recent study of 172 patients who underwent hepatic resection of metastatic neuroendocrine tumors showed that long-term survival can be achieved in many cases; the reported 10-year overall survival rate was 50.4%. Resection of the primary site in the setting of unresectable metastases is generally not indicated if the primary site remains asymptomatic and is relatively stable. However, it is not uncommon for patients with small bowel primary tumors to experience symptoms of intermittent abdominal pain from episodic bowel obstruction or bowel ischemia related to the primary tumor and surrounding fibrosis. Palliative small bowel resection is recommended in such patients.

Patients who have metastatic carcinoid tumors and carcinoid syndrome should be treated with octreotide. The long-acting release (LAR) formulation of octreotide is used for the chronic management of patients with carcinoid syndrome. Standard doses of octreotide LAR are 20-30 mg intramuscularly (IM) every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide are not achieved for 10 to 14 days following LAR injection. Short-acting octreotide (usually 150-250 mcg SC 3 times daily) can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. A cardiology consultation and echocardiogram to assess whether the patient has carcinoid heart disease should also be considered in patients with carcinoid syndrome with signs and symptoms of heart disease or with planned major surgery. Cardiac heart disease is frequent in patients with carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation. A recent study of 250 patients with carcinoid syndrome showed that patients with 5-HIAA levels of ≥300 μmol
(57mg)/24 hours and with ≥3 flushing episodes per day were more likely to have carcinoid heart disease. In patients who have clinically significant tumor burden, initiation of octreotide LAR is recommended. The recommendation to consider octreotide in such patients is based on the results of the PROMID study, a placebo controlled phase III trial of 85 patients with metastatic midgut carcinoid tumors, which showed that median time to tumor progression in the octreotide LAR group versus the placebo group was 14.3 and 6 months, respectively (P=0.000072). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group.

There is no clear consensus on the timing of octreotide initiation in asymptomatic metastatic carcinoid patients with low tumor burden. While initiation of octreotide can be considered in such patients it may also be appropriate to defer initiation of octreotide until there is evidence of tumor progression.

Patients with clinically significant progression of metastatic carcinoid tumors can pursue several options. In general, such patients should be started on treatment with octreotide if they are not already receiving it. For patients with hepatic-predominant disease, cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near complete treatment of tumor burden can be achieved (category 2B). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]), are recommended.

Interferon alpha has been shown in several large series to be associated with an antitumor effect, and can also be considered in patients with progressive metastatic carcinoid tumors (category 3). In general, responses to cytotoxic chemotherapy regimens are rare in patients with advanced, well differentiated carcinoid tumors, and such regimens have not been shown to result in improved progression-free survival. The panel lists cytotoxic chemotherapy for carcinoid tumors as a category 3 recommendation.

**Everolimus for advanced carcinoid tumors**

For patients with progressive metastatic carcinoid tumors, everolimus can also be considered (category 3). Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) that has been the subject of recent trials in patients with advanced neuroendocrine tumors. It was well tolerated and showed promising anti-tumor effects in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial. In the randomized phase III RADIANT-2 trial, 429 patients with advanced carcinoid tumors and carcinoid syndrome were randomized to receive octreotide LAR with everolimus or placebo. Based on central review, patients receiving octreotide plus everolimus had a median progression-free survival duration of 16.4 months, as compared to 11.3 months for patients receiving octreotide alone (P=0.026). This difference in the primary endpoint of progression-free survival did not, however, meet the pre-defined threshold for statistical significance. Adverse events associated with everolimus included stomatitis, rash, fatigue, and diarrhea. Other side effects have also been described. The panel lists consideration of everolimus for carcinoid tumors following progression as a category 3 recommendation.

**Radiolabeled somatostatin analogs for advanced carcinoid tumors**

Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced carcinoid tumors. This approach remains investigational, and randomized
trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in advanced carcinoid are needed.\textsuperscript{70}

\textit{Liver transplantation for liver metastases of carcinoid tumors}
Liver transplantation has been performed in patients with carcinoid tumors whose metastases are confined to the liver.\textsuperscript{71-75} While some highly selected patients have achieved long-term survival, the panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

\textbf{Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors)}

According to a population-based study, malignant pancreatic endocrine tumors account for approximately 1\% of pancreatic cancers by incidence and 10\% of pancreatic cancers by prevalence.\textsuperscript{76} Although the peak incidence of occurrence is between ages 40 and 69 years, a significant number of patients diagnosed with pancreatic neuroendocrine tumors are under the age of 35.\textsuperscript{76,77} Based on an analysis of pancreatic neuroendocrine tumors in the SEER database from 1973 to 2000, the annual incidence per 1 million was 1.8 in females and 2.6 in males.\textsuperscript{22} An estimated 40-91\% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms.\textsuperscript{8,22} The characteristics of functional endocrine tumors of the pancreas are summarized in Table 1.\textsuperscript{77} Of these functioning tumors, up to 70\% are insulinomas, and about 90\% of these are benign. Approximately 15\% are glucagonomas. Gastrinomas and somatostatinomas account for another 10\%; most (80\% to 90\%) of these are associated with a relatively high risk of metastases.\textsuperscript{77} The remaining rare islet cell tumors include VIPoma and pancreatic polypeptidoma (PPoma). Islet cell tumors occurring in patients with MEN 1 are typically multiple and require different treatment strategies than those used for patients with sporadic pancreatic endocrine tumors, which are usually solitary (see below). Gastrinoma and insulinoma are the most common pancreatic islet cell tumors in patients with MEN 1.\textsuperscript{78}

\textbf{Evaluation of Neuroendocrine Tumors of the Pancreas}
The family history of the patient should be considered to rule out MEN 1 syndromes. For nonfunctioning islet cell tumors, the recommended evaluation includes multiphasic CT or MRI scan. Serum chromogranin A (category 3) and pancreatic polyopeptide (category 3) may be tested as clinically appropriate. Functional tumors may give significant clinical symptoms even when very small, and lesion identification can therefore be difficult.\textsuperscript{77} Multiphasic, contrast-enhanced CT or MRI is recommended, and OctreoScan and endoscopic ultrasound can also be considered.

Chromogranin A levels are elevated in ≥60\% of patients with either functioning or nonfunctioning pancreatic endocrine tumors.\textsuperscript{80-82} Care should be taken in measuring Chromogranin A and interpreting the results, as spuriously elevated levels of Chromogranin A have been reported in patients using proton pump inhibitors, in patients with renal or liver failure, in patients with hypertension, and in those with chronic gastritis.

\textbf{Gastrinomas}
Gastrinoma is often suspected in patients with severe gastroduodenal ulcer symptoms such as dyspepsia, usually accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of basal and stimulated gastrin levels.\textsuperscript{83} Diagnosis of gastrinoma can be confounded by the concurrent use of proton pump inhibitors, which will elevate serum gastrin levels. Importantly, the vast majority of patients who are found to have an elevated level of serum
gastrin do not have a gastrinoma but have achlorhydria or are receiving proton pump inhibitors or antacids. Gastrin levels (basal or stimulated) must be measured after the patient is off proton pump inhibitor therapy for at least 1 week. In addition, imaging studies (multiphasic CT/MRI scan) often aid not only in localizing the tumor but also in confirming the diagnosis. Other tests such as an OctreoScan, EUS, and chromogranin A levels (category 3) may be carried out as appropriate. About 70% of patients with MEN 1 and gastrinoma have tumors situated in the duodenum.

**Insulinomas**

Insulinomas are generally small tumors that are best localized by EUS, which has been shown to localize about 82% of pancreatic endocrine tumors. Insulinomas can also be localized by injecting calcium into selective pancreatic arteries and measuring the insulin levels in the right (usually) or left hepatic vein (Imamura-Doppman procedure). Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative.

If the diagnosis of insulinoma is uncertain, it may also be helpful to determine the insulin/glucose ratio after a 48-72 hour observed or inpatient observed fast. An insulin level >3 mcIU/mL (usually >6 mcIU/mL) when blood glucose is <40-45 mg/dL, with an insulin-to-glucose ratio of ≥0.3 reflecting the inappropriate secretion of insulin at the time of hypoglycemia, document these tumors. Patients with insulinoma also have elevated levels of C-peptide. Testing for urinary sulfonylurea helps rule out factitious hypoglycemia.

CT or MRI scans should be performed to rule out metastatic disease. 90% of insulinomas pursue an indolent course and can be cured surgically. Insulinomas are less consistently octreotide-avid than other pancreatic neuroendocrine tumors, and OctreoScan may consequently be less useful as an imaging technique in insulinomas than in other tumor subtypes. OctreoScan should be performed only if octreotide is being considered as a treatment. Octreotide should only be administered to patients whose tumors are OctreoScan positive, because in the absence of somatostatin receptors, octreotide can profoundly worsen hypoglycemia (see ‘Preoperative management,’ below).

**Glucagonomas and VIPomas**

For patients with recent-onset diabetes, cachexia, and/or a necrolytic erythematous skin rash, the panel recommends a blood test for glucagon and blood glucose, multiphasic contrast enhanced CT or MRI, and OctreoScan as appropriate. For VIPomas with characteristic watery diarrhea, testing for vasoactive intestinal polypeptide (VIP) and electrolytes is recommended. A CT or MRI scan may be useful for identifying large tumors or metastatic disease and are recommended routinely for suspected VIPoma. OctreoScan can also be considered as appropriate.

**Primary Treatment of Locoregional Resectable Neuroendocrine Tumors of the Pancreas**

Resection is the primary treatment approach for localized pancreatic neuroendocrine tumors when possible and can result in excellent outcomes. Exceptions include patients with other life-limiting comorbidities or high surgical risk.

**Preoperative management**

Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. Octreotide can be considered in most pancreatic neuroendocrine tumor subtypes. For insulinomas, the panel
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advises stabilizing glucose levels with diet and/or diazoxide. Octreotide should be used with caution in patients with insulinoma because it can also suppress counter-regulatory hormones such as growth hormone, glucagon, and catecholamines. In this situation, octreotide can precipitously worsen hypoglycemia and can result in fatal complications in some cases.

For gastrinomas, gastrin hypersecretion may be treated with proton pump inhibitors. VIPomas and glucagonomas are generally sensitive to octreotide. Because of the severe weight loss common with patients with glucagonoma, total parenteral nutrition (TPN) may also be considered for these patients. All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group c).

Surgical management of nonfunctioning pancreatic neuroendocrine tumors
Patients with localized pancreatic neuroendocrine tumors should in general undergo surgical resection, absent any contraindications. Exceptions include patients with other life-limiting comorbidities, high surgical risk, or widely metastatic disease. Resection for larger (>2 cm) or malignant-appearing nonfunctional tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

Results of a recent retrospective analysis of 139 consecutive patients with incidentally found, nonfunctional pancreatic neuroendocrine tumors showed that even small tumors can be aggressive, including those originally classified as benign. In general, resection together with lymph node dissection should be considered since pancreatic neuroendocrine tumors that are 1-2 cm have a small but real risk of lymph node metastases.

However, another retrospective study of patients with incidentally discovered, nonfunctioning, early-stage pancreatic neuroendocrine tumors who opted against surgical resection suggested that in some cases these tumors can be safely followed, and some panel members have recommended interval follow-up and monitoring for selected patients with incidentally discovered, small (≤1.5 cm) pancreatic neuroendocrine tumors.

Surgical management of gastrinomas
The treatment approach for gastrinoma usually depends on the results of preoperative localization studies and on findings during exploratory laparotomy. In patients with occult gastrinoma (ie, no primary tumor or metastasis is seen on imaging), the panel recommends either (1) observation or (2) exploratory surgery including duodenotomy and intraoperative ultrasound with enucleation or local resection of tumors if identified at operation and removal of periduodenal nodes.

Gastrinomas in the duodenum are treated with duodenotomy and intraoperative ultrasound with local resection or enucleation of tumor(s) and periduodenal node dissection.

Gastrinomas in the head of the pancreas that are exophytic or peripheral as determined by imaging and are not immediately adjacent to the pancreatic duct should be enucleated. Removal of the periduodenal nodes should also be performed. Gastrinomas in the pancreatic head that are deeper or invasive and those with proximity to the main pancreatic duct should be managed by pancreateoduodenectomy.
Gastrinomas in the distal pancreas are treated with distal pancreatectomy with or without splenectomy.

**Surgical management of insulinomas**
The primary treatment for exophytic or peripheral insulinomas, because they are primarily benign, is enucleation. This procedure can be done laparoscopically for localized solitary tumors within the body and tail of the pancreas. Sporadic tumors are usually solitary whereas familial tumors are multiple. If enucleation is not possible due to invasion or the location of the tumor within the pancreas, then the following options may be considered (1) pancreatectoduodenectomy for tumors in the head of the pancreas; or (2) distal pancreatectomy, with preservation of the spleen for smaller tumors not involving splenic vessels. Distal pancreatectomy can be performed laparoscopically.

**Surgical management of glucagonomas**
Most glucagonomas are malignant and calcified and located in the tail of the pancreas, with regional node involvement. The recommended treatment is distal pancreatectomy with resection of the peripancreatic lymph nodes and splenectomy. For tumors in the pancreatic head, pancreatectoduodenectomy with resection of the peripancreatic lymph nodes is recommended. Small (<2 cm), peripheral glucagonomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas. Perioperative anticoagulation should be considered because of the increased risk of pulmonary emboli.

**Surgical management of VIPomas**
Distal VIPomas are treated with distal pancreatectomy with resection of peripancreatic lymph nodes and spleen. Pancreatectoduodenectomy with dissection of peripancreatic nodes is recommended for tumors in the head of the pancreas. Small (<2 cm), peripheral VIPomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas.

**Surgical management of rare tumors**
For rare tumors such as somatostatinoma, ACTHoma, PTH-rP-secreting tumors, and PPoma, the treatment recommendations are similar to that of nonfunctioning tumors. Tumors that are small (<2 cm) and peripheral can be enucleated with or without removal of regional nodes, or distal pancreatectomy can be performed with or without removal of regional nodes and with or without splenectomy. Deeper, larger (>2 cm), or invasive tumors are treated with pancreatectoduodenectomy if they are located in the head of the pancreas and with distal pancreatectomy and splenectomy if they are distally localized. Resection for larger (>2 cm) or malignant-appearing tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

**Surveillance**
Disease recurrence has been observed in 21-42% of patients with pancreatic neuroendocrine tumors and can occur after many years. Patients should undergo follow-up 3 to 12 months after resection, or earlier if the patient presents with symptoms, and every 6 to 12 months thereafter with an H&P, appropriate tumor markers, and imaging studies such as CT/MRI as clinically indicated. OctreoScan and PET scan are not recommended for routine surveillance. Surgical resection is recommended for resectable locoregional or oligometastatic recurrence.

**Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas**
Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases. In patients with limited hepatic
disease, surgical excision of both the primary tumor and liver metastases should be considered when possible and can be performed in a staged or synchronous fashion. When performing staged pancreateoduodenectomy and liver resection, hepatectomy should be considered prior to pancreatic resection in order to reduce the risk of perihepatic sepsis due to the contaminated biliary tree.\textsuperscript{97} While resection may provide clinical benefit, the majority of resected patients with metastatic disease will experience recurrence.\textsuperscript{98} Additional resection or ablation may be possible; a recent study of 172 patients who had liver resection of metastatic neuroendocrine tumors (55 with the primary tumor in the pancreas) showed that significant long-term survival can be achieved after recurrence in many patients, with a 10-year overall survival rate of 50.4%.\textsuperscript{38}

Unfortunately, most patients with advanced pancreatic neuroendocrine tumors have unresectable disease. For patients with unresectable disease who are asymptomatic with low tumor burden and stable disease, observation is recommended with marker assessment and imaging every 3 to 12 months until clinically significant disease progression occurs.

For unresectable symptomatic patients, those who initially present with clinically significant tumor burden, or those with clinically significant disease progression, several different options can be considered. Systemic options include treatment with biologically targeted agents (everolimus or sunitinib, category 2A), treatment with cytotoxic chemotherapy (category 2A), or treatment with octreotide (category 2B). These options, as well as hepatic-directed therapies, are discussed in more detail below.

### Biologically targeted therapies

The biologically targeted agents everolimus and sunitinib have recently been confirmed to have anti-tumor activity and to improve progression-free survival in patients with advanced pancreatic neuroendocrine tumors. Everolimus, administered orally at a dose of 10 mg once daily, was evaluated in a multi-center study (RADIANT-3) enrolling 410 patients with advanced, progressive pancreatic neuroendocrine tumors.\textsuperscript{61} In this study, the median progression-free survival duration for patients randomized to everolimus was 11.0 months, as compared to 4.6 months for patients receiving placebo, (P<0.001). Subset analyses of RADIANT-3 showed that the progression-free survival effect of everolimus is independent of prior or concurrent somatostatin analog therapy or prior chemotherapy.\textsuperscript{99,100} Adverse events associated with everolimus include stomatitis, hyperglycemia, and in rare cases pneumonitis.\textsuperscript{61} Other side effects have also been described.\textsuperscript{64}

Sunitinib, administered orally at a dose of 37.5 mg once daily, was compared to placebo in a multi-center randomized study of patients with advanced progressive metastatic pancreatic neuroendocrine tumors.\textsuperscript{101} The study was designed to enroll 340 patients, but was discontinued after enrollment of 171 patients, prior to the pre-defined efficacy analysis. At the time of study discontinuation, patients who received sunitinib had a median progression-free survival duration of 11.4 months, compared to 5.5 months for patients receiving placebo (P<0.001). The objective response rate seen with sunitinib was 9.3%.\textsuperscript{101} A large proportion of patients on the placebo arm subsequently received sunitinib at the time of progression, and no significant difference in overall survival was observed between the two arms.\textsuperscript{102} Adverse events associated with sunitinib include fatigue and, in rare cases, congestive heart failure.\textsuperscript{103} Other side effects have also been described.
Somatostatin analogs
Patients with symptoms of hormone secretion should, in most cases, receive treatment with octreotide and/or other medication to manage their symptoms as previously described. Patients without hormone-related symptoms who have a positive OctreoScan can also be considered for treatment with octreotide (category 2B). Although no randomized studies to date have demonstrated an anti-tumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial demonstrated an improvement in its primary endpoint of time to tumor progression (14.3 vs 6 months, P=0.000072) in carcinoid tumors of the midgut. The ongoing phase III CLARINET study is comparing lanreotide to placebo in patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors (clinicaltrials.gov NCT00353496).

Cytotoxic chemotherapy
Cytotoxic chemotherapy is another option (category 2A) for patients with unresectable or metastatic pancreatic neuroendocrine tumors. Streptozocin is FDA approved for use in patients with advanced pancreatic neuroendocrine tumors. The combination of doxorubicin and streptozocin was initially reported to be associated with an overall response rate of 69% and a survival benefit in a relatively small randomized study of patients with advanced pancreatic neuroendocrine tumors. A more recent retrospective review from the MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin. More recently, oral temozolomide-based therapy has become increasingly used in patients with advanced pancreatic neuroendocrine tumors. Temozolomide has been administered using different schedules and either alone or in combination with other agents. The combination of temozolomide with capecitabine has been reported in a retrospective series to be associated with an objective radiographical response rate of 70% and a median progression-free survival of 18 months.

Hepatic-directed therapies
Hepatic-directed therapies may be considered in patients with hepatic-predominant disease. The panel also lists cytoreductive surgery or ablative therapy (RFA, cryotherapy, microwave) as category 2B recommendations for these patients. While some groups report that the risks of cytoreductive surgery outweigh its benefits, others have reported good outcomes. No high-level evidence assessing cytoreductive surgery exists.

Additional options include hepatic regional therapies such as arterial embolization, radioembolization (category 2B), and chemoembolization. To date, there are no randomized clinical trials assessing the effectiveness of these therapies, and prospective data for these interventions are limited.

Liver transplantation
Liver transplantation has been performed in patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver. While some highly selected patients have achieved long-term survival, the panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

Neuroendocrine Tumors of Unknown Primary
According to a SEER database analysis, a primary tumor site could not be found in as many as 4,752 (13%) out of 35,618 neuroendocrine tumors. When a neuroendocrine tumor of unknown primary is diagnosed, attempts are first made to identify the origin of the neoplasm to help guide treatment decisions. If the primary tumor cannot be
identified, treatment decisions are generally guided by tumor histology (see Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors). Many of these tumors are poorly differentiated and aggressive.118

**Evaluation of Neuroendocrine Tumors of Unknown Primary**

The initial evaluation of a patient with neuroendocrine tumors of unknown primary includes patient family history, clinical manifestations, laboratory studies, imaging studies, and/or immunohistochemical studies. Family history is particularly relevant as it may identify affected relatives and patients who are at increased risk for multiple endocrine tumors, such as patients with MEN 1 or MEN 2.

Potential primary sites may be investigated with imaging studies, such as CT or MRI. Ultrasound or endoscopic ultrasound evaluation of the pancreas is useful for patients with possible insulinomas or other neuroendocrine tumors of the pancreas. Many neuroendocrine tumors express specific receptors for amines or peptides (e.g., somatostatin receptors), and OctreoScan may also be helpful in localizing certain neuroendocrine tumors.119 In addition, radionucleotide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. A 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan can occasionally be useful in finding a primary tumor, but is less sensitive in well-differentiated neuroendocrine tumors and should only be considered in cases of poorly differentiated tumors.

The possibility of functional adrenal neoplasms and carcinoid syndrome should be considered prior to biopsy or other invasive procedures. Alpha blockade and forced hydration should be used for suspected pheochromocytoma or paraganglioma, and octreotide premedication should be used prior to operation if carcinoid syndrome is suspected.

**Primary Treatment of Neuroendocrine Tumors of Unknown Primary**

If the primary tumor is not identified, poorly differentiated neuroendocrine tumors should be treated as described for Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors. Well-differentiated tumors should be treated similarly to typical carcinoid tumors, as described above.

**Adrenal Gland Tumors**

Adrenocortical carcinomas (ACCs) are rare (incidence 1 to 2 per million).120-122 There is a bimodal age distribution with peak incidences in early childhood and in the fourth to fifth decades of life. The female to male ratio is approximately 1.5 to 1.123,124 The majority of cases are sporadic, however ACCs have been observed in association with several hereditary syndromes including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and MEN 1.2,125-128 The underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated; however it appears that inactivating somatic mutations of the p53 tumor suppressor gene (chromosome 17p13129,130), as well as alterations at the 11p15 locus (site of the IGF-2 gene131,132) occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.120,133-135 Signs and symptoms associated with hypersecretion of cortisol, called Cushing’s syndrome, include weight gain, weakness (primarily in proximal muscles), hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae, buffalo hump, supraclavicular fat pad enlargement, hyperglycemia, and hypokalemia. Aldosterone-secreting tumors may present with hypertension, weakness, and hypokalemia. Androgen-secreting tumors in women may induce hirsutism, deepening of the voice, and oligo/amenorrhea.133 In men, estrogen-secreting tumors may induce gynecomastia and testicular atrophy. Hormonally
inactive ACCs typically produce symptoms related to tumor burden including abdominal pain, back pain, early satiety, and weight loss.\textsuperscript{133,136}

**Evaluation and Treatment of Adrenal Gland Tumors**

Evaluation of patients with adrenal gland tumors should take into account whether patients have a history of prior malignancy, which may raise suspicion that the tumor is metastatic. In such patients, an image-guided needle biopsy is recommended after a functioning adrenal neoplasm (in particular pheochromocytoma) is ruled out. If the clinical suspicion for pheochromocytoma is low and if plasma metanephrines are \(<2\) times the upper limit of normal, it is reasonable to proceed with an adrenal biopsy. If the tumor is determined to be a metastasis from another site, treatment should be according to the appropriate NCCN disease-specific treatment guideline. If biopsy reveals adrenal cortical tissue, than morphological and functional evaluation should proceed as described below.

The morphologic evaluation should include an adrenal protocol CT or MRI to determine the size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics. Functional evaluation should include evaluation for hyperaldosteronism, Cushing’s syndrome, and pheochromocytoma, as described below.

**Functional evaluation for pheochromocytoma**

A pheochromocytoma should be excluded with fractionated plasma free metanephrine and a 24-hour urine fractionated metanephrines and catecholamines for confirmation. Elevated levels of metanephrines are suggestive of pheochromocytoma.\textsuperscript{137,138} Concurrent medications should be reviewed before metanephrine testing for those that interfere with plasma metanephrines evaluation, including acetaminophen, certain beta- and alpha-adrenergic receptor blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors.\textsuperscript{139} Elevations in metanephrine levels that are \(4\) times above the upper limit for normal are diagnostic. Treatment of pheochromocytoma is discussed below.

**Evaluation and treatment of hyperaldosteronism**

When hyperaldosteronism (also called primary aldosteronism) is suspected, plasma aldosterone and renin activity should be assessed. Patients with primary aldosteronism have elevated plasma levels of aldosterone and low levels of renin activity. The plasma aldosterone to renin ratio in patients with primary hyperaldosteronism is usually \(>30\).\textsuperscript{140} Confirmatory testing with saline suppression test or salt loading test may be indicated, since both false positives and false negatives can occur. Electrolytes should also be measured, because excessive aldosterone production causes both retention of sodium and excretion of potassium. The Endocrine Society has developed detailed guidelines for the detection, diagnosis, and treatment of primary aldosteronism.\textsuperscript{141}

Hyperaldosteronism is rarely malignant, but malignancy should be suspected if the tumor has an irregular morphology, is lipid poor, does not wash-out on contrast-enhanced CT, is \(>3\) cm in size, or is secreting more than one hormone. When malignant hyperaldosteronism is suspected an open adrenalectomy is recommended, as these tumors are prone to rupture.\textsuperscript{142,143}

Benign hyperaldosteronism is much more common and can be caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia. Adrenal vein sampling for aldosterone is considered the standard for distinguishing these two causes of benign hyperaldosteronism and should be considered if the patient is a surgical candidate, since CT imaging is not always reliable. It may be reasonable, however, to exclude adrenal vein sampling in patients younger than 40 years old when imaging only shows one affected gland, because bilateral hyperplasia is rare in this population. Laparoscopic adrenalectomy is
recommended for adenoma, while medical management with spironolactone or eplerenone for hypertension and hypokalemia is recommended for patients with bilateral adrenal hyperplasia and for non-surgical candidates.

**Evaluation and treatment of Cushing’s syndrome**

When patients present with symptoms of Cushing’s syndrome, levels of serum ACTH, cortisol, and the sex steroid dehydroepiandrosterone sulfate (DHEA-S) are assessed. A confirmatory test [dexamethasone suppression (except when ACTH is already suppressed), repeated midnight salivary cortisol, or 24h urine] is recommended if cortisol levels are elevated.\(^{133,144}\) Elevated levels of cortisol are indicative of Cushing’s syndrome. Patients who experience symptoms secondary to increased adrenocortical steroid levels may require treatment for palliation of symptoms such as hypertension, hyperglycemia, hypokalemia, and muscle atrophy.

Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, and ectopic tumors in the lung, thyroid, pancreas, or bowel are probable sources. If an ectopic tumor is found, it should be removed if possible. If the primary tumor is unresectable, a bilateral laparoscopic adrenalectomy or medical management (see below) is recommended.

Cushing’s syndrome can also be caused by a benign adrenal tumor (adrenal adenoma) or a malignant adrenal tumor, neither of which produce ACTH. Malignancy should be suspected if the tumor is >5 cm or is inhomogeneous with irregular margins and/or local invasion. Imaging of the chest, abdomen, and pelvis is required to evaluate for metastases and local invasion. For malignant disease, please see the discussion of adrenal carcinoma, below. Benign adrenal tumors are removed by laparoscopic adrenalectomy, when feasible. Post-operative corticosteroid supplementation is required until recovery of the hypothalamus-pituitary-adrenal (HPA) axis.

ACTH-independent Cushing’s syndrome can also rarely be caused by bilateral multinodal hyperplasia. When the tumor appears benign and the contralateral gland appears abnormal, adrenal vein sampling of cortisol production determines treatment. If cortisol production is asymmetric, the laparoscopic unilateral adrenalectomy with removal of the most active side is recommended, again with post-operative corticosteroid supplementation. If cortisol production is symmetric, medical management is indicated.

Medical management of hypercortisolism is achieved with adrenostatic agents including ketoconazole and mitotane. Ketoconazole is most commonly used (at doses of 400-1200 mg per day) due to its easy availability and relatively tolerable toxicity profile. Octreotide can also be considered for ectopic Cushing’s syndrome if the tumor is OctreoScan positive, although it may be less effective in controlling ectopic ACTH secretion than it is in other contexts. Bilateral adrenalectomy is recommended when medical management of severe ectopic Cushing’s syndrome fails.

**Evaluation of pheochromocytomas/paragangliomas**

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla in 80% – 90% of cases. Ectopic/extra-adrenal pheochromocytomas that arise from para-aortic sympathetic ganglia are called paragangliomas. Pheochromocytomas and paragangliomas occur in 0.05% – 0.1% of hypertensive patients, and their combined annual incidence in the United States is estimated to be between 500 and 1600 cases.\(^{145}\)
Pheochromocytomas release catecholamines and their metabolites norepinephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. About 40% of paragangliomas are also functional. Although 73% – 90% of patients with pheochromocytomas have sporadic disease, pheochromocytomas occur in about 50% of patients with MEN 2A, MEN 2B, and other familial diseases (such as neurofibromatosis, von Hippel-Lindau syndrome, and Osler-Weber-Rendu syndrome). The peak incidence of occurrence for pheochromocytomas is between the third and fifth decade of life, but they generally occur at a younger age and are more likely to be bilateral in patients with familial disease. Paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% versus 10%). Pheochromocytomas and paragangliomas associated with a familial syndrome tend to be more aggressive and more likely to metastasize than sporadic tumors. In fact, a recent study showed that 87.5% of patients presenting with these tumors prior to age 20 harbored a germline mutation in one of several genes tested if they also had metastatic disease. For those without metastases, the rate of identification of these mutations was still high, at 64.7%. Delays as long as 30 years between presentation and metastasis have been reported in patients with familial paragangliomas, and many such patients survive long term following treatment of metastatic disease. Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance.

Functional evaluation of pheochromocytomas/paragangliomas is discussed above. Imaging studies, including chest/abdominal CT scan or MRI, are also recommended. A metaiodobenzylguanidine (MIBG) scan is highly effective in localizing pheochromocytomas (including extra-adrenal tumors) and is recommended as appropriate, especially when a tumor is not identified by either a MRI or CT scan. An OctreoScan is optional and is used if multiple tumors are suspected or if CT results are negative. A bone scan should be performed if clinically indicated. Genetic counseling should be offered, with genetic testing when appropriate.

**Primary treatment of pheochromocytomas/paragangliomas**

Surgical resection is the mainstay of treatment for both benign and malignant pheochromocytomas and paragangliomas. Surgery or stress can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Before surgery, the patient should receive preoperative treatment with alpha-adrenergic blockade (such as phenoxybenzamine, a non-selective alpha blocker), forced hydration, and sodium loading for at least 7 days. Additional adrenergic blockade of alpha1 receptors with prazosin, terazosin, or doxazosin can also be performed when long-term therapy is required for metastatic pheochromocytoma. The tyrosine hydroxylase inhibitor, alpha-methyltyrosine, can also be administered prior to surgery to help prevent hypertensive crisis. Beta-adrenergic blockade may be used after initiation of alpha-adrenergic blockade and 10 days before surgery to prevent or treat tachyarrhythmias after correction of hypovolemia. Choices include non-cardioselective beta blockers, such as propranolol, nadolol, or labetalol, or cardioselective beta blockers, such as atenolol and metoprolol. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The panel acknowledges that other effective agents can be used for alpha and beta blockade. The panel also points out that rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room to control blood pressure.
A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas.152 If possible, cytoreductive resection is also recommended for the treatment of isolated distant metastases. Cytoreductive resection is also recommended for locally unresectable disease, if possible, with or without radiation therapy. Symptoms can be controlled using alpha blockade with or without alpha-methyltyrosine and with or without beta blockade with an R2 resection. In addition, other options for distant metastases include: (1) clinical trial; (2) systemic chemotherapy with cyclophosphamide, vincristine, and dacarbazine153; or (3) iodine-131-MIBG therapy after confirming dosimetrically that tumors take up MIBG.154,155

Surveillance of pheochromocytomas/paragangliomas
Surveillance intervals for patients with pheochromocytomas or paragangliomas are similar to those for other neuroendocrine tumors. Following complete resection, H&P should be performed and blood pressure and tumor markers should be measured after 3 to 12 months, then every 6 months for the first 3 years, and annually thereafter. Patients with persistent disease need more frequent examination at intervals of every 3 to 4 months. In addition, imaging studies should be done as clinically indicated. Of course, timing for these surveillance events and procedures can be earlier if symptoms dictate. Surveillance for advanced disease is the same and should be performed every 3 to 4 months.

Evaluation and treatment of adrenal carcinoma (ACC)
Adrenal carcinoma should be strongly suspected in nonfunctioning tumors >4 cm with irregular margins or that are internally heterogenous.156 On CT scans with intravenous contrast, there may be adjacent lymph nodes or liver metastases. On unenhanced CTs, the Hounsfield Unit (HU) number is typically higher in carcinomas than in adenomas, and a threshold value of 10 HU has been proposed as a means of distinguishing benign from malignant adrenal tumors.157 If the HU attenuation value is >10 on unenhanced CT, then enhanced CT and washout at 15 minutes is recommended. If the enhancement washout value is >60% at 15 minutes, the tumor is likely benign.156 Chemical-shift MRI is highly sensitive and specific for differentiation of benign from malignant adrenal tumors, because most benign tumors contain fat, whereas most malignant tumors do not. MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.158,159 Whether CT or MRI scans are performed, they should be performed following an adrenal protocol to determine size,
heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics.

Imaging of the chest, abdomen, and pelvis is also recommended to evaluate for metastatic disease and local invasion when the primary tumor is >6 cm.

**Treatment of nonmetastatic adrenal carcinoma**

Surgical resection of the tumor with removal of adjacent lymph nodes is recommended in patients with localized adrenal carcinoma and may require removal of adjacent structures such as the liver, kidney, pancreas, spleen, and/or diaphragm for complete resection. Open adrenalectomy is preferred in tumors with a high risk of being malignant due to increased risk for local recurrence and peritoneal spread when done laparoscopically.142,143

Due to the rarity of ACCs, there are no published randomized, prospective trials of adjuvant therapy. The majority of retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticalolytic agent.160-162 The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany.163 In the Italian cohort, nearly half of the patients received adjuvant mitotane (47/102 patients) at doses ranging from 1 to 5 grams daily, whereas none of the 75 German patients received adjuvant mitotane. The median duration of treatment was 29 months. In follow-up, disease-free survival and overall survival were significantly longer in those treated with mitotane versus the controls, suggesting that adjuvant mitotane may be an effective post-operative strategy. The randomized phase III ADIUVO trial is currently underway to assess the efficacy of adjuvant mitotane in patients with ACCs considered to be at low to intermediate risk for progression (clinicaltrials.gov NCT00777244). Disease-free survival is the primary endpoint.

Based on the available data, adjuvant mitotane therapy can be considered following resection of adrenal carcinoma (category 3). Due to the adrenolytic effects of mitotane, lifelong replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed in order to prevent adrenal insufficiency. Due to the potential risks and uncertain benefits of adjuvant mitotane, several NCCN institutions do not advocate its use for patients with resected adrenal carcinomas.

For patients with high-grade adrenal carcinoma, adjuvant radiation therapy to the tumor bed can also be considered, particularly if there is concern for tumor spillage or close margins following surgery. Follow-up imaging and biomarkers (for functioning tumors) should be performed every 3 to 6 months.

**Management of metastatic adrenal carcinoma**

For low grade tumors, resection may be considered if >90% of the tumor and metastases can be removed. In low grade tumors, observation with imaging and relevant biomarkers every 3 months can also be considered, with systemic treatment initiated at tumor progression. Otherwise systemic therapy should be initiated. For high grade tumors, systemic chemotherapy is generally initiated without further observation. Choices of systemic therapy for advanced adrenal carcinoma are mitotane monotherapy or various combinations of cisplatin, carboplatin, etoposide, doxorubicin, streptozocin, and mitotane.

Mitotane monotherapy has been studied in the setting of locally advanced or metastatic disease.164-166 Partial response rates are thought to be around 10-30% at most.167 Several studies have evaluated the combination of mitotane with other cytotoxic agents, including cisplatin and etoposide. One of the larger studies analyzed the combination of mitotane (4 grams daily) with cisplatin, etoposide, and doxorubicin in 72
patients with unresectable adrenal carcinoma, yielding an overall response rate of 49% (by WHO criteria) and a complete hormonal response in 16 of 42 patients with functioning tumors.\textsuperscript{168} Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%.\textsuperscript{169} Of 12 patients in this study with advanced disease, 3 (25%) were converted to a resectable status with this therapy and remained disease-free or with stable disease 3 to 18 years following surgery; 1 (8%) had stable disease for 3 months, and the other 8 (67%) showed no response. Analysis of results from an international randomized trial comparing treatment of metastatic adrenocortical carcinoma with etoposide, doxorubicin, cisplatin, and mitotane to treatment with streptozotocin and mitotane (FIRM-ACT) is underway (clinicaltrials.gov NCT00094497).\textsuperscript{170} The toxicity of concurrent chemotherapy plus mitotane should be considered when making treatment decisions.

The optimal doses and duration of mitotane treatment for metastatic disease have not yet been standardized, but some institutions recommend target levels of 14-20 mcg/ml if tolerated. Higher doses may be difficult for patients to tolerate, while lower doses may be less effective.\textsuperscript{167} Steady-state levels may be reached several months after initiation of mitotane. Due to the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed in order to prevent adrenal insufficiency.

Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors

The classic small cell neuroendocrine tumor is poorly differentiated (high grade or anaplastic) and occurs in the lung. Although rare, extrapulmonary small cell carcinomas occur in a wide variety of organs. The most frequent organs involved, listed in order of decreasing frequency, are the cervix, esophagus, pharynx and larynx, colon and rectum, and prostate. Most extrapulmonary small cell carcinomas are aggressive and require combined multimodality treatment. These tumors are rarely associated with a hormonal syndrome.

Evaluation of Poorly Differentiated or Small Cell Tumors

CT scans of the chest, abdomen, and pelvis are recommended to locate potential primary sites. Brain MRI or CT should be performed as clinically indicated, and should be considered routinely in poorly differentiated neuroendocrine carcinomas of the thorax and neck. Plasma ACTH or other biochemical markers are recommended, as indicated.

Primary Treatment of Poorly Differentiated or Small Cell Tumors

For resectable anaplastic/small cell tumors, surgical resection and chemotherapy with a small cell lung cancer regimen (see NCCN Small Cell Lung Cancer Guidelines) with or without radiotherapy are advised. For unresectable locoregional disease, radiotherapy in combination with chemotherapy (again, with a small cell lung cancer regimen) is recommended. If metastatic tumors are present, chemotherapy alone (with a small cell lung cancer regimen) is recommended. Octreotide therapy can be considered for hormone-secreting tumors that are unresectable or metastatic.

Surveillance

After surgery, surveillance consists of a routine H&P along with appropriate imaging studies every 3 months for the first year and every 6 months thereafter. Patients with locoregional, unresectable disease and with metastatic disease should be monitored at least every 3 months.
Multiple Endocrine Neoplasia (MEN)

The MEN syndromes are characterized by tumors that affect endocrine organs. There are two main types of MEN: MEN 1 and MEN 2. MEN 1 is an autosomal dominant inherited syndrome mainly affecting the parathyroid glands (causing hyperparathyroidism), pituitary gland, and endocrine pancreas; MEN 1 may also be associated with carcinoid tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas. MEN 2 is also an autosomal dominant inherited syndrome and is associated with medullary thyroid cancer (MTC; 98%); pheochromocytoma (50%), often bilateral; and hyperparathyroidism (25%).

Once the diagnosis of either MEN 1 or MEN 2 syndromes is made, genetic counseling is recommended, which may include genetic testing when appropriate. Familial MTC occurs in patients with MEN 2 syndromes as well as in those with isolated MTC. Both MEN 1 and MEN 2 syndromes as well as familial MTC are inherited as autosomal dominant diseases. MEN 1 is associated with the germline mutation or inactivation of a tumor suppressor gene MEN1 (chromosomal locus 11q13 encoding the menin protein),¹⁷¹ whereas MEN 2 and familial MTC are associated with germline mutations of the proto-oncogene, RET (chromosomal locus 10q11.2), that lead to activation of the tyrosine kinase receptor RET.¹⁷² Table 2 summarizes the tumors in patients with MEN. Of interest, somatic mutation of the MEN1 gene is the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids.² Somatic RET mutations are also found in sporadic MTC.¹⁷³ All patients with MTC should be tested for germline mutation, as about 10% of patients with presumed sporadic MTC have a germline mutation of the RET oncogene.

MEN 1

MEN 1 (or Wermer syndrome), as previously mentioned, involves mainly the parathyroid glands, pituitary gland, and pancreas, but may also be associated with carcinoid tumors (eg, thymus, bronchial), adrenal tumors, and multiple lipomas and skin angiomas. Over 98% of patients with this syndrome either have or will develop primary hyperparathyroidism, and about 50% develop symptoms from functioning benign or malignant neoplasms of the pancreas.² About 35% of patients have functioning tumors of the pituitary, and an additional 20% of patients also have or develop nonfunctioning islet cell tumors.¹⁷⁴ Examples of functional syndromes include hypercalcemia related to multiple abnormal parathyroid glands; galactorrhea or amenorrhea associated with a prolactinoma; Zollinger-Ellison syndrome associated with gastrinoma and hypersecretion of gastrin; and Cushing’s syndrome or acromegaly related to a pituitary tumor or solitary or bilateral adrenal tumors. Ectopic Cushing’s syndrome may be caused by a pancreatic islet cell tumor, a thymic carcinoid, a bronchial carcinoid, or MTC. In addition, although rare, patients may develop symptoms as a result of an excess of several hormones from one or more glands, such as hyperparathyroidism and a simultaneous gastrinoma, insulinoma, or a functioning pituitary tumor. However, in most patients, a single hormonal syndrome dominates the clinical picture.

About 80% of patients with MEN 1 and hypoglycemia related to insulinoma have multiple islet cell neoplasms. Patients with MEN 1 and Zollinger-Ellison syndrome also frequently have more than one islet cell tumor. Of these tumors, 70% are gastrin-secreting carcinoids in the duodenum and/or periduodenal lymph nodes. Nonfunctioning pancreatic islet cell tumors are usually larger when clinically detected and are more likely to be malignant. Overall, about 10% of insulinomas...
and up to 90% of gastrinomas are malignant. Malignant islet cell tumors and carcinoid tumors of the thymus are the most common causes of death associated with MEN 1. The clinical characteristics of pancreatic endocrine tumors are summarized in Table 1.

**Evaluation of MEN 1 Syndromes**
The guidelines list a series of possible tests to further define sites of involvement for patients known to have or suspected of having MEN 1. The recommended tests include: (1) laboratory tests evaluating hormone, glucose, and/or calcium levels; (2) imaging tests needed to localize the site of the tumor or hyperplasia; and (3) genetic counseling, which may include genetic testing to identify one of the characteristic predisposing germline mutations. OctreoScan is also frequently recommended depending on the tumor type suspected. A thorough family history should be obtained from the patient, and family members should be considered for further testing for MEN1 gene status, hypercalcemia, and elevated chromogranin A levels. Specific additional recommendations based on tumor type are detailed below.

**Pancreatic tumors in MEN 1**
Approximately 75% of patients with MEN 1 and islet cell tumors have functioning tumors. The various characteristics of endocrine tumors of the pancreas (eg, gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma) are summarized in Table 1. The workup for pancreatic islet cell tumors in the context of MEN 1 is similar to that for sporadic islet cell tumors. For details on the evaluation for pancreatic tumors, see the section on Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors) above.

**Parathyroid tumors in MEN 1**
Primary hyperparathyroidism with parathyroid tumors is the most common component of MEN 1. Parathyroid hormone (PTH) testing and measuring of serum calcium levels are recommended if hyperparathyroidism is suspected. An additional test that may be considered is a 24-hour urinary calcium and creatinine test to rule out benign familial hypocalciuric hypercalcemia. The presence of elevated or high-normal levels of serum calcium and elevated levels of PTH confirm a diagnosis of primary hyperparathyroidism in a patient without hypocalciuria.

Imaging of the parathyroid glands using sestamibi scanning and/or ultrasound is optional but may aid in identifying ectopically situated parathyroids. The technetium 99m sestamibi (Tc99m sestamibi) and ultrasound scanning are about 80% and 70% sensitive, respectively, for identifying solitary parathyroid adenomas found in most patients with sporadic hyperparathyroidism. However, these scans are only about 35% accurate in patients with familial hyperparathyroidism. Neither scan can distinguish between adenomatous and hyperplastic parathyroid glands. Because most patients with familial hyperparathyroidism have multiple abnormal parathyroid glands, preoperative localization studies are less accurate and abnormal parathyroid glands are best identified during surgery.176,177

**Pituitary tumors in MEN 1**
Various laboratory tests are available for evaluating suspected pituitary tumors. These tests include an overnight dexamethasone suppression test and a 24-hour urinary free cortisol test for patients with Cushing’s syndrome. Following an MRI of the sella with contrast, bilateral petrosal vein sampling for basal and corticotropin releasing hormone (CRH)-stimulated ACTH can distinguish between a possible ACTH-secreting pituitary tumor and an ectopic source of ACTH if no tumor is identified. Patients with ectopic Cushing’s syndrome have markedly elevated ACTH levels and usually a more dramatic onset and progressive clinical course. Those with Cushing’s disease (pituitary adenoma) have
moderately increased ACTH levels. In contrast, those with Cushing’s syndrome due to benign or malignant adrenal tumors have suppressed levels of ACTH.

For patients with a possible prolactinoma, determination of the serum prolactin level as well as MRI of the pituitary gland with contrast may aid in the diagnosis.

Growth hormone levels, such as insulin-like growth factor-1 (IGF-1) and an oral glucose suppression test of growth hormone, are necessary to diagnose acromegaly. An MRI of the sella with contrast is also indicated.

When pituitary tumors are suspected because of hyperthyroidism, then alpha subunit, thyroid-stimulating hormone (TSH), T3, and T4 levels should be analyzed. An MRI scan of the sella with contrast is also recommended, as is consideration of the measurement of sex hormone binding globulin (SHBG) levels.

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol also aid in the recognition of nonfunctioning tumors together with IGF-1. In addition, an MRI of the sella with contrast is recommended to evaluate whether a pituitary adenoma is present.

**Primary Treatment of MEN 1 Syndromes**
Primary therapy of locoregional disease in MEN 1 patients focuses on treatment of the specific hormonal syndrome and/or treatment of the underlying hyperplasia or tumor. In most instances, surgical excision by an experienced surgeon is the initial treatment of choice for functioning tumors, whereas asymptomatic tumors (such as pituitary tumors) may be treated medically or with observation if no local mass effects are present. All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus influenza b, meningococcus group C) preoperatively. Furthermore, in patients undergoing abdominal surgery in whom octreotide treatment is planned, prophylactic cholecystectomy can be considered, because cholelithiasis and biliary symptoms are common side effects of octreotide. 

Metastatic disease is treated according to the appropriate tumor type the same way in MEN 1 patients as in patients with neuroendocrine tumors arising sporadically.

**Primary treatment of pancreatic tumors in MEN 1**
Initial treatment of pancreatic islet cell tumors associated with MEN 1, similar to sporadic islet cell tumors, focuses on surgical excision preceded by medical management (if necessary). However, in contrast to patients with sporadic disease where a tumor is usually solitary, islet cell tumors associated with MEN 1 are frequently multiple; thus, surgery may be more extensive. For example, removal of a single functioning tumor, although a reasonable approach for sporadic tumors, usually misses additional (possibly malignant) tumors in the setting of MEN 1. Furthermore, the largest tumor may not be the functioning tumor.

Therefore, surgical treatment of insulinoma, in the setting of MEN 1, typically consists of a distal pancreatectomy with enucleation of tumors in the head of the pancreas, as identified with intraoperative ultrasound. Resection of dominant tumors (>2-2.5 cm) helps symptom management. Glucose levels can be managed preoperatively with diet and diazoxide. Octreotide should be used with caution in insulinoma, because it can also suppress counter-regulatory hormones such as growth hormone, glucagon, and catecholamines. In this situation, octreotide can precipitously worsen hypoglycemia. 

For gastrinomas, any symptoms of gastrin hypersecretion may be treated with proton pump inhibitors before surgical intervention. In patients with MEN 1, 70% of gastrinomas are associated with
extrapancreatic tumors in the duodenum; thus, treatment generally includes duodenotomy with excision of small (usually multiple) tumors and periduodenal lymph node dissection. For patients with gastrinoma, resection of dominant tumors (>2-2.5 cm) may decrease the risk of developing metastatic disease. For gastrinomas that are exophytic or peripheral as determined by imaging and not immediately adjacent to the pancreatic duct, enucleation should be done with duodenotomy. Removal of the periduodenal nodes may be considered along with enucleation of coexisting pancreatic tumors. If the tumor is occult, the panel recommends 2 options: (1) observation (category 2B); and (2) exploratory surgery with duodenotomy and tumor enucleation with periduodenal node dissection with or without spleen-preserving distal pancreatectomy (category 2B). Gastrinomas that are deeper or invasive or with proximity to the main pancreatic duct should be managed by pancreateoduodenectomy with periduodenal node dissection.

Gastrinomas in the distal pancreas are treated with either distal pancreatectomy with spleen preservation or tumor enucleation and duodenotomy with regional lymphadenectomy.

Glucagonomas are typically situated in the tail of the pancreas and are usually malignant. Preoperative medical management of glucagonomas includes stabilization of glucose levels with diet or octreotide and consideration of a perioperative anticoagulant. Recommended options for resectable disease include: (1) tumor excision with peripancreatic node dissection; or (2) distal pancreatectomy and peripancreatic lymph node dissection. Splenectomy is almost always performed, because the tumors are usually malignant, relatively large, and situated in the tail of the pancreas.

For patients with VIPoma, the panel recommends either the excision of the tumor with resection of peripancreatic lymph nodes or pancreateoduodenectomy with dissection of peripancreatic lymph nodes, depending on the position of the tumor. Patients should be stabilized preoperatively with IV fluids and octreotide, and electrolyte imbalances should be corrected.

For PPoma, somatostatinoma, and other nonfunctional tumors of the pancreas, the panel recommends resection with lymph node dissection.

Primary treatment of parathyroid tumors in MEN 1
Treatment options for parathyroid hyperplasia in patients with MEN 1 include subtotal parathyroidectomy with removal of the bilateral upper thymus (which is a common site of ectopic parathyroid glands and thymic carcinoid tumors) with or without cryopreservation of parathyroid tissue. Total parathyroidectomy with autotransplantation of parathyroid tissue with or without bilateral removal of the upper thymus, and with or without cryopreservation of parathyroids (category 2B), is another recommended option. Adverse outcomes include persistent hyperparathyroidism (2% – 5%) and hypocalcemia (1%) because of inadequate or excessive resection, respectively, even by expert surgeons. Additionally, postoperative bleeding or hoarseness due to injury to the recurrent laryngeal nerve may occur in about 1% of patients. In contrast to sporadic hyperparathyroidism, patients with familial hyperparathyroidism (including MEN 1), isolated familial hyperparathyroidism, or hyperparathyroidism associated with jaw tumor syndrome are more likely to develop recurrent disease. The latter patients are also more likely to have or develop parathyroid carcinoma. Follow up includes determining blood calcium levels every 6 months for 3 years and yearly thereafter.

Primary treatment of pituitary tumors in MEN 1
The recommended treatment for pituitary tumors associated with MEN 1 depends on which hormone is present in excess and whether the tumor causes localized symptoms.
Prolactinoma: The primary treatment recommended for pituitary prolactinoma is a dopamine agonist (eg, bromocriptine, pergolide). If the patient is asymptomatic or demonstrates a good response, treatment should be continued. For a patient with a symptomatic pituitary prolactinoma (as evidenced by visual changes or increasing pituitary size), with no response or intolerance to a dopamine agonist, or with disease of sudden onset (indicating intratumoral hemorrhage), surgery may be necessary. If complete resection is not achieved, recommendations include re-excision and postoperative radiotherapy.

For patients with prolactinoma who desire pregnancy, surgical resection can be considered. Alternatively, the dopamine agonist can be continued until pregnancy is achieved. For patients with microadenoma (<1 cm), the dopamine agonist is stopped during pregnancy and the patient is followed symptomatically. After pregnancy and cessation of lactation, the dopamine agonist can be resumed if necessary. For pregnant patients with macroadenoma (≥1 cm), the dopamine agonist is continued throughout pregnancy. The patient should be followed symptomatically with imaging as needed. Evidence suggests that dopamine agonists can be safe during pregnancy.

Target organ hormone replacement therapy may be required following surgery or dopamine agonist therapy.

Acromegaly: For pituitary acromegaly indicated by increased levels of growth hormone or goiter with or without hyperthyroidism due to a TSH-producing adenoma, transsphenoidal surgery is recommended for tumors ≤1 cm without associated visual changes. However, for tumors >1 cm or those associated with visual changes or symptoms, preoperative treatment with a somatostatin analog for 2 weeks or less (category 2B) or somatostatin analog therapy in lieu of surgery (category 2B) may be considered. The growth hormone receptor antagonist, pegvisomant, is another option and is often administered when other treatments fail or are inappropriate. In the case of incomplete resection, somatostatin analog therapy with or without radiation or pegvisomant with or without radiation is given. Target organ hormone replacement therapy may be required following treatment for acromegaly.

Nonfunctioning tumor: Patients with nonfunctioning adenomas without visual changes may be observed. However, transsphenoidal surgical resection is indicated for patients with enlarging tumors or visual changes, which suggests progression. For all incompletely resected tumors, radiation therapy is recommended. Alternatively, radiation can be delayed until tumor growth is observed.

Surveillance
All patients with MEN 1 should be followed with a H&P, tumor markers, and calcium levels as appropriate and with imaging studies such as CT/MRI 3 to 6 months following resection. The follow-up tests should be repeated every 6 months for the first 3 years after surgery and annually thereafter. All close family members of patients with MEN 1 should be genetically counseled, and genetic testing should be considered.
MEN 2

MEN 2 can be further subdivided into MEN 2A (Sipple's syndrome) and MEN 2B based on the spectrum of accompanying endocrine tumors and disorders, as noted in Table 2. MTC is seen in nearly 100% of patients with MEN 2A and MEN 2B and is often the first manifestation of the syndrome. Patients with MEN 2A may also have or develop pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%). Some MEN 2A patients have lichen planus amyloidosis or Hirschsprung’s disease. Most patients with MEN 2B have mucosal neuromas, intestinal ganglioneuromas, or ectopic lenses as well as a Marfanoid habitus in addition to MTC; 50% of these patients have pheochromocytoma, but almost none have hyperparathyroidism (<1%).

MTC is a calcitonin-secreting tumor of the parafollicular or C cells of the thyroid, accounting for about 4% to 7% of thyroid cancers but about 15% of all thyroid cancer deaths. About 75% of MTC cases are sporadic, whereas approximately 25% are considered familial or hereditary. Familial MTC associated with MEN 2 normally arises in the first to third decades of life, but sporadic MTC is typically diagnosed in the fourth to fifth decades of life. All types of familial MTC are typically multifocal and preceded by C-cell hyperplasia; however, sporadic MTC is usually unifocal. Familial MTC arising in the absence of other endocrine malignancies or disorders is least aggressive, whereas MTC associated with MEN 2B is the most aggressive. MEN 2A, MEN 2B, and familial MTC are all autosomal dominant inherited diseases and are associated with germline mutations of the proto-oncogene, RET.\(^1,184\)

The initial symptoms associated with MEN 2A and MEN 2B include a mass in the thyroid gland (with or without adjacent central or lateral cervical lymph node adenopathy) and, less frequently, symptoms of excess hormone production related to MTC (such as diarrhea and facial flushing), pheochromocytoma (headaches, increased perspiration, and rapid heart rate), or hyperparathyroidism. In addition, nearly all MEN 2B patients have Marfanoid habitus, mucosal neuromas, poor dentition, and/or intestinal ganglioneuromas. Some patients also have ectopic lenses in the eye or very flexible joints.

For a full discussion of the management of MTC, consult the NCCN Thyroid Cancer Guidelines. The following discussion focuses on the presentation of MEN 2 and on the issues unique to MTC in this setting.

**Evaluation of MEN 2A, MEN 2B, and Familial MTC**

All patients with MTC should be screened by genetic testing for a mutation in the RET proto-oncogene. If the test is positive, the patient and family members should be referred to a genetic counselor for further testing. Before surgical resection of MTC in these patients, basal calcitonin and carcinoembryonic antigen (CEA) levels should be measured, because these test results help guide the extent of nodal dissection required, particularly in patients with occult disease detected by screening. Patients with low calcitonin and high CEA levels usually have more aggressive tumors. Localization tests selectively include ultrasound, CT, or MRI.

MEN 2 patients presenting with MTC should be evaluated for a coexisting pheochromocytoma (see Evaluation of Pheochromocytoma / Paraganglioma above) before administration of anesthetic or before any invasive procedure. Because patients with pheochromocytoma have persistent vasoconstriction, these patients must be treated preoperatively with alpha-adrenergic blockade (phenoxylbenzamine) or with alpha methyltyrosine to avoid a hypertensive crisis during surgery on the thyroid or adrenal glands. The intravascular volume is expanded preoperatively with increased oral salt and fluid intake. Forced hydration along with alpha blockade is necessary to prevent hypotension.
immediately after the tumor is removed. After institution of alpha blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

As mentioned previously, a total of about 25% of patients with MEN 2A either have or will develop hyperparathyroidism. A parathyroid workup is therefore recommended for MEN 2 patients; it consists of 25-hydroxy vitamin D levels, calcium and PTH determinations, and a 24-hour urine collection to assess both calcium and creatinine levels. A neck ultrasound or a sestamibi scan should be performed as appropriate in patients with primary hyperparathyroidism.

A physical exam is also recommended for MEN 2 patients to evaluate for the presence of thyroid nodules with or without cervical adenopathy, mucosal neuromas, ectopic lenses, megacolon, and lichen planus amyloidosis.

In patients with a positive RET oncogene test that are scheduled for a prophylactic thyroidectomy (see below), a preoperative neck ultrasound scan of the thyroid gland and cervical lymph nodes is essential to document intrathyroidal tumors and to possibly identify enlarged cervical lymph node metastases. If masses are not observed in the thyroid gland and if basal and stimulated calcitonin tests are negative in patients with RET mutation, prophylactic central node dissection is probably unnecessary.185,186

Primary Treatment of MEN 2A, MEN 2B, and Familial MTC
In patients with a positive RET oncogene test who are otherwise asymptomatic, prophylactic thyroidectomy is performed at diagnosis or during the first year of life in patients with MEN 2B and before the age of 5 for patients with MEN 2A and familial MTC.185-187

The treatment of both MTC and pheochromocytoma associated with MEN 2 is similar to the management of their sporadic counterparts (see Primary Treatment of Pheochromocytoma/Paraganglioma above and see the NCCN Thyroid Carcinoma Guidelines). However, patients with familial disease are much more likely to have bilateral thyroid carcinomas and bilateral pheochromocytomas.

Patients with MEN 2 and familial MTC are also more prone to postoperative hypoparathyroidism, because the thyroid gland is removed for treatment of C-cell hyperplasia or MTC. The consensus of the panel is for selective resection of abnormal parathyroid glands and for leaving normal parathyroid glands (marked with a clip or stitch during thyroid surgery) in situ when possible. However, some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC. Another situation for autotransplantation of the parathyroid gland is when the blood supply to a parathyroid gland is possibly compromised. For patients with sporadic hyperparathyroidism, MEN 2B, or familial MTC without MEN, the parathyroid gland should be transplanted to the sternocleidomastoid muscle as it will rarely become hyperplastic. However, when a normal parathyroid gland cannot be preserved in patients with MEN 2A, it should be autotransplanted to the forearm, since recurrent primary hyperparathyroidism occurs in almost 20% of these patients. If hyperparathyroidism recurs with a documented elevated PTH level in the ipsilateral basilic vein, the tumor can be removed or subtotally resected.

Surveillance
For MEN 2 patients, a routine H&P including blood pressure and markers should be performed 3 to 6 months after resection, then every 6 months during the first 3 years, and annually thereafter. Imaging studies (ie, ultrasound, CT, MRI) should be performed selectively, as
clinically indicated. After surgery for MTC, repeat calcitonin and CEA tests should be performed at 3 to 6 months and then annually if negative. As indicated elsewhere in these guidelines, surveillance timing is dictated by patient symptoms and laboratory testing.

Future Trial Design
Recent successes have demonstrated that large randomized controlled trials studying treatments for neuroendocrine tumors can provide practice-changing results. The National Cancer Institute recently convened a task force to set priorities for future studies and to recommend appropriate standards for trials in this disease. Among their recommendations are the following:

- Pancreatic neuroendocrine tumors should be studied separately from tumors in other locations.
- Well-differentiated and poorly differentiated neuroendocrine tumors should be studied in separate trials.
- Progression-free survival is an appropriate primary endpoint for phase III trials and many phase II trials.
- Trials studying treatment for hormonal symptoms are as critical as those assessing effects on tumor progression and should include quality-of-life endpoints.

Rigorous studies will allow continued progress in the development of improved treatments for patients with neuroendocrine tumors.
### Table 1: Characteristics of Neuroendocrine Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Major Clinical Symptom</th>
<th>Predominant Hormone</th>
<th>Islet Cell Type</th>
<th>Malignant Potential</th>
<th>Other Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>Recurrent peptic ulcer disease</td>
<td>Gastrin</td>
<td>γ</td>
<td>Very high</td>
<td>Diarrhea/steatorrhea</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia (fasting or nocturnal)</td>
<td>Insulin</td>
<td>β</td>
<td>Low</td>
<td>Catecholamine excess</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Diabetes mellitus, migratory necrolytic erythema</td>
<td>Glucagon</td>
<td>α</td>
<td>Very high</td>
<td>Panhypoaminoaciduria, Thromboembolism, Weight loss</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)</td>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>δ</td>
<td>High</td>
<td>Metabolic acidosis, Hyperglycemia, Hypercalcemia, Flushing</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Diabetes mellitus, diarrhea/steatorrhea</td>
<td>Somatostatin</td>
<td>δ</td>
<td>Very high</td>
<td>Hypochlorhydria, Weight loss, Gall bladder disease</td>
</tr>
<tr>
<td>PPoma</td>
<td>Hepatomegaly, Abdominal pain</td>
<td>Pancreatic polypeptide (PP)</td>
<td>PP cells</td>
<td>Very high</td>
<td>Occasional watery diarrhea</td>
</tr>
</tbody>
</table>

### Table 2: Tumors in Patients with Multiple Endocrine Neoplasia

<table>
<thead>
<tr>
<th>Organ</th>
<th>Neoplasm</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Hyperplasia</td>
<td>98</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Adenoma</td>
<td>35</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Islet cell</td>
<td>50</td>
</tr>
<tr>
<td>Multiple</td>
<td>Carcinoid</td>
<td>3</td>
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<tr>
<td>Adrenal</td>
<td>Cortical adenoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Cortical carcinoma</td>
<td>rare</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Adenoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Papillary</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>Lipoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>MEN 2A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
<td>98</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Pheochromocytoma</td>
<td>50</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Hyperplasia</td>
<td>25</td>
</tr>
<tr>
<td><strong>MEN 2B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
<td>98</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Pheochromocytoma</td>
<td>50</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Hyperplasia</td>
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<tr>
<td>Neurona</td>
<td>Mucosal neuroma</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Intestinal ganglioneuroma</td>
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</table>
References


