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### NCCN Guidelines Panel Disclosures

- ¶ Surgery/Surgical oncology
- † Medical oncology
- ð Endocrinology
- ≠ Pathology
- ¶Internal medicine
  * Discussion Section Writing Committee
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.

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NCCN Guidelines Version 2.2016 Updates
Neuroendocrine Tumors

Updates in Version 2.2016 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2016 include:

**MS-1**
- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.1.2016 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.1.2015 include:

**NET-1**
- After locoregional disease, the following criteria were revised: "Larger (>2 cm), invasive, or node-positive tumors."

**PanNET-1**
- For surveillance recommendations after complete resection of primary tumor and metastases, a link has been added to PanNET-6.
- Asymptomatic, low tumor burden, and stable disease, first option was revised: "Observe with markers and imaging multiphasic CT or MRI every 3–12 mo."
- Footnote "v" has been revised: "Somatostatin analogs For patients with insulinoma, octreotide or lanreotide should be used only if somatostatin scintigraphy is positive. If used, they should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia."
NCCN Guidelines Version 2.2016 Updates
Neuroendocrine Tumors

Updates in Version 1.2016 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2015 include:

**Pheochromocytoma**

**PHEO-1**
- Evaluation options have been revised and divided into two categories, "Recommended" and "As appropriate, if metastatic disease suspected."
- Second bullet under recommended has been revised: "Contrast-enhanced chest/abdominal/pelvic multiphasic CT or MRI."
- Footnote "d" has been revised: "For cervical paranglioma, consider measuring serum and/or 24-hour urine fractionated catecholamines (for dopamine)."
- The following line has been added to footnote "e": "Certain genetic variants may require more frequent follow-up."

**PHEO-2**
- This page has been significantly revised. The recommendations that were previously on PHEO-1 regarding alpha blockade have been moved to this page and revised.
- Alpha blockade recommendation has been revised: "Alpha blockade with volume repletion and high salt diet for 7–14 days or until stable."
- After alpha blockade, a new column was added for the additional medical therapies that may be considered after alpha blockade.
- Footnote "F" has been added: "Alpha 1 selective receptor blockers include terazosin, doxazosin, prazosin, and non-selective receptors include phenoxybenzamine. Therapy for 7–14 days is recommended prior to surgical therapy. Nonselective alpha blockade phentolamine (IV) can be used intraoperatively."
- Footnote "g" has been rewritten as follows: "Alpha blockade is first-line therapy for all hormonally secreting pheochromocytoma and parangliomias. After alpha blockade, if additional blood pressure (bp) support is needed, the addition of dihydropyridine calcium channel blockers can be used. This is not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Methyltyrosine can also be used in addition to alpha blockade to stabilize bp. Beta blockade can be added to alpha blockade for tachycardia. B1 selective blockers or nonselective beta blockers can be used. Combination beta/alpa blockers are not recommended."
- The following option has been removed from the list of surveillance options: "Genetic counseling and testing as clinically indicated"
- For locally unresectable and distant metastases, the following recommendation has been added: "Continue medical therapy for secreting tumors."

**Poorly Differentiated Carcinomas/Large or Small Cell**

**PDNEC-1**
- The following has been removed from evaluation options: "Other scans as clinically indicated."
- Under Surveillance, the imaging recommendations have been clarified as follows: "(MRI, CT, or FDG-PET/CT)."

**Multiple Endocrine Neoplasia, Type 1**

**MEN1-2**
- Recommended clinical evaluation options for parathyroid have been changed to: "Serum calcium + 25-OH vitamin D and biochemical evaluation as clinically indicated (See NE-B)."
  - Options that are included in the biochemical evaluation options listed on NE-B have been removed from this page.
- A new algorithm has been added to include the evaluation and surveillance options for bronchial/thymic MEN1 tumors. (Also on MEN1-3)

**MEN1-3**
- Under the MEN1 surveillance heading, the following has been added: "Patients with MEN1 should be screened for all of the following tumor types."
  - For parathyroid:
    - If calcium rises, the first sub-bullet has been revised: "Serum PTH and 25-OH vitamin D."
    - If calcium rises, the third sub-bullet has been revised: "Consider MRI cross-sectional imaging (CT or MRI) of neck."
    - After surveillance, "consider referral to a specialist" has been removed.
  - For PanNET, the following two bullets have been removed:
    - "Serum gastrin annually."
    - "Serum chromogranin A and/or pancreatic polypeptide annually (category 3)."
  - For pituitary:
    - The second bullet has been revised: "Repeat Prolactin, IGF-1, and other previously abnormal pituitary hormones annually every 3–5 y or as symptoms indicate."
    - After surveillance, "If tumor grows or hormones increase, consider referral to specialist," has been removed.
    - The following line has been deleted from footnote "g" and incorporated into the algorithm: "Surveillance is indicated for all MEN tumors regardless of patient's tumor type. For patients at risk for bronchial or thymic carcinoid tumors, chest imaging can be considered every 1–3 y."

Continued on next page
Updates in Version 1.2016 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2015 include:

**Multiple Endocrine Neoplasia, Type 2**

**MEN2-1**
- In the first sub-bullet, the term "close relatives" has been further defined to "first-degree relatives."

**MEN2-2**
- Under the recommended evaluation options for parathyroid, "Serum calcium + 25-OH vitamin D" has been added.

**Principles of Biochemical Testing**

**NE-B (1 of 3)**
- The following has been added to the first bullet: "Screening for hormones in asymptomatic individuals is not routinely required."
- The following two bullets have been removed:
  - "For most of the blood studies, an 8-hour fast is generally recommended in addition to certain dietary adjustments depending on the test."
  - "Also be aware that many medications can affect the results of specific tests."
- The last bullet has been revised: "If Multiple Endocrine Neoplasia Type 2 (MEN2) is suspected, then all patients should be evaluated for pheochromocytoma/paraganglioma in addition to pituitary or pancreatic tumors prior to any procedures. Recommended annual screening for pancreatic NET is gastrin, glucagon, VIP, pancreatic polypeptide, chromogranin A, and insulin."
- Significant revisions have been made to the table of biochemical testing recommendations. (Also on NE-B, 2 of 3)

**NE-B (3 of 3)**
- References have been updated.
Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus (carcinoid tumors)b
Clinical presentations:
• Jejunal, ileal, colon (See NET-1)
• Duodenal (See NET-1)
• Appendix (See NET-2)
• Rectal (See NET-3)
• Gastric (See NET-4)
• Bronchopulmonary, thymus (See NET-5)
• Atypical lung carcinoid
• Locoregional unresectable disease and/or distant metastases (See NET-6)

Neuroendocrine tumors of the pancreasb
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)b

Adrenal gland tumors (See AGT-1)c

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated neuroendocrine carcinoma/Large or small cell carcinoma other than lung (See PDNEC-1)

Multiple endocrine neoplasia, type 1 (See MEN1-1)
• Parathyroid
• Pancreatic neuroendocrine tumors (PanNETs)
• Pituitary tumor

Multiple endocrine neoplasia, type 2 (See MEN2-1)
• Medullary thyroid carcinoma (Also see NCCN Guidelines for Thyroid Carcinoma)
• Parathyroid
• Pheochromocytoma

Merkel cell carcinoma (See NCCN Guidelines for Merkel Cell Carcinoma)

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## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

### CLINICAL LOCATION

- **Jejunal/ileal/colon**
  - Recommended:
    - Abdominal/pelvic multiphasic CT or MRI
  - As appropriate:
    - Somatostatin receptor scintigraphy
    - Colonoscopy
    - Small-bowel imaging (CT enterography or capsule endoscopy)
    - Chest CT
    - Biochemical evaluation as clinically indicated (See NE-B)
  - Locoregional disease
  - Metastatic disease
  - Bowel resection(s) with regional lymphadenectomy<sup>c,f</sup>
  - **Metastatic Disease (NET-6)**

- **Duodenal**
  - Recommended:
    - Abdominal/pelvic multiphasic CT or MRI
  - As appropriate:
    - Somatostatin receptor scintigraphy
    - EGD/endoscopic ultrasound (EUS)
    - Chest CT
    - Biochemical evaluation as clinically indicated (See NE-B)
  - Locoregional disease
  - Metastatic disease
  - **Metastatic Disease (NET-6)**
  - Endoscopic resection<sup>c,g</sup>
  - Local excision (transduodenal)<sup>c</sup>
  - ± lymph node sampling
  - Pancreatoduodenectomy<sup>c</sup>

### EVALUATION<sup>a,b</sup>

### PRIMARY TREATMENT OF NON-METASTATIC DISEASE<sup>c</sup>

### SURVEILLANCE<sup>d,e</sup>

#### Jejunal/ileal/colon

3–12 mo postresection:
- H&P
- Consider abdominal/pelvic multiphasic CT or MRI
- Biochemical evaluation as clinically indicated (See NE-B)

> 1 y postresection up to 10 y:
- Every 6–12 mo
  - H&P
  - Consider multiphasic CT or MRI
  - Biochemical evaluation as clinically indicated (See NE-B)

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

<sup>b</sup>See Principles of Biochemical Testing (NE-B).

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

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

<sup>e</sup>Somatostatin receptor scintigraphy and FDG-PET/CT scans are not recommended for routine surveillance.

<sup>f</sup>Should include:
- Careful examination of the entire bowel, as multiple synchronous lesions may be present.
- Assessment of the proximity to or involvement of the superior mesenteric artery and superior mesenteric vein.

<sup>g</sup>If endoscopic resection performed, follow-up EGD as appropriate.

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## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

### CLINICAL LOCATION

<table>
<thead>
<tr>
<th>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;d,e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 cm and confined to the appendix</td>
<td>Simple appendectomy&lt;sup&gt;c,i&lt;/sup&gt;</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>&gt;2 cm or incomplete resection (nodes, margins)</td>
<td>Recommended: • Abdominal/pelvic multiphasic CT or MRI As appropriate: • Chest CT • Biochemical evaluation as clinically indicated (See NE-B)</td>
<td>• Re-exploration • Right hemicolecotomy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3–12 mo postresection: • H&amp;P • Consider abdominal multiphasic CT/MRI • Biochemical evaluation as clinically indicated (See NE-B) &gt;1 y postresection up to 10 y: • Every 6–12 mo ‣ H&amp;P ‣ Consider multiphasic CT or MRI • Biochemical evaluation as clinically indicated (See NE-B)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>Metastatic Disease (NET-6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>b</sup>See Principles of Biochemical Testing (NE-B).

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

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

<sup>e</sup>Somatostatin receptor scintigraphy and FDG-PET/CT scans are not recommended for routine surveillance.

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

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**NET-2**

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**Clinical Location**

**EVALUATION**

- **Rectal**
  - **T1**
    - Endorectal MRI or EUS
  - **T2-T4**
    - Recommended:
      - Colonoscopy
      - Abdominal/Pelvic multi-phase CT or MRI
      - Endorectal MRI or EUS
    - As appropriate:
      - Somatostatin receptor scintigraphy
      - Chest CT
      - Biochemical evaluation as clinically indicated (See NE-B)

**Primary Treatment of Non-Metastatic Disease**

- Resection (transanal or endoscopic excision, if possible)
- ≤2 cm
  - ≤1 cm: No follow-up required
  - 1–≤2 cm: Endoscopy with rectal MRI or EUS at 6 and 12 mo, then as clinically indicated
- >2 cm
  - >1 y postresection up to 10 y:
    - Every 6–12 mo
      - H&P
      - Consider multiphasic CT or MRI
      - Biochemical evaluation as clinically indicated (See NE-B)

**Surveillance**

- ≤2 cm
  - 3–12 mo postresection:
    - H&P
    - Consider abdominal/pelvic multiphasic CT or MRI
    - Biochemical evaluation as clinically indicated (See NE-B)

- >1 y postresection up to 10 y:
  - For 1- to 2-cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.

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

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See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
See Principles of Biochemical Testing (NE-B).
See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
Earlier, if symptoms.
Somatostatin receptor scintigraphy and FDG-PET/CT scan are not recommended for routine surveillance.
For 1- to 2-cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.
**Gastric**

**EVALUATION**

- EGD
- Gastric biopsy
- Serum gastrin level
- Consider gastric pH, as appropriate

**CLINICAL LOCATION**

- Hypergastrinemic patients

**Type 1 (Atrophic gastritis or high gastric pH)**

- Vitamin B12 level
- EUS as clinically indicated

**Type 2 (Zollinger-Ellison; no atrophic gastritis, low gastric pH)**

- Multiphasic CT or MRI of abdomen
- Consider somatostatin receptor scintigraphy
- EUS as clinically indicated

- Multiphasic CT or MRI of abdomen
- Consider somatostatin receptor scintigraphy

- EUS
- Multiphasic CT or MRI of abdomen
- Consider somatostatin receptor scintigraphy

**PRIMARY TREATMENT**

- Annual endoscopic surveillance and endoscopic resection of prominent tumors and
- Consider antrectomy if gastric tumors are increasing significantly in size or number.

**Metastatic disease (See NET-6)**

- Resect primary gastrinoma
- If primary not resected:
  - consider endoscopic surveillance and endoscopic resection of prominent tumors and/or
  - Octreotide or lanreotide

**Metastatic disease (See NET-6)**

- If no evidence of lymphadenopathy on EUS, consider endoscopic or surgical wedge resection
- Radical resection with lymphadenectomy

**Metastatic disease (See NET-6)**

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See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
See Principles of Biochemical Testing (NE-B).
See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. It should ideally be checked when fasting and off PPI for >1 week.
Elevated gastrin levels are usually diagnostic of type 1 or type 2 tumors.
If gastric pH is low or there is clinical or radiographic evidence, see gastrinoma on PanNET-2.

Type 3 gastric carcinoid tumors are sporadic, unifocal, and unassociated with either atrophic gastritis or Zollinger-Ellison syndrome.
Patients with metastatic, unresectable gastrinoma are unlikely to require surveillance of type 2 gastric NET.
Endoscopic resection should be reserved for small (<1 cm), superficial, low-grade tumors.
**NCCN Guidelines Version 2.2016**

**Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)**

**CLINICAL LOCATION**

**EVALUATION**

**PRIMARY TREATMENT OF NON-METASTATIC DISEASE**

**SURVEILLANCE**

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### Bronchopulmonary

- **Recommended:**
  - Chest CT and abdominal multiphasic CT or MRI
- **As appropriate:**
  - Somatostatin receptor scintigraphy
  - Bronchoscopy
  - Biochemical workup for Cushing’s syndrome if clinically indicated *(See NE-B)*
  - Other biochemical evaluation as clinically indicated *(See NE-B)*

### Thymus

- **Recommended:**
  - Chest/mediastinal multiphasic CT and abdominal multiphasic CT or MRI
- **As appropriate:**
  - Somatostatin receptor scintigraphy
  - Bronchoscopy
  - Biochemical workup for Cushing’s syndrome if clinically indicated *(See NE-B)*
  - Other biochemical evaluation as clinically indicated *(See NE-B)*

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**Localized disease**

- **Resect**

**Locoregional disease**

- **Resect**

**Metastatic disease**

- **Metastatic Disease (NET-6)**

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**3–12 mo postresection:**

- **H&P**
- **Biochemical evaluation as clinically indicated (See NE-B)**
- **Chest/mediastinal multiphasic CT or MRI**

**>1 y postresection up to 10 y:**

- **Every 6–12 mo**
  - **H&P**
  - **Consider CT or MRI**
  - **Biochemical evaluation as clinically indicated (See NE-B)**

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

*b* See *Principles of Biochemical Testing (NE-B)*.

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

*d* Earlier, if symptoms.

*e* Somatostatin receptor scintigraphy and FDG-PET/CT scan are not recommended for routine surveillance.

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

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

<table>
<thead>
<tr>
<th>Locoregional unresectable disease and/or distant metastases</th>
<th>Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If complete resection possible</td>
<td>Refer to surveillance for appropriate primary disease sites (See NET-1 through NET-5)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic, low tumor burden</td>
<td>Clinical significant progressive disease</td>
</tr>
<tr>
<td>Locally symptomatic from primary tumor</td>
<td>Consider cytoreductive surgery/ablative therapy (category 2B)</td>
</tr>
<tr>
<td>Clinically significant tumor burden</td>
<td>Consider everolimus (10 mg/d) (category 3)</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Consider interferon alfa-2b (category 3)</td>
</tr>
<tr>
<td>Observe with markers and multiphasic CT or MRI every 3–12 mo or Octreotide(^o) or lanreotide(^o)</td>
<td>Consider cytotoxic chemotherapy (category 3), if no other options feasible</td>
</tr>
<tr>
<td></td>
<td>Consider hepatic regional therapy (arterial embolization, chemoembolization, radioembolization [category 2B])</td>
</tr>
</tbody>
</table>

\(^b\)See Principles of Biochemical Testing (NE-B).
\(^c\)See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
\(^d\)See Principles of Systemic Anti-Tumor Therapy (NE-D).
\(^e\)Noncurative debulking surgery might be considered in select cases.
\(^u\)Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

\(^v\)Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

\(^w\)Only if near complete resection can be achieved.

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CLINICAL LOCATION

EVALUATION\textsuperscript{b,c,d}

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE\textsuperscript{e,f}

Nonfunctioning pancreatic tumors\textsuperscript{a}

Recommended:
- Multiphasic CT or MRI
- As appropriate:
  - Somatostatin receptor scintigraphy
  - EUS
  - Biochemical evaluation as clinically indicated (See NE-B)

Locoregional disease\textsuperscript{h}

Small (\leq 2 \text{ cm})

- Enucleation ± regional nodes\textsuperscript{e,g}
- Distal pancreatectomy ± regional nodes/ splenectomy\textsuperscript{e}
- Pancreatoduodenectomy ± regional nodes\textsuperscript{e}
- Consider observation in selected cases\textsuperscript{h}

Large (\textgreater 2 \text{ cm}), invasive, or node-positive tumors

Head

- Pancreatoduodenectomy + regional nodes\textsuperscript{e}

Distal

- Distal pancreatectomy\textsuperscript{e} + splenectomy + regional nodes

Metastatic disease

See Metastases (PanNET-7)

\textsuperscript{a}For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway.

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

\textsuperscript{c}See Principles of Biochemical Testing (NE-B).

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

\textsuperscript{e}See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

\textsuperscript{f}Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

\textsuperscript{g}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.

\textsuperscript{h}Observation can be considered in select cases: tumors <1 cm, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities.

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**CLINICAL LOCATION**

**EVALUATION**

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

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**Gastrinoma** (usually duodenal or head of pancreas)

**Recommended:**
- Gastrin levels (basal, stimulated as clinically indicated)
- MultIPHASIC CT or MRI

**Locoregional disease**

**Recommended:**
- Gastrin levels (basal, stimulated as clinically indicated)
- MultIPHASIC CT or MRI

**As appropriate:**
- Somatostatin receptor scintigraphy
- EUS
- Other biochemical evaluation as clinically indicated (See NE-B)

**Metastatic disease**

**See Metastases (PanNET-7)**

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**Duodenum**

**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**

---

**Head**

**Exophytic or peripheral tumors by imaging**

**Enucleation of tumor + periduodenal node dissection**

---

**Distal**

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

**Pancreateo- duodenectomy**

**Distal pancreatectomy ± splenectomy**

---

**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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**PanNET-2**
**EVALUATION**

**CLINICAL LOCATION**

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

---

**Insulinoma**

- **Recommended:**
  - Multiphasic CT or MRI
- **As appropriate:**
  - EUS
  - Biochemical evaluation as clinically indicated (See NE-B)

**Locoregional disease**

- Stabilize glucose levels with diet and/or diazoxide

**Exophytic or peripheral tumors by imaging**

- **Head or Distal**
- Tumor enucleation, consider laparoscopic resection

**Deeper or invasive tumors and those in proximity to the main pancreatic duct**

- **Head** → Pancreatoduodenectomy

**Metastatic disease**

- As appropriate:
  - Somatostatin receptor scintigraphy

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

---

**Locoregional disease**

- **Distal**
- Tumor enucleation, consider laparoscopic resection

**Metastatic disease**

- As appropriate:
  - Somatostatin receptor scintigraphy

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

---

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**Glucagonoma (usually tail)**

**Recommended:**
- Glucagon/blood glucose
- Multiphasic contrast-enhanced CT or MRI

**As appropriate:**
- Somatostatin receptor scintigraphy
- EUS
- Biochemical evaluation as clinically indicated (See NE-B)

**CLINICAL LOCATION**

**EVALUATION**\(^{b,c,d}\)

**Locoregional disease**

- **Recommended:**
  - Glucagon/blood glucose
  - Multiphasic contrast-enhanced CT or MRI

- **As appropriate:**
  - Somatostatin receptor scintigraphy
  - EUS
  - Biochemical evaluation as clinically indicated (See NE-B)

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**\(^{e,f}\)

**Head**

- (rare)

- Stabilize glucose levels with IV fluids and octreotide\(^{1}\) or lanreotide\(^{1}\)
- Treat hyperglycemia and diabetes, as appropriate

**Distal**

- Distal pancreatectomy
- Pancreatoduodenectomy
  - + peripancreatic lymph nodes\(^{e,p}\)

**Metastatic disease**

- See Metastases (PanNET-7)

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

\(^{c}\)See Principles of Biochemical Testing (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).

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

\(^{f}\)Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

\(^{1}\)See Principles of Systemic Anti-Tumor Therapy (NE-D).

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

\(^{p}\)Hypercoaguable state has been described. Perioperative anticoagulation can be considered.

---

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CLINICAL LOCATION | EVALUATION\textsuperscript{b,c,d} | MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE\textsuperscript{e,f} \\
--- | --- | --- \\
VIPoma | \textbf{Recommended:} \begin{itemize} \item Electrolytes \item VIP levels \item Multiphasic CT or MRI \end{itemize} \textbf{As appropriate:} \begin{itemize} \item Somatostatin receptor scintigraphy \item EUS \item Biochemical evaluation as clinically indicated (See NE-B) \end{itemize} | \textbf{Locoregional disease} \begin{itemize} \item Stabilize with IV fluids and octreotide\textsuperscript{j} or lanreotide\textsuperscript{j} \item Correct electrolyte imbalance (K\textsuperscript{+}, Mg\textsuperscript{2+}, HCO\textsubscript{3}\textsuperscript{-}) \end{itemize} \textbf{Head} \textsuperscript{q} \rightarrow \textbf{Pancreatoduodenectomy + peripancreatic lymph nodes}\textsuperscript{e} \textbf{Metastatic disease} \textbf{See Metastases (PanNET-7)} \textbf{Distal} \textsuperscript{q} \rightarrow \textbf{Distal pancreatectomy + peripancreatic lymph node dissection + splenectomy}\textsuperscript{e, f} \textbf{See Surveillance (PanNET-6)} \\

\textsuperscript{b}See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).  \\
\textsuperscript{c}See Principles of Biochemical Testing (NE-B).  \\
\textsuperscript{d}For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).  \\
\textsuperscript{e}See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).  \\
\textsuperscript{f}Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.  \\
\textsuperscript{j}See Principles of Systemic Anti-Tumor Therapy (NE-D).  \\
\textsuperscript{q}Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph node dissection may be considered.  \\

**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.
SURVEILLANCE\textsuperscript{r,s}

RECURRENT DISEASE

MANAGEMENT OF RECURRENT DISEASE\textsuperscript{e}

\begin{itemize}
\item 3–12 mo postresection:
  \begin{itemize}
  \item H&P
  \item Consider biochemical markers as clinically indicated\textsuperscript{c}
  \item Multiphasic CT or MRI
  \end{itemize}
\item >1 y postresection to a maximum of 10 y:
  \begin{itemize}
  \item Every 6–12 mo
    \begin{itemize}
    \item H&P
    \item Consider biochemical markers as clinically indicated\textsuperscript{c}
    \item Consider multiphasic CT or MRI
    \end{itemize}
  \end{itemize}
\end{itemize}

Locoregional disease

\begin{itemize}
\item Resectable \rightarrow \text{Resection}\textsuperscript{e}
\item Unresectable
\end{itemize}

Distant metastases

\textbullet\text{See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)}

\begin{itemize}
\item See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)

\textsuperscript{c}See Principles of Biochemical Testing (NE-B).
\textsuperscript{e}See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
\textsuperscript{r}Earlier, if symptoms.
\textsuperscript{s}Somatostatin receptor scintigraphy and FDG-PET/CT scan are not recommended for routine surveillance.

\textbf{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.
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

If complete resection possible

Resect metastases + primary

See Surveillance (PanNET-6)

Locoregional unresectable disease and/or Distant metastases

Asymptomatic, low tumor burden, and stable disease

Observe with markers and multiphasic CT or MRI every 3–12 mo

Consider treatment with octreotide or lanreotide

Clinically significant progressive disease, see below

Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease

Manage clinically significant symptoms as appropriate

Consider octreotide or lanreotide if not already receiving and/or

- Everolimus (10 mg/d)
- Sunitinib (37.5 mg/d)
- Cytotoxic chemotherapy
- Hepatic regional therapy (ie, arterial embolization, chemoembolization, radioembolization [category 2B])
- Cytoreductive surgery/ablative therapy (category 2B)

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

See Principles of Systemic Anti-Tumor Therapy (NE-D).

Noncurative debulking surgery might be considered in select cases.


For patients with insulinoma, octreotide or lanreotide should be used only if somatostatin scintigraphy is positive. If used, they should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).

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.
**INITIAL WORKUP**

- **Tumor-directed localizing studies:**
  - Multiphasic CT or MRI
  - Consider somatostatin receptor scintigraphy, ultrasound, or EUS
  - Bone scan, if symptoms
  - Consider FDG-PET/CT scan, and brain imaging (CT or MRI) in poorly differentiated carcinomas only
  - Consider EGD and/or colonoscopy

- **Biopsy-proven neuroendocrine tumors (NET) of unknown primary**
  - Primary not discovered
  - Primary found

- **Poorly differentiated**
  - See Primary Treatment for poorly differentiated neuroendocrine carcinoma (PDNEC-1)

- **Well-differentiated**
  - See Carcinoid Tumors (NET-6)

---

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**References:**
- Consider possibility of functioning adrenal neoplasms and suspected carcinoid tumor syndrome prior to biopsy. Evaluate plasma or 24-hour urine fractionated metanephrines prior to biopsy or manipulation of adrenal masses. Alpha blockade is required prior to biopsy or manipulation for suspected pheochromocytoma or paraganglioma. Octreotide premedication is required before biopsy in a suspected functioning carcinoid tumor.
- Sequence of initial workup may vary.
- See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
- Consider small bowel primary tumor based on symptoms and associated radiologic findings.
- See Principles of Biochemical Testing (NE-B).
Adrenal Gland Tumors

**CLINICAL PRESENTATION**

- History of prior or current malignancy with risk of or suspicion of adrenal metastasis
- No history of prior or current malignancy

**EVALUATION**

- Adrenal gland tumor on imaging
- Morphologic evaluation

- Biochemical workup as clinically indicated (See NE-B) for:
  - Hyperaldosteronism
  - Cushing’s syndrome
  - Pheochromocytoma

- Adrenal protocol (CT scan or MRI) to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics

**CLINICAL DIAGNOSIS**

- Hyperaldosteronism
- Cushing’s syndrome
- Non-functioning tumor
- Pheochromocytoma
- Multiple hormones

---

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See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
See Principles of Biochemical Testing (NE-B).
If unenhanced is <+10 HU, then the tumor is probably benign. If unenhanced is >+10 HU, then use enhanced and washout. If >60% washout 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.)
Screening for pheochromocytoma should be considered for asymptomatic patients if radiologic findings are suspicious and surgery is planned.

---

Adrenal Gland Tumors

CLINICAL DIAGNOSIS

History of prior or current malignancy with risk of or suspicion of adrenal metastasis

ADDITIONAL EVALUATION

• Rule out pheochromocytoma
• Check plasma or 24-hour urine fractionated metanephrines (See NE-B)

Consider image-guided needle biopsy if not pheochromocytoma

Adrenal cortical tissue → See Evaluation (AGT-1)

Metastasis from other site discovered → See NCCN disease-specific treatment guidelines

Not a surgical candidate

Hyperaldosteronism, suspect benign

Surgical candidate

Consider adrenal vein sampling for aldosterone and cortisol

Bilateral aldosterone production

Unilateral aldosterone production

Adrenalectomy, laparoscopic preferred

Open adrenalectomy

Hyperaldosteronism, suspect malignant

Medical management of hypertension and hypokalemia with spironolactone or eplerenone

CLINICAL DIAGNOSIS ADDITIONAL EVALUATION PRIMARY TREATMENT

History of prior or current malignancy with risk of or suspicion of adrenal metastasis

• Rule out pheochromocytoma
• Check plasma or 24-hour urine fractionated metanephrines

Consider image-guided needle biopsy if not pheochromocytoma

Adrenal cortical tissue → See Evaluation (AGT-1)

Metastasis from other site discovered → See NCCN disease-specific treatment guidelines

Notes:

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Adrenal Gland Tumors

CLINICAL DIAGNOSTIC

Tumor <4 cm, contralateral gland normal, circumscribed tumor, and other benign imaging characteristics

ADDITIONAL EVALUATION

Asymmetric cortisol production

PRIMARY TREATMENT

Adrenalectomy, laparoscopic preferred
Postoperative corticosteroid supplementation until hypothalamic-pituitary-adrenal (HPA) axis recovery

Tumor <4 cm, benign imaging characteristics, and contralateral gland abnormal

Adrenal vein sampling for cortisol

Symmetric cortisol production

Medical management of hypercortisolism from presumed multinodular hyperplasia of the adrenal with ketoconazole, mitotane

Tumor >4 cm or inhomogeneous, irregular margins, local invasion, or other malignant imaging characteristics

CT or MRI of chest, abdomen, and pelvis to evaluate for metastases and local invasion

Apparent localized disease, locally resectable disease, or regionally advanced disease

Adrenalectomy for suspected carcinoma (laparoscopic generally not appropriate)

Metastatic disease

Bilateral adrenalectomy if severe Cushing’s syndrome and medical failure

ACTH-independent Cushing’s syndrome

ACTH-dependent Cushing’s syndrome

Assess and treat for pituitary ACTH production or ectopic sources of ACTH production

Note: All recommendations are category 2A unless otherwise indicated.
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See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

Consider octreotide or lanreotide for symptom control, if somatostatin receptor scintigraphy is positive.

May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.

See Adrenal Carcinoma (AGT-5)
#### Adrenal Gland Tumors

**CLINICAL DIAGNOSIS**

- **Benign-appearing adenoma (<4 cm) by CT\(^c\) or MRI criteria or Myelolipoma by radiographic features (any size) without symptoms**
  - **Additionnal Evaluation:**
    - **Unchanged** → **No further follow-up**
    - **Enlarging** → **Consider adrenalectomy or Short-interval follow-up**
  - **Primary Treatment\(^i\)**

- **Non-functioning tumor**
  - **Benign-appearing adenoma of intermediate size (4–6 cm) by CT\(^c\) or MRI criteria**
    - **Additionnal Evaluation:**
      - **Repeat imaging in 3–6 mo**
    - **Primary Treatment\(^i\)**

- **Suspected carcinoma**
  - **CT or MRI of chest, abdomen, and pelvis to evaluate for metastases and local invasion**
  - **Intermediate-size tumor (4–6 cm) with aggressive features\(^l\)**
    - **Adrenalectomy for suspected carcinoma\(^m\)**
      - **See Adrenal Carcinoma (AGT-5)**
  - **Large tumor (>6 cm) with aggressive features**
    - **See Adrenal Carcinoma (AGT-5)**

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---

\(^c\)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.)

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

\(^i\)AGgressive features such as inhomogeneous, irregular margins, and local invasion.

\(^m\)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.
### Adrenal Gland Tumors

#### ADRENAL CARCINOMA

**Localized disease**
- Resect tumor and adjacent lymph nodes
  - Open adrenalectomy recommended

**Metastatic disease**
- Consider observation with CT or MRI 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, preferably in clinical trial
  - Cisplatin or carboplatin + etoposide ± doxorubicin ± mitotane (life-long hydrocortisone replacement may be required)
  - Streptozocin ± mitotane (life-long hydrocortisone replacement may be required)
  - Mitotane monotherapy (life-long hydrocortisone replacement may be required)

#### TREATMENT

- Consider external-beam RT to tumor bed
- Consider adjuvant mitotane therapy (category 3)
- 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.

#### FOLLOW-UP

- Every 3–12 mo up to 5 y (after 5 y as clinically indicated)
  - Consider CT or MRI and biomarkers, if tumor initially functional

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1. See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
2. May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.
3. Cross-sectional imaging to stage disease.
4. Increased risk for local recurrence and peritoneal spread when done laparoscopically.
5. 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.
6. Mitotane may have more benefit for control of hormone symptoms than control of tumor.
8. High-risk local recurrence features include: positive margins, rupture of capsule, large size, and high grade.
<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EVALUATION&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>PRIMARY 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>• Plasma free or 24-hour urine fractionated metanephrines&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
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<td></td>
<td>• Contrast-enhanced chest/abdominal/pelvic multiphasic CT or MRI</td>
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<td></td>
<td>• Genetic counseling recommended&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>As appropriate, if metastatic disease suspected:</td>
<td></td>
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<tr>
<td></td>
<td>• MIBG scan</td>
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<td>• Somatostatin receptor scintigraphy</td>
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<td>• FDG-PET/CT</td>
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<tr>
<td></td>
<td>• Bone scan, if bone symptoms</td>
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</tbody>
</table>

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

<sup>b</sup>See *Principles of Biochemical Testing (NE-B)*.

<sup>c</sup>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.

<sup>d</sup>For cervical paraganglioma, consider measuring serum and/or 24-hour urine fractionated catecholamines (for dopamine).

<sup>e</sup>Genetic counseling and genetic testing are recommended when appropriate. A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. Certain genetic variants may require more frequent follow-up. (See Discussion)

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**Pheochromocytoma/Paraganglioma**

### PRIMARY TREATMENT

**Resectable**
- Consider adding:
  - Dihydropyridine calcium channel blockade
  - Beta blockade
  - Methyltyrosine
- Continue medical therapy for secreting tumors and
- Radiation therapy ± cytoreductive (R2) resection, when possible
- Continue medical therapy for secreting tumors and
- Cytoreductive (R2) resection, when possible
- Clinical trial or
- Systemic chemotherapy (e.g., CVD [cyclophosphamide, vincristine, and dacarbazine] or temozolomide) or
- 131I-MIBG (requires prior positive MIBG scan with dosimetry)

**Locally unresectable**
- Resection (laparoscopic preferred when safe and feasible)

**Distant metastases**
- Alpha blockade with volume repletion and high salt diet for 7–14 days or until stable
- Consider adding:
  - Dihydropyridine calcium channel blockade
  - Beta blockade
  - Methyltyrosine

### SURVEILLANCE

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

- **>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 FDG-PET/CT

---

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---

**b** See Principles of Biochemical Testing (NE-B).

**e** Genetic counseling and genetic testing are recommended when appropriate.

A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. Certain genetic variants may require more frequent follow-up. (See Discussion)

**f** Alpha 1 selective receptor blockers include terazosin, doxazosin, and prazosin, and non-selective receptors include phenoxybenzamine. Therapy for 7–14 days is recommended prior to surgical therapy. Nonselective alpha blockade phenolamine (IV) can be used intraoperatively.

**g** Alpha blockade is first-line therapy for all hormonally secreting pheochromocytomas and paragangliomas. After alpha blockade, if additional blood pressure (bp) support is needed, the addition of dihydropyridine calcium channel blockers can be used. This is not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Methyltyrosine can also be used in addition to alpha blockade to stabilize bp. Beta blockade can be added to alpha blockade for tachycardia. B1 selective blockers or nonselective beta blockers can be used. Combination beta/alpha blockers are not recommended.

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

**i** Earlier, if symptoms.
Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell

**TUMOR TYPE**

| Poorly differentiated neuroendocrine carcinoma | Large or small cell carcinoma other than lung |

**EVALUATION**

- Recommended:
  - Chest/abdominal/pelvic CT
- As appropriate:
  - Brain MRI or CT
  - FDG-PET/CT scan
  - Somatostatin receptor scintigraphy
  - Plasma ACTH or other biochemical markers as clinically indicated (See NE-B)

**PRIMARY TREATMENT**

- Resectable → Resection + chemotherapy ± RT or Consider definitive chemoradiation (See NCCN Guidelines for Small Cell Lung Cancer)
- Locoregional, unresectable → RT + chemotherapy
- Metastatic → Chemotherapy

**SURVEILLANCE**

- H&P + appropriate imaging studies (MRI, CT, or FDG-PET/CT):
  - Every 3 mo for 1 y, then every 6 mo

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

**b** Earlier, if symptoms.

**c** Small cell lung cancer regimens such as cisplatin or carboplatin and etoposide are generally recommended as primary treatment. However, evolving data suggest that tumors with intermediate Ki-67 level in the 20%–50% range may not respond as well to platinum/etoposide as patients with small cell histology or extremely high Ki-67. Clinical judgment should be used. See NCCN Guidelines for Small Cell Lung Cancer.

**d** Consider octreotide or lanreotide for symptom control, if somatostatin receptor scintigraphy is positive.
Multiple Endocrine Neoplasia, Type 1

DIAGNOSIS OF OR CLINICAL SUSPICION OF MEN1

• A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors: multi-gland parathyroid hyperplasia; pancreatic NET; or pituitary tumors.\textsuperscript{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.\textsuperscript{a,b}
  ▶ Patients with MEN1 are more likely to have multiple PanNETs than those with sporadic tumors.
• For patients known or suspected to have MEN1, a clinical evaluation includes: See MEN1 Clinical Evaluation and 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\textsuperscript{a,b,c,d}
  ▶ An at-risk relative of an individual with a known germline MEN1 mutation\textsuperscript{a}
• MEN1 clinical evaluation should be offered to the following:
  ▶ Individuals with a clinical diagnosis or suspicion of MEN1 even with a 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

\textsuperscript{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.)
\textsuperscript{d} 10% of cases have \textit{de novo} MEN1 mutations.
**Diagnosis of or clinical suspicion of MEN1 (See MEN1-1)**

### Parathyroid:
- **Recommended**
  - Serum calcium + 25-OH vitamin D
  - Biochemical evaluation as clinically indicated *(See NE-B)*
- **As appropriate**
  - Neck ultrasound
  - Parathyroid sestamibi scan

### Pancreatic neuroendocrine tumors (PanNET):
- **Recommended**
  - Biochemical evaluation as clinically indicated *(See NE-B)*
  - Multiphasic CT or MRI
- **As appropriate**
  - EUS
  - Somatostatin receptor scintigraphy

### Pituitary:
- **Recommended**
  - Pituitary MRI
  - Biochemical evaluation as clinically indicated *(See NE-B)*

### Bronchial/Thymic:
- **Multiphasic CT or MRI**
- **Biochemical evaluation as clinically indicated *(See NE-B)*

### TREATMENT
- **Parathyroid:** Subtotal parathyroidectomy ± cryopreservation of parathyroids ± thymectomy or Total parathyroidectomy with autotransplantation ± cryopreservation of parathyroids ± thymectomy
- **Pancreatic neuroendocrine tumors (PanNET):** See Treatment of PanNETs Specific to MEN1 Patients (MEN1-B) and See appropriate sporadic PanNET workup and treatment (PanNET-1 through PanNET-5)
- **Pituitary:** Consider referral to endocrinology for further workup
- **Bronchial/Thymic:** See appropriate bronchopulmonary/thymus workup and treatment *(NET-5)*

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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.
MEN1 SURVEILLANCE
Patients with MEN1 should be screened for all of the following tumor types:

<table>
<thead>
<tr>
<th>Parathyroid:</th>
<th>If calcium rises:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calcium annually</td>
<td>‣ Serum PTH and 25-OH vitamin D</td>
</tr>
<tr>
<td></td>
<td>‣ Reimage with neck ultrasound and/or parathyroid sestamibi scan</td>
</tr>
<tr>
<td></td>
<td>‣ Consider cross-sectional imaging (CT or MRI) of neck</td>
</tr>
</tbody>
</table>

PanNET:
• Follow previously elevated serum hormones or as symptoms indicate
• Consider cross-sectional imaging every 1–3 y
• Consider serial EUS

Pituitary:
• MRI of pituitary every 3–5 y
• Prolactin, IGF-1, and other previously abnormal pituitary hormones every 3–5 y or as symptoms indicate

Bronchial/Thymic
• Consider cross-sectional chest imaging (CT or MRI) every 1–3 y

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

See appropriate bronchial/thymic workup and treatment (NET-5)


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

- The most common MEN1 neoplasm is parathyroid hyperplasia (affecting 98% of patients), followed by islet cell tumors of the pancreas (50%), pituitary adenomas (35%), and/or lung/thymus carcinoid tumors (10%).
- Type 2 gastric carcinoid tumors occur frequently in MEN1 patients with gastrinoma.
- A higher incidence of adrenal tumors is also observed in MEN1.
- Hyperparathyroidism is usually treated first in MEN-1 patients with hyperparathyroidism and pancreatic neuroendocrine tumors.


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.
TREATMENT OF PanNETs SPECIFIC TO MEN1 PATIENTS

- 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. The role of surgery remains controversial in patients with multifocal tumors.
- 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:
  - Symptomatic functional tumors refractory to medical management
  - 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.

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.
DIAGNOSIS OF OR CLINICAL SUSPICION OF MEN2

- MEN2 is subdivided into MEN2A and MEN2B. Medullary thyroid cancer (MTC) occurs in nearly all patients with 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 tumors (MTC, pheochromocytoma, or hyperparathyroidism) in a single individual or in first-degree relatives.
  - 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, “marfanoid” body habitus, or inability to cry tears.

- 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.
  - An at-risk relative of an individual with a known germline RET mutation.
    - Genetic testing of at-risk family members at a very early age. 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 or if RET genetic testing has not been performed in the affected or at-risk family member.

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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.
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 + 25-OH vitamin D
  - Biochemical evaluation as clinically indicated (See NE-B)
- As appropriate
  - Neck ultrasound
  - Parathyroid sestamibi scan

**Pheochromocytoma:**
- Recommended:
  - Biochemical evaluation (See NE-B)
  - MRI or multiphasic CT of abdomen
- As appropriate:
  - MIBG scan
  - Somatostatin receptor scintigraphy

**Treatment**

See NCCN Guidelines for Thyroid Carcinoma

**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.
TUMORS IN PATIENTS WITH MEN2

• The most common MEN2A neoplasm is medullary carcinoma of the thyroid (affecting 98% of patients), followed by adrenal pheochromocytoma (50%), and/or parathyroid hyperplasia (25%).¹

• The most common MEN2B neoplasm is medullary carcinoma of the thyroid (98%), followed by mucosal neuroma or intestinal ganglioneuroma (95%), adrenal pheochromocytoma (50%), and/or parathyroid hyperplasia (<1%).¹

• Other physical exam findings for MEN2 patients include:
  ▶ Ectopic lenses (type 2B)
  ▶ Marfanoid features (type 2B)
  ▶ Lichen planus amyloidosis (type 2A)
  ▶ Hirschsprung’s disease (megacolon)
    ◊ Hirschsprung’s disease is found in 2%–5% of MEN2A neoplasms and familial medullary thyroid cancers only.

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>Gastroenteropancreatic (GEP) NETs</th>
<th>Lung and Thymus</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade (G1)</td>
<td>&lt;2 mitoses/10 HPF AND/OR &lt;3% Ki-67 index</td>
<td>&lt;2 mitoses/10 HPF AND/OR no necrosis</td>
<td>Well-differentiated NET</td>
</tr>
<tr>
<td>Intermediate Grade (G2)</td>
<td>2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index</td>
<td>2–10 mitoses/10 HPF AND/OR foci of necrosis</td>
<td>Well-differentiated NET</td>
</tr>
<tr>
<td>High Grade (G3)</td>
<td>&gt;20 mitoses/10 HPF AND/OR &gt;20% Ki-67 index</td>
<td>&gt;10 mitoses/10 HPF</td>
<td>Poorly differentiated neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

Table 1 should be used as a general guide. Definitions vary between lung, thymus, and GEP-NETs in some classification systems. It is recognized that occasionally a morphologically “well-differentiated” NET may have a proliferation index by Ki-67, which technically falls into the “high-grade” category by this measure alone. Clinical judgment should be used in such discordant cases. In general, this discordance should not cause a reclassification of a well-differentiated NET as a “poorly differentiated NEC.” In these cases, the tumor should be reported as a well-differentiated NET (so-called “atypical carcinoid” terminology in lung and thymus) with the specific mitotic rate and Ki-67 proliferation index included in the report as additional information (See NE-A 3 of 4).

Functional status

- 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, 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.

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 CD56 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 for GEP NETs 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.\(^1,10\)
Mitotic rate

- Mitotic rate 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.¹
- Note that in cases where an accurate mitotic rate is precluded by inadequate tissue, such as in small biopsy samples including 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 used to assign classification.¹¹
- It is recognized that occasionally a morphologically “well-differentiated” NET may have a proliferation index by Ki-67, which technically falls into the “high-grade” category by this measure alone. Clinical judgment should be used in such discordant cases. In general, this discordance should not cause a reclassification of a well-differentiated NET as a “poorly differentiated NEC.” In these cases, the tumor should be reported as a well-differentiated NET (so-called “atypical carcinoid” terminology in lung and thymus) with the specific mitotic rate and Ki-67 proliferation index included in the report as additional information.
- The pathologist should report the actual parameters used to assign grade (ie, mitotic rate, proliferation index) so clinicians have the necessary information to make informed treatment decisions.
- Although the 2004 WHO³ 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 suggest that Ki-67 proliferation rates of <20% exclude small cell lung carcinoma.¹²
PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

REFERENCES


**PRINCIPLES OF BIOCHEMICAL TESTING (1 OF 3)**

- Some neuroendocrine tumors can secrete specific neuroendocrine hormones. Hormonal workup should be guided by the presence of symptoms of the excess hormone. Screening for hormones in asymptomatic individuals is not routinely required.
- Proton pump inhibitors are known to cause false elevations in serum gastrin and chromogranin A.
- If Multiple endocrine neoplasia type 2 (MEN2) is suspected, then patients should be evaluated for pheochromocytoma/paraganglioma prior to any procedures.\(^9\)

<table>
<thead>
<tr>
<th>Neuroendocrine Tumors of Gastrointestinal Tract, Lung, and Thymus (carcinoid tumors)</th>
<th>Location</th>
<th>Symptoms</th>
<th>Testing</th>
</tr>
</thead>
</table>
| Primary tumors in GI tract (ileum, appendix, rectum) | • Primary tumors in the GI tract usually not associated with symptoms of hormone secretion unless extensive liver metastasis.  
• Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction.  
• Bronchial/thymic tumors may be associated with Cushing's syndrome. | Chromogranin A (category 3)  
• 24-hour urine 5-HIAA  
› Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts.  
• ACTH (bronchial/thymic) | |

| Pancreatic NET (see subtypes below) | Pancreas | Depends on hormone secreted, can be clinically silent | Serum pancreatic polypeptide (category 3)  
• Serum chromogranin A (category 3) |

| Insulinoma | Pancreas | Hypoglycemia | Serum insulin  
• Pro-insulin  
• C-peptide |

| VIPoma | Most common in pancreas, can be extra pancreatic | Diarrhea, hypokalemia | Serum VIP |

| Glucagonoma | Pancreas | Flushing, diarrhea, hyperglycemia, dermatitis | Serum glucagon |

| Gastrinoma | Pancreas or duodenum | Gastric ulcers, duodenal ulcers, diarrhea | Serum gastrin* |

*Basal, stimulated as indicated.

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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>Location</th>
<th>Symptoms</th>
<th>Testing</th>
</tr>
</thead>
</table>
| Pheochromocytoma/Paraganglioma   | Hypertension, tachycardia, sweating, syncope  | • Plasma free or 24-hour urine fractionated metanephrines**  
• Cervical paragangliomas: consider serum or urine dopamine or methoxytyramine (the metabolite of dopamine)** |
| Pituitary Tumor                  | May be asymptomatic, depends on the hormone secreted | • Serum IGF-1 (category 2B)  
• Serum prolactin  
• LH/FSH  
• Alpha subunits  
• TSH (free T4) |
| Cushing's Syndrome               | Central weight gain, striae, hypertension, hyperglycemia, depression, hirsutism | • Screen for hypercortisolemia with 1 of the following tests:  
  › 1 mg overnight dexamethasone suppression test  
  › 2–3 midnight salivary cortisols  
  › 24-hour urinary free cortisol  
• Confirmatory testing if positive  
• If hypercortisolemic, then serum ACTH (8 am cortisol) should be done |
| Hyperaldosteronism               | Hypertension, hypokalemia                      | • Serum aldosterone/plasma renin activity ratio  
• Confirmatory testing if positive |

PRINCIPLES OF BIOCHEMICAL TESTING (3 OF 3)

References


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 pancreatoduodenectomy (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 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 pancreateoduodenectomy 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 and be discontinued the next day if there are no issues.

- 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.

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 SYSTEMIC ANTI-TUMOR THERAPY
Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

- Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for carcinoid tumors.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for carcinoid tumors.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.

Systemic Treatment Options for Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

- Somatostatin analogues (somatostatin analog dosing also applicable for locoregional disease)
  - Octreotide* LAR 20–30 mg intramuscular injection, monthly\(^1\)
  - Lanreotide 120 mg deep subcutaneous injection, monthly\(^2\)

- Consider the following systemic therapies (listed in alphabetical order)
  - Cytotoxic chemotherapy (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.)
  - Everolimus\(^3\) (category 3)
  - Interferon alfa-2b\(^4\) (category 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.

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 SYSTEMIC ANTI-TUMOR THERAPY
Unresectable and/or Metastatic Pancreatic Neuroendocrine Tumors

- Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for pancreatic neuroendocrine tumors.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms and complications with octreotide or lanreotide, see PanNET-1 through PanNET-5.

Systemic Treatment Options for Unresectable and/or Metastatic Pancreatic Neuroendocrine Tumors

- Somatostatin analogues (somatostatin analog dosing also applicable for locoregional disease)
  - Octreotide*:† LAR 20–30 mg intramuscular injection, monthly
  - Lanreotide 120 mg deep subcutaneous injection, monthly
- Everolimus5 10 mg by mouth, daily
- Sunitinib6 37.5 mg by mouth, daily
- Cytotoxic chemotherapies:
  - There is no panel consensus on which cytotoxic chemotherapy regimen is best. The following anticancer agents can be considered in patients with bulky, symptomatic, and/or progressive disease: 5-FU, capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide. (See Discussion for details.)
  - Commonly used regimens include:
    - Temozolomide/capecitabine
    - 5-FU/doxorubicin/streptozocin (FAS)
    - Streptozocin/doxorubicin
    - Streptozocin/5-FU

*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.
†Although no randomized studies to date have directly shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial showed an improvement in its primary endpoint of time to tumor progression in carcinoid tumors of the midgut. Lanreotide and octreotide share the same mechanism of action, and the panel believes that either lanreotide or octreotide are appropriate options for tumor control in this setting.

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.


## 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

<table>
<thead>
<tr>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<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>
<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>

### Duodenum/Ampulla/Jejunum/Ileum

<table>
<thead>
<tr>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<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 For any T, add (m) for multiple tumors</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>

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

TNM

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Description</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td>Stage 0 Tis N0 M0</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>Stage I T1 N0 M0</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa and size 2 cm or less</td>
<td>Stage IIA T2 N0 M0</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor size less than 1 cm in greatest dimension</td>
<td>Stage IIB T3 N0 M0</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor size 1–2 cm in greatest dimension</td>
<td>Stage IIIA T4 N0 M0</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa</td>
<td>Stage IIIB Any T N1 M0</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues</td>
<td>Stage IV Any T Any N M1</td>
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</tbody>
</table>

**Regional Lymph Nodes (N)**

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

**Distant Metastases (M)**

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

For any T, add (m) for multiple tumors

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

### Pancreatic Neuroendocrine Tumors

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

Primary Tumor (T)

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ*
- **T1**: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- **T2**: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- **T3**: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- **T4**: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

Distant Metastases (M)

- **M0**: No distant metastases
- **M1**: Distant metastasis

* This also includes the “PanInIII” classification.

### ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
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<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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.
### Staging

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

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

#### Appendiceal Carcinoid

**TNM**

**Primary Tumor (T)**

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **T1**: Tumor 2 cm or less in greatest dimension
- **T1a**: Tumor 1 cm or less in greatest dimension
- **T1b**: Tumor more than 1 cm but not more than 2 cm
- **T2**: Tumor more than 2 cm but not more than 4 cm or with extension to the cecum
- **T3**: Tumor more than 4 cm or with extension to the ileum
- **T4**: Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle

**Regional Lymph Nodes (N)**

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

**Distant Metastases (M)**

- **M0**: No distant metastases
- **M1**: Distant metastasis

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

- **Stage I**: T1 N0 M0
- **Stage II**: T2, T3 N0 M0
- **Stage III**: T4 N0 M0
- **Stage IV**: Any T Any N M1

**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.

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.

*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.

Continued on next page
# Staging

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

## Adrenal

<table>
<thead>
<tr>
<th>TNM</th>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor (T)</td>
<td>Stage I</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 5 cm, no extra-adrenal invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size with local invasion, but not invading adjacent organs*</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with invasion of adjacent organs*</td>
</tr>
<tr>
<td>Regional Lymph Nodes (N)</td>
<td>Stage II</td>
</tr>
<tr>
<td>NX</td>
<td>Nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>T4</td>
<td>N1</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

* 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.
Neuroendocrine Tumors

Discussion

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 tumors (most commonly arising in the lungs and bronchi (so-called bronchopulmonary), small intestine, appendix, rectum, and thymus) and pancreatic neuroendocrine tumors. Other less common neuroendocrine tumors include those arising in the parathyroid, thyroid, adrenal, and pituitary glands.

An analysis of the 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 incidence of neuroendocrine tumors is increasing, and that the prevalence of individuals with neuroendocrine tumors in the United States may exceed 100,000. Other independent analyses of the SEER database also found that the incidence of gastrointestinal (GI) neuroendocrine tumors increased from 1975 to 2008. The reasons for this increase are unclear, although it seems likely that improved diagnosis and classification is one factor.

Most neuroendocrine tumors seem to be sporadic, and 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 (MEN) types 1 and 2. Multiple endocrine neoplasia type 1 (MEN1), associated with mutations in the menin gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands. Multiple endocrine neoplasia type 2 (MEN2), 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. These 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.

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), and medical, radiation, and surgical oncologists.

These 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, although poorly differentiated/high-grade/large or small cell carcinomas are also addressed (see Poorly Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas, below). Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Neuroendocrine Tumors, an electronic search of the PubMed database...
Histologic Classification

Neuroendocrine tumors are classified histologically based on tumor differentiation (well or poorly differentiated) and tumor grade (grades 1–3). Most neuroendocrine tumors fall into 3 broad histologic categories: well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); and poorly differentiated, high-grade (G3).

Tumor differentiation and tumor grade often correlate with mitotic count and Ki-67 proliferation index. In fact, most commonly used histologic classification schemes, including both the European Neuroendocrine Tumor Society 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. In most cases, well-differentiated, low-grade tumors have a mitotic count of less than 2/10 high-power field (HPF) and/or a Ki-67 index of less than 3%. Well-differentiated, intermediate-grade tumors usually have a mitotic count of 2 to 20/10 HPF and/or a Ki-67 index of 3% to 20%. In high-grade tumors, the mitotic count usually exceeds 20/10 HPF and/or the Ki-67 index exceeds 20%.

Grade is generally defined by mitotic count and/or Ki-67 index, whichever is higher. In some cases, however, tumors may not fall clearly into one category. For example, a morphologically well-differentiated neuroendocrine tumor with a low mitotic index may have a Ki-67 proliferation index that falls into the high-grade category. While technically classified as a high-grade tumor, clinical judgment should be used in making treatment decisions for such cases. A key recommendation is that tumor differentiation, mitotic rate, and Ki-67 index should all be included in the pathology report. Doing so allows the...
treating physician to factor these data into the clinical picture to make appropriate treatment decisions.

The classification of lung and thymus carcinoids varies from that of gastroenteropancreatic neuroendocrine tumors in some classification systems, and in particular does not include Ki-67 and includes the assessment of necrosis. Well-differentiated neuroendocrine tumors of the lung and thymus are either considered typical (low-grade, <2 mitoses/10 HPF and no necrosis) or atypical (2–10 mitosis/10 HPF and/or foci of necrosis).

Poorly differentiated neuroendocrine carcinomas are of either small cell or large cell cytology, with greater than 10 mitoses/10 HPF. Considerable debate remains as to the most appropriate Ki-67 proliferative threshold for the determination of tumor grade and consequent treatment decisions. A retrospective database review of 252 patients with high-grade GI neuroendocrine carcinoma suggested that platinum-based chemotherapy is most active in those with a Ki-67 index of greater than or equal to 55%. These results suggest that a higher Ki-67 cutoff than is currently recommended may be more appropriate to classify tumors as high-grade. Conversely, for low-grade tumors, some studies have suggested that the currently accepted cutoff may be too low. An analysis of data from 274 patients with pancreatic neuroendocrine tumors found that a 5% Ki-67 cutoff (rather than 2%) was the optimal prognostic indicator.

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 retrospective analysis of 425 patients with pancreatic neuroendocrine tumors treated at the Moffitt Cancer Center between 1999 and 2010 validated this system, with 5-year overall survival rates of 92%, 84%, 81%, and 57% for stages I through IV, respectively \((P < .001)\).\(^3\) Although 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.\(^3\)\(^9\),\(^4\)\(^0\) 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%.\(^4\)\(^0\)

### Pathologic Reporting

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 included in the pathology report; some studies have suggested that these factors may also have prognostic significance.\(^4\)\(^1\),\(^4\)\(^2\)

Whether or not tumors are associated with symptoms of hormone hypersecretion (“functioning” or “non-functioning”) is in general a part of the clinical rather than histologic diagnosis. Thus, functional status is usually not 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.

### Other Potential Prognostic Markers

Chromogranin A is a secreted protein that may be elevated in patients with neuroendocrine tumors; elevated levels have been associated with poorer prognosis. The molecular basis of neuroendocrine tumors remains poorly understood, and additional molecular predictors of outcome remain investigational. A recent study found that overexpression of mammalian target of rapamycin (mTOR) or its downstream targets was associated with shorter overall survival in 195 neuroendocrine tissue samples (15% were located in the pancreas; 85% were GI carcinoids).\(^4\)\(^3\) Small bowel carcinoid tumors have been found to have recurrent mutations in the cyclin-dependent kinase inhibitor, CDKN1B (p27),\(^4\)\(^4\) and loss of CDKN1B expression has been reported to be an adverse prognostic factor in gastroenteropancreatic neuroendocrine tumors.\(^4\)\(^5\) Circulating tumor cells (CTCs) have also been studied as possible prognostic markers, based on the idea that tumor cells in the blood would be indicative of more disseminated disease. A recent study found that the presence of greater than or equal to 1 CTC in 7.5 mL of blood was independently associated with worse progression-free survival (PFS) and overall survival in patients with varyingly pre-treated metastatic neuroendocrine tumors from various primary sites.\(^4\)\(^6\)

More research is required, however, before these and other new molecular assays are routinely used in the clinic. A multinational consensus meeting of experts concluded that, to date, no single currently available biomarker is sufficient as a diagnostic, prognostic, or predictive marker in patients with neuroendocrine tumors.\(^4\)\(^7\)

### Sporadic Neuroendocrine Tumors

#### Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

Approximately one-third of carcinoid tumors arise in the lungs or thymus, and two-thirds arise in the GI tract. Sites of origin within the GI tract include the stomach, small intestine, appendix, and rectum.\(^1\) 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).

Neuroendocrine tumors of the GI tract, lung, or thymus may secrete various hormones and vasoactive peptides. Bronchial and thymic neuroendocrine tumors have been associated with adrenocorticotropic hormone (ACTH) production and are a cause of Cushing’s syndrome.48,49 Neuroendocrine 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.50 Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.51

The metabolic products released by intestinal neuroendocrine tumors are rapidly destroyed by liver enzymes in the portal circulation. Thus, the classical syndrome, occurring in approximately 8% to 28% of patients with neuroendocrine tumors,52,53 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.

These 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 Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

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 CT and MRI. Neuroendocrine tumors of the GI tract, lung, and thymus are highly vascular and can appear isodense with liver on conventional CT scan, depending on contrast phase. Multiphase CT or MRI scans should therefore be used for evaluation of liver metastasis. Chest CT is also recommended as appropriate to assess for lung metastases. Because most neuroendocrine tumors express high-affinity receptors for somatostatin,50,54 radiolabeled somatostatin receptor scintigraphy, performed using the radiolabeled somatostatin analog [111In-DTPA]-octreotide, may also be used in the initial evaluation of patients with neuroendocrine tumors. Additional recommendations vary by disease site and include colonoscopy and small bowel imaging with CT enterography or capsule endoscopy as appropriate for jejunal, ileal, and colonic neuroendocrine tumors; endoscopic ultrasound (EUS) and/or esophagogastroduodenoscopy (EGD) as appropriate for duodenal and gastric neuroendocrine tumors; proctoscopic examination for rectal neuroendocrine tumors; and bronchoscopy as appropriate for bronchopulmonary and thymic neuroendocrine tumors.

Biochemical evaluation can also be helpful in the initial diagnostic evaluation, particularly in patients who have symptoms that are suggestive of hormone hypersecretion. Evaluation of serotonin secretion, using a 24-hour urine collection for 5-HIAA, is generally recommended in patients with metastatic lung or GI carcinoid tumors, particularly if carcinoid syndrome, manifested by symptoms of flushing and diarrhea, is suspected. Screening for hormones in asymptomatic individuals is not routinely recommended. Chromogranin A is sometimes used as a biochemical marker in non-functioning tumors (category 3). Whereas one meta-analysis calculated the sensitivity and specificity of chromogranin A to be 73% and 95%, respectively, for diagnosis of neuroendocrine tumors,55 others have questioned its value. Chromogranin A is elevated in patients with renal or hepatic impairment and in patients receiving proton pump inhibitors, and in general should...
not be relied upon in isolation as a diagnostic test. A workup for Cushing’s syndrome (discussed in Evaluation and Treatment of Cushing’s Syndrome, below) may also be indicated in cases of bronchopulmonary or thymic neuroendocrine tumors if signs and symptoms of hypercortisolemia are suspected. Details of the evaluation and diagnosis of a patient with Cushing’s syndrome from a bronchial neuroendocrine tumor have recently been published.56

Management of Locoregional Disease
The management of locoregional neuroendocrine tumors of the GI tract, lung, and thymus depends on tumor size, primary site, and the general condition of the patient. Resection is the primary treatment approach for most localized carcinoid tumors. Although symptoms of hormone hypersecretion are more common in patients with metastatic disease, for patients with locoregional disease and symptoms of hormone hypersecretion, symptom control with octreotide or lanreotide is paramount (see Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus, below). Specific recommendations for management of neuroendocrine tumor subtypes are described herein.

Gastric Neuroendocrine Tumors
Three types of gastric neuroendocrine tumors are recognized: type 1 (associated with chronic atrophic gastritis or high gastric pH); type 2 (associated with antrum-sparing type A Zollinger-Ellison syndrome); and type 3 (sporadic, unifocal, unassociated with either atrophic gastritis or Zollinger-Ellison syndrome).57 Types 1 and 2 gastric neuroendocrine tumors are both associated with hypergastrinemia; the major difference between them is that patients with type 1 gastric neuroendocrine tumors generally have antrum-sparing atrophic gastritis with a loss of the usual negative feedback loop on the gastrin-producing cells of the antrum by acid, resulting in hypergastrinemia and excess stimulation of the endocrine cells of the fundus, and patients with type 2 gastric neuroendocrine tumors have evidence of acid hypersecretion secondary to gastrinoma (Zollinger-Ellison syndrome).57 Type 1 gastric neuroendocrine tumors pursue an indolent course, with a rate of metastases of <5%. Evidence suggestive of type 1 disease includes a histologic diagnosis of atrophic gastritis on gastric biopsy, elevated gastric pH, vitamin B12 deficiency, and positive anti-intrinsic factor antibodies (not all tests need to be done to make a diagnosis). Type 2 tumors are rare and occur in the setting of gastrinoma in which elevated gastrin levels produce gastric neuroendocrine hyperplasia and multifocal gastric neuroendocrine tumors.

Annual endoscopic surveillance and endoscopic resection of prominent tumors is recommended for patients with locoregional type 1 gastric neuroendocrine tumors. Antrectomy can be considered if gastric tumors are increasing significantly in size or number. For locoregional type 2 gastric neuroendocrine tumors, the primary gastrinoma should, in general, be resected. If the primary tumor is not resected, endoscopic surveillance and endoscopic resection of prominent gastric carcinoid tumors should be considered and/or octreotide or lanreotide can be given. Patients with nonmetastatic gastric neuroendocrine tumors and normal gastrin levels (type 3) often have more aggressive tumors and are usually treated with radical resection of the tumor with regional lymphadenectomy. For early stage, smaller tumors, endoscopic or wedge resection can be considered if there is no evidence of lymphadenopathy on EUS.58 Endoscopic resection should be reserved for small (<1 cm), superficial, low-grade tumors.

Thymic Neuroendocrine Tumors
Localized and locoregional neuroendocrine tumors in the thymus are treated with surgical resection, generally without adjuvant therapy. After incomplete resection of locoregional disease, however, radiation
therapy (RT) and/or chemotherapy is recommended (category 3). If chemotherapy is offered, capecitabine or 5-FU at radiosensitizing doses may be considered in patients with low-grade tumors. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.

**Bronchopulmonary Neuroendocrine Tumors**

For localized or locoregional bronchopulmonary tumors, please refer to the Lung Neuroendocrine Tumors algorithm in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer (to view the most recent version of these guidelines, visit the NCCN website at [www.NCCN.org](http://www.NCCN.org)).

**Neuroendocrine 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 pancreatoduodenectomy are other options for primary treatment of nonmetastatic duodenal neuroendocrine tumors. If endoscopic resection was performed, follow-up upper endoscopy (EGD) should be performed as appropriate.

For patients presenting with tumors in the jejunum, ileum, or colon, surgical resection(s) 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. In addition, the proximity to or involvement of the superior mesenteric artery and superior mesenteric vein should be assessed during surgery.

**Appendiceal Neuroendocrine Tumors**

Most appendiceal neuroendocrine tumors are identified incidentally, during appendectomy performed for appendicitis. Most appendiceal neuroendocrine tumors have well-differentiated histology, and for most appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient because metastases are uncommon. However, some controversy exists regarding the management of appendiceal neuroendocrine tumors measuring less than 2 cm with more aggressive histologic features. A population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal neuroendocrine tumors 2 cm or smaller. Some NCCN Member Institutions thus consider more aggressive treatment for 1- to 2-cm tumors with poor prognostic features, such as lymphovascular or mesoappendiceal invasion or atypical histologic features. In a retrospective case series that included 79 patients with appendiceal carcinoid tumors, small-vessel invasion was a risk factor for metastases in patients with tumors <2 cm.

Patients with an incomplete resection or tumors larger than 2 cm are at risk for locoregional or distant metastases. These patients should be staged with abdominal/pelvic CT or MRI scans. If no distant disease is identified, they should undergo reexploration with a right hemicolectomy. Additionally, a small proportion of appendiceal neuroendocrine tumors may also contain evidence of adenocarcinoma (ie, “adenocarcinoid” or “goblet cell carcinoid”). These tumors should be managed according to the NCCN Guidelines® for Colon Cancer (available at [www.NCCN.org](http://www.NCCN.org)).

**Neuroendocrine 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 minimally invasive (T1), endoscopic or transanal excision is recommended. Given the higher risk of invasion...
with larger tumors, examination under anesthesia and/or EUS before the procedure should be considered for tumors 1 to 2 cm in size. A recent retrospective review found that metastases were present in 66% of 87 patients with well-differentiated rectal neuroendocrine tumors of 11 to 19 mm.63

Tumors larger than 2 cm, those with invasion of the muscularis propria, or those associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection.64

**Surveillance of Resected Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

Surveillance of bronchopulmonary and GI neuroendocrine tumors should include complete patient history and physical examination (H&P) and consideration of multiphasic CT or MRI (usually abdominal and/or pelvic). Most patients with neuroendocrine tumors of the jejunum/ileum/colon, duodenum, rectum, and thymus, and type 3 gastric neuroendocrine tumors with normal gastrin levels should be reevaluated 3 to 12 months after resection (earlier if the patient is symptomatic) and then every 6 to 12 months for up to 10 years.

Relevant biochemical evaluations can also be performed based on pre-resection findings. Chromogranin A may be used as a tumor marker (category 3); although not diagnostic, elevated levels have been associated with recurrence.65,66 In addition, an analysis of a large prospective database showed that chromogranin A levels elevated twice the normal limit or higher were associated with shorter survival times for patients with metastatic neuroendocrine tumors (HR, 2.8; 95% CI, 1.9–4.0; P < .001).67 Chromogranin A levels can be elevated in several 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 looks stable on 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 metastatic small-intestinal neuroendocrine tumors. During monitoring of patients after treatment of a carcinoid tumor, decreasing levels of 5-HIAA indicate a response to treatment, whereas increasing or excessive concentration indicates that the treatment has not been successful. However, a patient with symptoms may still have a neuroendocrine 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/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts for 48 hours before the start of and during urine collection. 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 is not routinely recommended for surveillance after 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 GI neuroendocrine 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 with rectal MRI or EUS are recommended for rectal tumors that are
between 1 and 2 cm, 6 and 12 months after primary therapy, and then as clinically indicated.

For appendiceal tumors 2 cm or smaller without aggressive features, follow-up examinations are done as clinically indicated. Patients with small, well-differentiated appendiceal neuroendocrine tumors are at very low risk for recurrence, and some institutions recommend no follow-up in these patients. Other institutions recommend a follow-up examination 1 year after simple appendectomy and then with decreasing frequency. However, because recurrences have rarely been reported even after resection of small appendiceal tumors, any patients with symptoms of hormone hypersecretion should be more fully evaluated.

Follow-up recommendations also differ to some extent for hypergastrinemic patients with type 1 or 2 gastric neuroendocrine tumors. For these patients, follow-up endoscopies are recommended every 6 to 12 months for the first 3 years and annually thereafter if no evidence of progression is seen. Because gastrin levels remain persistently high in patients with atrophic gastritis, gastrin levels are generally uninformative in patients with type 1 gastric neuroendocrine tumors. 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 neuroendocrine tumors if new lesions or increasing tumor burden is observed.

**Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

Baseline imaging recommendations for patients suspected to have distant metastatic disease include multiphase technique CT or MRI. Baseline levels of chromogranin A (category 3) or 24-hour urine 5-HIAA may also be considered to monitor subsequent progression (discussed above). Somatostatin scintography can also be considered both to assess sites of metastases and to assess somatostatin receptor status if treatment with octreotide or lanreotide is being considered. The most common sites of metastases from intestinal neuroendocrine tumors include regional/mesenteric lymph nodes, liver, and bones.

**Resection of Metastatic Disease**

In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection of the primary tumor and metastases with curative intent. One study of 172 patients who underwent hepatic resection of metastatic neuroendocrine tumors showed that long-term survival can be achieved in selected cases: the reported 10-year overall survival rate was 50.4%. A recent meta-analysis reported 5-year OS rates ranging from 41% to 100% in patients undergoing hepatic resection. Most patients with resected metastatic disease, however, will eventually experience recurrence. Noncurative debulking surgery can also be considered in select cases, especially if the patient is symptomatic either from tumor bulk or hormone production.

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 these patients.

If resection is performed and future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy can be considered given the association between long-term treatment with...
Somatostatin analogs and the development of biliary symptoms and gallstones.77

**Somatostatin Analogs for Control of Symptoms and Tumor Growth**

Patients who have metastatic neuroendocrine tumors and carcinoid syndrome should be treated with octreotide or lanreotide.77 The long-acting release (LAR) formulation of octreotide is commonly used for the chronic management of symptoms in patients with carcinoid syndrome. Standard doses of octreotide LAR are 20 to 30 mg intramuscularly every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels are not achieved for 10 to 14 days after LAR injection. Short-acting octreotide (usually 150–250 mcg subcutaneously 3 times daily) can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.78-80

Lanreotide has a similar mechanism of action as octreotide, but is administered as a deep subcutaneous injection. Several studies have shown it to be effective at controlling symptoms of hormone secretion in patients with carcinoid tumors, gastrinomas, or tumors secreting vasoactive intestinal peptide (VIPomas).81-85 The multinational phase III ELECT trial randomized 115 patients with carcinoid syndrome who were either naïve to or responsive to octreotide to receive 120 mg of lanreotide or placebo and evaluated the number of days patients required use of rescue octreotide.86 Patients in the lanreotide arm required less frequent rescue octreotide than those in the placebo arm (34% vs.49%; P = .02), supporting the use of lanreotide for symptom control.

A cardiology consultation and echocardiogram to assess whether the patient has carcinoid heart disease should also be performed every 2 to 3 years.77 Cardiac heart disease is frequent in patients with carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation.87,88 A study of 250 patients with carcinoid syndrome showed that patients with 5-HIAA levels of 300 μmol or greater (57 mg) over 24 hours and with 3 or more flushing episodes per day were more likely to have carcinoid heart disease.89

In patients who have clinically significant tumor burden or progressive disease, initiation of either octreotide or lanreotide is recommended to potentially control tumor growth if they are not already receiving it. The recommendation to consider octreotide in these patients is based on the results of the PROMID study, a placebo-controlled phase III trial of 85 patients with metastatic midgut neuroendocrine tumors, which showed median times to tumor progression of 14.3 and 6 months in the octreotide LAR and placebo groups, respectively (P = .000072).90 After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and in 37.2% of patients in the placebo group. Results of long-term survival of patients in the PROMID study were recently reported.91 After long-term follow-up, median OS was not significantly different between the arms (83.7 months in the placebo arm and 84.7 months in the octreotide arm; HR, 0.83; 95% CI 0.44–1.46; P = .51).92 However, post-study treatment included octreotide in 38 of 43 patients in the placebo arm, possibly confounding interpretation of long-term survival results.

The recommendation that lanreotide be considered for control of tumor growth in patients with clinically significant tumor burden or progressive disease is based on results of the CLARINET study. The CLARINET study randomized 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors to receive either lanreotide or placebo and followed patients for PFS. Results from this trial showed that treatment with lanreotide for 2 years resulted in an improvement in PFS over placebo (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; P < .001).93
No clear consensus exists on the timing of octreotide or lanreotide initiation in asymptomatic patients with metastatic neuroendocrine tumors and low tumor burden. Although initiation of octreotide or lanreotide can be considered in these patients, deferring initiation until evidence of tumor progression is seen may also be appropriate in selected patients.

Patients with clinically significant progression of metastatic bronchopulmonary and GI neuroendocrine tumors can pursue several other options, as discussed below.

**Hepatic-directed Therapies for Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

For patients with unresectable, hepatic-predominant, progressive disease, hepatic-directed therapies may be considered, mainly with the palliative goals of extending life and relieving hormonal symptoms.\(^{94-97}\)

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).\(^{98-102}\) For unresectable liver metastases, hepatic regional therapy (arterial embolization,\(^{103}\) chemoembolization,\(^{104-106}\) or radioembolization [category 2B])\(^ {106-113}\) is recommended.

**Everolimus for Advanced Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

For patients with progressive metastatic carcinoid tumors, everolimus can also be considered (category 3). Everolimus is an inhibitor of mTOR and was well tolerated and showed evidence of antitumor effect in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial.\(^ {114}\) In the randomized phase III RADIANT-2 trial, 429 patients with advanced neuroendocrine tumors and carcinoid syndrome were randomized to receive octreotide LAR with everolimus or placebo.\(^ {115}\) Based on central review, patients receiving octreotide plus everolimus had a median PFS of 16.4 months, compared with 11.3 months for patients receiving octreotide alone (\(P = .026\)). This difference in the primary endpoint of PFS did not, however, meet the predefined threshold for statistical significance. Adverse events associated with everolimus included stomatitis, rash, fatigue, and diarrhea.\(^ {115}\) Other side effects have also been described.\(^ {116-118}\)

A subsequent trial, RADIANT-4, was an international, double-blind, placebo-controlled, phase 3 trial that randomized 302 patients with progressive, non-functional, lung or gastrointestinal neuroendocrine tumors 2:1 to receive everolimus or placebo.\(^ {119}\) In contrast to RADIANT 2, patients in RADIANT 4 were not receiving a somatostatin analog at the time of study enrollment and concurrent somatostatin analog was not a study requirement. Median PFS was 11.0 months (95% CI, 9.2–13.3) in the everolimus arm and 3.9 months (95% CI, 3.6–7.4) in the placebo arm. The hazard ratio for progression or death was 0.48 (95% CI, 0.35–0.67; \(P < .001\)). Drug-related grade 3/4 adverse events included stomatitis (9% vs. 0%), infections (7% vs. 0%), diarrhea (7% vs. 2%), anemia (4% vs. 1%), fatigue (3% vs. 1%), and hyperglycemia (3% vs. 0%). A recent report highlights the outcomes of 169 pre-treated patients with advanced neuroendocrine tumors of the pancreas (\(n = 85\)) or other sites (\(n = 84\)) who received everolimus through a compassionate use program.\(^ {120}\) An increased risk of adverse events in patients who had received previous radiolabeled peptide therapy or chemotherapy was noted.

**Systemic Therapy for Advanced Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

**Cytotoxic chemotherapy:** The benefits associated with cytotoxic chemotherapy in patients with advanced carcinoid tumors appear, at
best, to be modest. Tumor response rates are generally low, and no PFS benefit has been clearly demonstrated.\textsuperscript{121}

Capecitabine was tested in patients with metastatic carcinoid tumors in a phase II trial; no objective responses were reported although 13 of 19 patients were reported to have experienced stable disease.\textsuperscript{122} The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23\% in patients with poorly differentiated neuroendocrine tumors and 30\% in well-differentiated disease.\textsuperscript{123} 5-FU was assessed in the phase III E1281 trial in combination with streptozocin or doxorubicin.\textsuperscript{124} Response rates in both arms were around 16\%. Dacarbazine was given following progression, with a response rate of 8\%. Responses to temozolomide in advanced carcinoid are rare.\textsuperscript{125}

A phase II trial assessed bevacizumab plus capecitabine and included 49 patients with gastrointestinal neuroendocrine tumors.\textsuperscript{126} A PFS of 23.4 months was reported, with 18\% of patients achieving a partial response and 70\% achieving stable disease.

The panel lists cytotoxic chemotherapy for neuroendocrine tumors of the GI tract, lung, and thymus as a category 3 recommendation. While some panelists believe the toxicity of systemic therapy does not warrant its wide-spread use in this population, others believe that it is an important alternative for patients without other options for treatment.

**Alpha Interferon:** Use of interferon in the setting of advanced carcinoid tumors is a category 3 recommendation. Interferon alpha has been shown in several large, non-randomized series to be associated with an antitumor effect in patients with advanced carcinoid tumors.\textsuperscript{79,127-130} In a recent, large randomized study led by the Southwest Oncology Group, treatment with alpha interferon (5 million units 3 d/wk) was compared to treatment with bevacizumab (15 mg/kg administered every 21 days) in over 400 patients with progressive neuroendocrine tumors.\textsuperscript{131} Treatment with octreotide was included in both arms of this study. In a preliminary report of the results, no significant difference in PFS was observed; however, the long PFS durations in both arms of the study (15.4 and 16.6 months for interferon and bevacizumab, respectively) suggest both drugs may be active in this setting.\textsuperscript{131} Because of its potential side effects, interferon is usually not initiated until failure of somatostatin analog treatment.\textsuperscript{121}

**Radiolabeled Somatostatin Analogs for Advanced Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus**

Several early studies initially reported that treatment with radiolabeled somatostatin analogs was associated with tumor responses in patients with advanced carcinoid tumors.\textsuperscript{132-136} A prospective phase II study of radiolabeled somatostatin analogs in 90 patients with metastatic carcinoid tumors refractory to octreotide showed that treatment was associated with improvement in symptoms; radiographic regression, however, was relatively uncommon.\textsuperscript{137} Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.\textsuperscript{138-140}

A recent prospective study randomized over 200 patients with advanced midgut neuroendocrine tumors to receive treatment with either \textsuperscript{177}Lu-DOTATATE or high-dose octreotide. Preliminary results of this study suggest that treatment with \textsuperscript{177}Lu-DOTATATE was associated with a significant improvement in PFS (not reached vs. 8.4 months; $P < .0001$).\textsuperscript{141} Objective tumor responses were observed in 19\% of patients who received \textsuperscript{177}Lu-DOTATATE. Final results of this study are awaited.
Liver Transplantation for Liver Metastases of Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus

Several series have now reported the results of liver transplantation patients with carcinoid tumors whose metastases are confined to the liver. Results from a multicenter database of 85 patients at 28 centers who underwent liver transplantation for neuroendocrine tumors were also reported. A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence. 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 the Pancreas

According to a population-based study, malignant pancreatic neuroendocrine tumors account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence. Although the peak incidence of occurrence is between ages 40 and 69 years, a significant number of patients diagnosed with pancreatic neuroendocrine tumors are younger than 35 years. 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 women and 2.6 in men. An estimated 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms. Consistent with these numbers, analysis of the NCCN Neuroendocrine Outcomes Database found that 22% of patients with pancreatic neuroendocrine tumors had a hormonal syndrome. Of these functioning tumors, up to 70% are insulinomas, and only 10% are associated with metastases. Approximately 15% are glucagonomas. Gastrinomas and somatostatinomas account for another 10%; gastrinomas and somatostatinomas (80%-90%) are associated with a relatively high risk for metastases. The remaining rare pancreatic neuroendocrine tumors include VIPomas, and the recently described cholecystokininoma (CCKoma). Pancreatic neuroendocrine tumors occurring in patients with MEN1 are typically multiple and require different treatment strategies from those used for patients with sporadic pancreatic neuroendocrine tumors, which are usually solitary (see MEN1, below). Gastrinoma and insulinoma are the most common pancreatic neuroendocrine tumors in patients with MEN1.

Evaluation of Neuroendocrine Tumors of the Pancreas

Personal and family history should be evaluated for the possibility of MEN1 (see Multiple Endocrine Neoplasia, below). The recommended evaluation also includes multiphasic CT or MRI scan. Hormone-secreting tumors may result in significant clinical symptoms even when very small, and lesion identification can be difficult. Somatostatin scintography and EUS can also be considered as appropriate. Biochemical evaluation is also often considered in patients with pancreatic neuroendocrine tumors because many pancreatic neuroendocrine tumors secrete specific hormones. Biochemical evaluation is generally guided by the presence of symptoms that might indicate the presence of excess hormone. Screening for hormones in asymptomatic individuals is not routinely recommended. The range of symptoms associated with hormonal secretion is diverse. Classic syndromes include those associated with insulinomas, which secrete insulin, resulting in fasting or nocturnal hypoglycemia. Gastrinomas secrete gastrin, and patients often present with recurrent peptide ulcers. Glucagonomas are associated with the development of diabetes mellitus and/or migratory necrolytic erythema. Patients with
somatostatinomas may also present with diabetes mellitus and/or diarrhea/steatorrhea from secretion of somatostatin. VIPomas are characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) from secretion of vasoactive intestinal polypeptide (VIP). The guidelines describe appropriate tests for each of these situations. For nonfunctioning tumors, pancreatic polypeptide (PP; category 3) and chromogranin A (category 3) may also be tested as appropriate.

Chromogranin A levels are elevated in 60% or more of patients with either functioning or nonfunctioning pancreatic endocrine tumors. In addition, analysis of a large prospective database found that chromogranin A levels elevated twice the normal limit or higher were associated with shorter survival times for patients with metastatic neuroendocrine tumors (HR, 2.8; 95% CI, 1.9–4.0; P < .001). Chromogranin A was also found to be a prognostic factor in a prospective study of patients treated with everolimus. Care should be taken in measuring chromogranin A and interpreting the results, because spuriously elevated levels of chromogranin A have been reported in patients using proton pump inhibitors, those with renal or liver failure, those with hypertension, and those with chronic gastritis.

Evaluation of Gastrinomas
Gastrinoma should be suspected in patients with severe and refractory gastroduodenal ulcers or symptoms such as dyspepsia, usually accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of basal and stimulated gastrin levels. Diagnosis of gastrinoma can be confounded by the concurrent use of proton pump inhibitors, which will elevate serum gastrin levels. Importantly, most 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. To be useful for diagnosis, gastrin levels (basal or stimulated) must be measured after the patient is off proton pump inhibitor therapy for at least 1 week. After excluding retained gastric antrum by history, a combination of fasting serum gastrin level greater than 10 times elevated and a gastric pH less than 2 is diagnostic of a gastrinoma. Patients who have clinical manifestations suspicious for a gastrinoma and a gastric pH less than 2 but with less than 10 times elevation of serum gastrin levels require further testing.

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 somatostatin scintography, EUS, and chromogranin A levels (category 3), may be performed as appropriate. Approximately 70% of patients with MEN1 and gastrinoma have tumors situated in the duodenum.


Evaluation of Insulinomas
Insulinomas are generally small tumors that are best localized with EUS, which has been shown to localize approximately 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.

Serum insulin, pro-insulin, and c-peptide should be tested. An insulin level greater than 3 mU/mL (usually >6 mU/mL), C-peptide concentrations of at least 0.6 ng/mL, and proinsulin levels of greater
than or equal to 5 pmol/L when fasting blood glucose is less than 55 mg/dL indicated the presence of these tumors.\textsuperscript{165}

Multiphasic CT or MRI scans should be performed to rule out metastatic disease. Ninety percent of insulinomas pursue an indolent course and can be cured surgically. Insulinomas are less consistently octreotide-avid than other pancreatic neuroendocrine tumors, and somatostatin scintigraphy may consequently be less useful as an imaging technique in insulinomas than in other tumor subtypes. Somatostatin scintigraphy should be performed only if octreotide or lanreotide is being considered as a treatment for metastatic disease. Octreotide or lanreotide should only be administered to patients whose tumors are somatostatin scintigraphy-positive, and patients with insulinoma should be carefully monitored when receiving octreotide or lanreotide because in some cases these drugs can profoundly worsen hypoglycemia (see Preoperative Management, below).\textsuperscript{166}

The New England Journal of Medicine published a case report describing the diagnosis of insulinoma in a lactating patient presenting with periodic numbness and prolonged episodes of confusion and lethargy.\textsuperscript{167}

\textbf{Evaluation of Glucagonomas and VIPomas}

For patients with recent-onset diabetes, cachexia, and/or a necrotic erythematous skin rash, the panel recommends a blood test for glucagon and blood glucose and multiphase contrast-enhanced CT or MRI. Somatostatin scintigraphy and EUS can be performed as appropriate.

For suspected VIPomas with characteristic watery diarrhea, testing for VIP and electrolytes is recommended. A multiphase CT or MRI scan may be useful for identifying large tumors or metastatic disease, and is recommended routinely for suspected VIPoma. Somatostatin scintigraphy and EUS can also be considered as appropriate. A recent case report describes the diagnosis and treatment of a patient with VIPoma.\textsuperscript{168}

\textbf{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 to surgery include patients with other life-limiting comorbidities or high surgical risk, particularly if tumors are small and indolent.

\textbf{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 or lanreotide can be considered for symptom control in most pancreatic neuroendocrine tumor subtypes.\textsuperscript{77} Octreotide or lanreotide should be used with caution in patients with insulinoma because they can also suppress counterregulatory hormones, such as growth hormone (GH), glucagon, and catecholamines. In this situation, octreotide and lanreotide can precipitously worsen hypoglycemia, and can result in fatal complications.\textsuperscript{166} Octreotide and lanreotide should not be used in patients with insulinoma in patients who have a negative result by somatostatin scintigraphy.

In addition, specific measures are often recommended based on symptoms. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Everolimus can also be considered in this scenario.\textsuperscript{169} For gastrinomas, gastrin hypersecretion may be treated with proton pump inhibitors. For patients with glucagonoma, appropriate
measures should be taken to treat hyperglycemia and diabetes, including the use of IV fluids. All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcus group c).

**Surgical Management of Nonfunctioning Pancreatic Neuroendocrine Tumors**

Most patients with localized pancreatic neuroendocrine tumors should undergo surgical resection, absent any contraindications. Exceptions include patients with other life-limiting comorbidities, high surgical risk, or widely metastatic disease. Additionally, several studies have suggested that patients with incidentally discovered tumors <1 cm in size may be safely followed in some cases, depending on the site of the tumor.\(^{170,171}\) Other studies, including an analysis of the SEER database, suggest that some small tumors (measuring <2 cm in size in these studies) can pursue a more aggressive course.\(^{172-174}\) Other retrospective studies suggest nonoperative management can be safe for nonfunctioning pancreatic neuroendocrine tumors that are <1.7 cm or <3 cm.\(^{175,176}\) Based on these limited data, the panel includes observation alone as an option for selected cases of incidentally discovered pancreatic neuroendocrine tumors measuring ≤1 cm, but recommends surgical resection for larger tumors absent contraindications.

Resection for larger (>2 cm), node-positive, or malignant-appearing nonfunctional tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes. Lymph node resection should also be considered for tumors of 1 to 2 cm, because of the small but real risk of lymph node metastases.\(^{177,178}\)

**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 observation or 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 tumors 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. The periduodenal nodes should also be removed. Gastrinomas in the pancreatic head that are deeper or invasive and those with proximity to the main pancreatic duct should be managed with pancreatoduodenectomy.

Gastrinomas in the distal pancreas are treated with distal pancreatectomy. The role of routine splenectomy in such cases is debated. Gastrinomas in some cases may be associated with lymph node metastases,\(^{179}\) which are removed with splenectomy. However, no firm data support splenectomy in all cases. A third alternative is the “Warshaw technique,” which, with resection of splenic vessels but preservation of the spleen,\(^{180}\) can achieve lymph node retrieval comparable to distal pancreatectomy with en-bloc splenectomy.

**Surgical Management of Insulinomas**

The primary treatment for exophytic or peripheral insulinomas, because they are primarily benign, is enucleation. This procedure can be performed 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 because of
invasion or the location of the tumor within the pancreas, then
pancreatoduodenectomy for tumors in the head of the pancreas or
distal pancreatectomy with preservation of the spleen for smaller tumors
not involving splenic vessels may be considered. Distal pancreatectomy
can be performed laparoscopically, and a recent meta-analysis reported
that laparoscopic procedures are safe for patients with insulinomas and
may be associated with shorter hospital stays.\textsuperscript{181}

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 splenectomy and resection of
the peripancreatic lymph nodes. For tumors in the pancreatic head,
pancreatoduodenectomy 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. A hypercoagulable state has been reported in 10\% to 33\% of
patients with glucagonoma.\textsuperscript{182,183} Therefore, perioperative
anticoagulation can 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. Pancreatoduodenectomy 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 Other Pancreatic Neuroendocrine Tumors
The treatment recommendations for tumors secreting hormones such
as somatostatinoma, ACTH, PTHrP, and PP are similar to those for
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 pancreatoduodenectomy 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 of Resected Pancreatic Neuroendocrine Tumors
Disease recurrence has been observed in 21% to 42% of patients with
pancreatic neuroendocrine tumors and can occur after many years.\textsuperscript{184-186}
Higher lymph node ratio and Ki-67 status may indicate a higher chance
of recurrence.\textsuperscript{184} Patients should undergo follow-up 3 to 12 months after
resection, or earlier if the patient presents with symptoms, and then
every 6 to 12 months for a maximum of 10 years with an H&P and
appropriate biochemical markers. Multiphasic CT or MRI can also be
considered. Less frequent surveillance may be appropriate for low-risk
tumors such as well-differentiated stage I pancreatic neuroendocrine
tumors. Somatostatin scintography and 18F-fluorodeoxyglucose
FDG-PET/CT scans are not recommended for routine surveillance.

The optimal duration of surveillance is unknown. In one study of 123
patients with resected sporadic pancreatic neuroendocrine tumors, most
recurrences occurred within 5 years of resection, and all recurrences
occurred within 10 years.\textsuperscript{187} Surgical resection is recommended for
reseparable locoregional or oligometastatic recurrence.
Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas

Metastases in patients with neuroendocrine tumors of the pancreas, when they develop, often occur first in the liver. In patients with limited hepatic disease, surgical excision of both the primary tumor and liver metastases should be considered with curative intent when possible and can be performed in a staged or synchronous fashion. A recent meta-analysis reported that 5-year OS ranges from 41% to 100% in this population of patients. Noncurative debulking surgery can also be considered in select cases. When performing staged pancreatectoduodenectomy and liver resection, hepatectomy should be considered before pancreatic resection to reduce the risk of perihepatic sepsis from the contaminated biliary tree. Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence. Additional resection or ablation may be possible. A 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%. If resection is performed and future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy can be considered given the association between long-term treatment with somatostatin analogs and the development of biliary symptoms and gallstones.

Unfortunately, most patients who present with advanced pancreatic neuroendocrine tumors have unresectable disease. For selected patients with unresectable disease who are asymptomatic and have low tumor burden and stable disease, observation can be considered, with marker assessment and multiphasic CT or MRI every 3 to 12 months until clinically significant disease progression occurs. In addition, however, treatment with lanreotide or octreotide can be considered (see discussion below). The optimal time to begin therapy in this patient population is not known.

For symptomatic patients with unresectable disease, 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 octreotide or lanreotide, biologically targeted agents (everolimus or sunitinib, category 2A), or treatment with cytotoxic chemotherapy (category 2A). These options, as well as hepatic-directed therapies, are discussed in more detail in the following sections.

Somatostatin Analogs

Patients with pancreatic neuroendocrine tumors and symptoms of hormone secretion should, in most cases, receive treatment with either lanreotide or octreotide and/or other medication to manage their symptoms as previously described. Patients without hormone-related symptoms who have uptake with somatostatin scintography can also be considered for treatment with octreotide or lanreotide. Results from the CLARINET study, in which 204 patients with gastroenteropancreatic neuroendocrine tumors (including both carcinoid and pancreatic neuroendocrine tumors) were randomized to receive treatment with either lanreotide or placebo, showed that treatment with lanreotide was associated with an improvement in PFS (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; P < .001). Although no randomized studies to date have directly shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial showed an improvement in its primary endpoint of time to tumor progression (14.3 vs. 6 months; P = .000072) in carcinoid tumors of the midgut. Lanreotide and octreotide share the same mechanism of action.
action, and the panel believes that either lanreotide or octreotide are appropriate options for tumor control in this setting.

Additional therapies can be given in place of or in addition to octreotide or lanreotide, as discussed below.

**Molecularly Targeted Therapies**
The molecularly targeted agents everolimus and sunitinib have been confirmed to have antitumor activity and to improve PFS in patients with advanced pancreatic neuroendocrine tumors.

Everolimus, administered orally at a dose of 10 mg once daily, was evaluated in a multicenter study (RADIANT-3) enrolling 410 patients with advanced, progressive, pancreatic neuroendocrine tumors. In this study, the median PFS duration for patients randomized to everolimus was 11.0 months, compared with 4.6 months for patients receiving placebo ($P < .001$). Subset analyses of RADIANT-3 suggested that the PFS benefit associated with everolimus is independent of prior or concurrent somatostatin analog therapy or prior chemotherapy. Adverse events associated with everolimus include stomatitis, hyperglycemia, and, in rare cases, pneumonitis. Other side effects have also been described.

Cytotoxic Chemotherapy for Advanced Pancreatic Neuroendocrine Tumors

Cytotoxic chemotherapy is another option for patients with unresectable or metastatic pancreatic neuroendocrine tumors (category 2A). While a number of regimens have been associated with antitumor activity in this setting, there is no panel consensus on which cytotoxic chemotherapy regimen is best. The alkylating agents streptozocin and temozolomide appear to have the most antitumor activity in 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 retrospective review from MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin. A phase II trial assessed bevacizumab combined with 5-FU and streptozocin. A PFS of 23.7 months was reported, with 56% of patients achieving a partial response and 44% achieving stable disease.
More recently, oral temozolomide-based therapy has been used in patients with advanced pancreatic neuroendocrine tumors. Temozolomide has been administered using different schedules, either alone or in combination with other agents. A retrospective series reported that the combination of temozolomide with capecitabine was associated with an objective radiographic response rate of 70% and a median PFS of 18 months. Another retrospective review of the temozolomide and capecitabine combination reported a 61% response rate in 18 patients, with 1 surgically proven complete pathologic response. A small recent retrospective study (7 patients) reported a response rate of 43%.

Temozolomide-based combination regimens have also been formally evaluated in prospective, phase II studies. One such study assessed the safety and efficacy of temozolomide administered with bevacizumab, a monoclonal antibody targeted against vascular endothelial growth factor (VEGF). Five of the 15 patients (33%) with pancreatic neuroendocrine tumors had a radiographic response (with no responses in the 19 patients with carcinoid tumors), and the toxicity was acceptable. The combination of temozolomide with everolimus has also been studied and found to be safe, with partial responses observed in 40% of patients with pancreatic neuroendocrine tumors.

These results suggest that the activity of temozolomide in pancreatic neuroendocrine tumors is at least comparable to that of streptozocin, and support its use in pancreatic neuroendocrine tumors. The combination of temozolomide with everolimus has also been studied. There is no current consensus, however, on the optimal temozolomide dosing regimen or whether temozolomide should be administered alone or in combination with other agents.

Other cytotoxic agents appear to be less active than streptozocin or temozolomide in pancreatic neuroendocrine tumors. 5-FU was assessed in the phase II/III E1281 trial in combination with streptozocin or doxorubicin in patients with neuroendocrine tumors of various locations, including the pancreas. Response rates in both arms were around 16%. Dacarbazine was given following progression, with a response rate of 8%. Other studies have also shown the combination of 5-FU and streptozocin to be effective in this setting. The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23% in patients with poorly differentiated neuroendocrine tumors and 30% in well-differentiated disease.

Hepatic-Directed Therapies
Hepatic-directed therapies may be considered in patients with progressive hepatic-predominant metastatic disease, to reduce tumor bulk and relieve symptoms of hormone hypersecretion. The panel lists cytoreductive surgery or ablative therapy (RFA, cryotherapy, microwave) as category 2B recommendations for these patients. Although some groups report that the risks of cytoreductive surgery outweigh its benefits, others have reported good outcomes.

Additional options include hepatic regional therapies including bland hepatic arterial embolization, radioembolization (category 2B), and chemoembolization. Whereas embolization in general is considered an effective approach in patients with hepatic-predominant disease, only limited data compare the various embolization techniques, and the optimal embolization approach remains uncertain.

Radiolabeled Somatostatin Analogs for Advanced Pancreatic Neuroendocrine Tumors
Treatment with radiolabeled somatostatin analogs has been reported to result in tumor responses in patients with advanced pancreatic
Neuroendocrine tumors. Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach. In general, these studies have enrolled only patients with evidence of high tumoral somatostatin receptor expression. A recent randomized study of 177Lu-DOTATATE has been completed in patients with advanced neuroendocrine tumors, and preliminary results from this study suggest this approach is both safe and associated with improved PFS. At this time, treatment with radiolabeled somatostatin analogs remains investigational in patients with pancreatic neuroendocrine tumors, and randomized trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in patients with advanced pancreatic neuroendocrine tumors have not yet been performed.

Liver Transplantation
Several series have now reported the results of liver transplantation in patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver. A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence. 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
In a SEER database analysis, a primary tumor site could not be found in as many as 4,752 (13%) of 35,618 neuroendocrine tumors. When a neuroendocrine tumor of unknown primary is diagnosed, attempts are usually 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 Histologic Classification and Staging of Neuroendocrine Tumors, above). Many of these tumors are poorly differentiated and aggressive.

Evaluation of Neuroendocrine Tumors of Unknown Primary
The initial evaluation of a patient with biopsy-proven neuroendocrine tumors of unknown primary includes 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 MEN1 or MEN2.

Given the differences in systemic treatment approaches for carcinoid and pancreatic neuroendocrine tumors, establishing whether or not a patient has a primary pancreatic neuroendocrine tumor can have important treatment implications. Potential primary sites may be investigated with imaging studies, such as multiphasic CT or MRI. Ultrasound or EUS 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 (eg, somatostatin receptors), and somatostatin scintigraphy may also be helpful in localizing certain neuroendocrine tumors. In addition, radionuclide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. An FDG-PET/CT scan and brain imaging (CT or MRI) can occasionally be useful in finding a primary tumor, but are less sensitive in well-differentiated neuroendocrine tumors and should only be considered in cases of poorly differentiated tumors. Emerging technologies, such as 68Ga-DOTATATE PET/CT, may help identify a primary tumor in these patients, but whether such identification alters clinical outcomes remains to be determined.
Colonooscopy can also be considered, especially in cases of well-differentiated liver metastases, to identify possible primary tumors in the small intestine or colon.\textsuperscript{219} It is not uncommon for small bowel carcinoid tumors to be small and difficult to visualize, although in some cases imaging may demonstrate an associated mesenteric mass. Exploratory surgery is generally not recommended for purely diagnostic purposes. However, if a small bowel primary tumor is suggested by symptoms and radiologic findings and if metastases are completely resectable, surgery can be considered.\textsuperscript{219}

The possibility of functional adrenal neoplasms and carcinoid syndrome should be considered prior to biopsy or other invasive procedures. Plasma or 24-hour urine fractionated metanephrines can be used to screen for functional adrenal neoplasms (see Evaluation for Pheochromocytoma/Paragangliomas, below). Alpha blockade and forced hydration should be used before procedures 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 Carcinomas/Large or Small Cell Carcinomas, below. In the absence of a primary tumor identified in the pancreas, well-differentiated tumors should be treated similarly to typical carcinoid tumors, as described above.

**Adrenal Gland Tumors**

Adrenocortical carcinomas (ACCs) are rare (incidence, 1–2 per million).\textsuperscript{220-222} ACC has a bimodal age distribution, with peak incidences in early childhood and the fourth to fifth decades of life. The female-to-male ratio is approximately 1.5 to 1.\textsuperscript{223,224} Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and MEN1.\textsuperscript{5,225-228} The underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated; however, inactivating somatic mutations of the \textit{p53} tumor suppressor gene (chromosome 17p13\textsuperscript{229,230}) and alterations at the 11p15 locus (site of the \textit{IGF-2} gene\textsuperscript{231,232}) seem to occur frequently.

Approximately 60\% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.\textsuperscript{220,223-235} 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.\textsuperscript{233} 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{233,236}

**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. Such a history raises suspicion that the tumor represents a metastatic site rather than a primary site. In these patients, an image-guided needle biopsy can be considered. Usually, a functioning adrenal neoplasm (in particular pheochromocytoma) should be ruled out before biopsy with plasma or 24-hour urine fractionated metanephrines. Such screening for pheochromocytoma should be considered even for asymptomatic patients if radiologic findings are suspicious and surgery is planned. If
the clinical suspicion for pheochromocytoma is low and plasma or urine fractionated metanephrines are less than 2 times the upper limit of normal, it is reasonable to proceed with an adrenal biopsy. False-negative biopsies are possible; therefore, proceeding directly to surgery can also be considered in selected cases. If the tumor is determined to be a metastasis from another site, treatment should be according to the appropriate NCCN disease-specific treatment guideline (to see the NCCN Guidelines Table of Contents, go to www.NCCN.org). If biopsy reveals adrenal cortical tissue, then morphologic and functional evaluation should proceed as described here.

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 here and below. Most adrenal cortical carcinomas express multiple hormones. Therefore, when the evaluation shows that several hormones are expressed, adrenal cortical carcinomas is likely.

**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 greater than 30. Confirmatory testing is indicated for positive results, because false positives 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.

Hyperaldosteronism is rarely associated with malignancy, but malignancy should be suspected if the tumor has an irregular morphology, is lipid-poor, does not wash out on contrast-enhanced CT, is larger than 3 cm, or is secreting more than one hormone. When malignant hyperaldosteronism is suspected, an open adrenalectomy is recommended, because these tumors are prone to rupture.

Benign hyperaldosteronism is much more common and can be caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia. Adrenal vein sampling for aldosterone and cortisol can be considered for distinguishing these 2 causes of benign hyperaldosteronism and should be considered if the patient is a surgical candidate, because CT imaging is not always reliable. It may be reasonable, however, to exclude adrenal vein sampling in patients younger than 40 years when imaging only shows one affected gland, because bilateral hyperplasia is rare in this population. Laparoscopic adrenalectomy is recommended for adenoma, whereas medical management with spironolactone or eplerenone for hypertension and hypokalemia is recommended for patients with bilateral adrenal hyperplasia and for nonsurgical candidates.

**Evaluation and Treatment of Cushing’s Syndrome**

Patients who present with symptoms of Cushing’s syndrome should be screened for evidence of hypercortisolemia with 1 of the following tests: 1) overnight 1-mg dexamethasone suppression test with 8 AM plasma cortisol; 2) 2 to 3 midnight salivary cortisols; or 3) free cortisol in a 24-hour urine sample. Confirmatory testing should be performed if positive. Elevated levels of cortisol are indicative of Cushing’s syndrome. In addition to treatment of the underlying hypercortisolemia, patients who experience symptoms secondary to increased adrenocortical steroid levels often require aggressive treatment of
associated conditions such as hypertension, hyperglycemia, and hypokalemia.

Patients who are hypercortisolemic should have levels of serum ACTH assessed by an 8am cortisol measurement. Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, or neuroendocrine tumors in the lung, thyroid, pancreas, or bowel are possible sources. These patients should be assessed and treated for pituitary or ectopic sources of ACTH production. A case report from the Massachusetts General Hospital provides an example of the evaluation, diagnosis, and treatment of a patient with Cushing’s syndrome resulting from a bronchial carcinoid.\textsuperscript{56}

Cushing’s syndrome can also be associated with either benign adrenal tumors (adrenal adenoma) or malignant adrenal tumors. Malignancy should be suspected if the tumor is larger than 4 cm or is inhomogeneous with irregular margins and/or local invasion and other malignant imaging characteristics. CT or MRI of the chest, abdomen, and pelvis is required to evaluate for metastases and local invasion. Benign adrenal tumors (ie, <4 cm, contralateral gland normal, circumscribed tumor, other benign imaging characteristics) are generally resected with a laparoscopic adrenalectomy, when feasible. Postoperative corticosteroid supplementation is required until recovery of the hypothalamic-pituitary-adrenal (HPA) axis.

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

Medical management of hypercortisolism is achieved with adrenostatic agents, including ketoconazole and/or mitotane. Ketoconazole is most commonly used (at doses of 400–1200 mg/d) because of its easy availability and relatively tolerable toxicity profile. The data supporting use of other individual drugs for the management of Cushing’s disease are limited.\textsuperscript{243} Octreotide or lanreotide can also be considered for ectopic Cushing’s syndrome if the tumor is somatostatin scintigraphy-positive, although it may be less effective in controlling ectopic ACTH secretion than it is in other contexts. Bilateral adrenalectomy is generally recommended when medical management of ectopic Cushing’s syndrome fails.

Treatment of Nonfunctioning, Benign Adrenal Tumors

Adrenal tumors that do not secrete hormones are often discovered incidentally during scans for unrelated reasons (incidentalomas). Most nonfunctioning tumors are benign and can be left untreated. Masses showing radiographic features of myelolipoma are considered benign. In addition, tumors smaller than 4 cm that are homogenous, with smooth margins, and that appear lipid-rich according to CT or MRI criteria are also usually benign. If no change in size is noted on repeat imaging in 6 to 12 months, no further follow-up is required. Adrenalectomy can be considered if the mass is enlarging. Alternatively, these masses can be observed with short-interval follow-up. Larger tumors (4–6 cm) can be left untreated, but repeat imaging is recommended sooner (3–6 months). Without evidence of growth, repeat imaging can be performed in 6 to 12 months. If these larger tumors continue to grow, however, malignancy should be suspected and adrenalectomy is recommended. This procedure can be performed laparoscopically if the tumor and the concern for malignancy...
are small, with a planned conversion to an open procedure if evidence of local invasion is observed during surgery.

**Evaluation of Adrenal Carcinoma**
ACC should be strongly suspected in nonfunctioning tumors larger than 4 cm with irregular margins or that are internally heterogenous. On CT scans with intravenous contrast, adjacent lymph nodes or liver metastases may be present. 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. If the HU attenuation value is greater than 10 on unenhanced CT, then enhanced CT and washout at 15 minutes is recommended. If the enhancement washout value is greater than 60% at 15 minutes, the tumor is likely benign. MRLs more clearly document local invasion and involvement of the inferior vena cava than CT scans. Whether CT or MRI scans are performed, they should be performed using an adrenal protocol to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics.

CT or MRI of the chest, abdomen, and pelvis is also recommended to evaluate for metastatic disease and local invasion when the primary tumor is larger than 4 cm and carcinoma is suspected.

A recent analysis found that approximately 3% of patients with ACC have Lynch syndrome, leading the authors to recommend that patients with ACC and a personal or family history of Lynch syndrome-associated tumors undergo genetic counseling.

**Treatment and Surveillance 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 because of increased risk for local recurrence and peritoneal spread when performed laparoscopically.

Because of the rarity of ACCs, no randomized, prospective trials of adjuvant therapy have been published. Most retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticolytic agent. The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany. In the Italian cohort, nearly half of the patients received adjuvant mitotane (47/102 patients) at doses ranging from 1 to 5 g/d, whereas none of the 75 German patients received adjuvant mitotane. The median duration of treatment was 29 months. In follow-up, disease-free and overall survivals were significantly longer in those treated with mitotane versus the controls, suggesting that adjuvant mitotane may be an effective postoperative 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 identifier: NCT00777244). Disease-free survival is the primary endpoint.

Based on the available data, adjuvant therapy can be considered if the patient is at high risk for local recurrence based on positive margins, ruptured capsule, large size, or high grade. Adjuvant RT to the tumor bed can be considered in these cases, particularly if concern exists regarding tumor spillage or close margins after surgery. Adjuvant mitotane therapy can also be considered after resection of adrenal carcinoma, although its use in this setting is controversial (category 3). Because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed to
prevent adrenal insufficiency if it is used; corticosteroids may be required for the rest of the patient’s life. Because of the potential risks and uncertain benefits of adjuvant mitotane, several NCCN Member Institutions do not advocate its use in the adjuvant treatment of patients with resected adrenal carcinomas.

Follow-up CT or MRI and biomarkers (for functioning tumors) should be performed every 3 to 12 months for up to 5 years, and then as clinically indicated. Recurrences after 5 years are thought to be very rare.

**Management of Metastatic Adrenal Carcinoma**

Resection may be considered if greater than 90% of the tumor and metastases can be removed. Otherwise, systemic therapy should be initiated. Observation with CT or MRI and relevant biomarkers every 3 months can also be considered for clinically indolent disease, with systemic treatment initiated at tumor progression.

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. Partial response rates are thought to be 10% to 30% at most.

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 g/d) with cisplatin, etoposide, and doxorubicin in 72 patients with unresectable adrenal carcinoma, yielding an overall response rate of 49% (according to WHO criteria) and a complete hormonal response in 16 of 42 patients with functioning tumors. Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%. 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 after surgery; 1 (8%) had stable disease for 3 months; and the other 8 (67%) showed no response.

Analysis of results from the international randomized controlled phase III FIRM-ACT trial comparing treatment of metastatic ACC with etoposide, doxorubicin, cisplatin, and mitotane versus treatment with streptozotocin and mitotane with a crossover design found no difference between the regimens in the primary endpoint of overall survival (14.8 vs. 12.0 months; HR, 0.79; 95% CI, 0.61–1.02; \( P = .07 \)). However, response rates and PFS were improved with the 4-drug regimen and an overall survival benefit was seen in those who did not cross over to the other combination (17.1 vs. 4.7 months). Rates of serious adverse events were similar in the arms.

However, the toxicity of concurrent chemotherapy plus mitotane should be considered when making treatment decisions, and mitotane monotherapy may still be appropriate in selected cases. The optimal doses and duration of mitotane treatment for metastatic disease have not yet been standardized, but some institutions recommend target levels of 14 to 20 mcg/mL, if tolerated. Higher doses may be difficult for patients to tolerate, whereas lower doses may be less effective. Steady-state levels may be reached several months after initiation of mitotane. As noted above, because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed to prevent adrenal insufficiency. This replacement therapy may be needed for the remainder of the patient's lifetime.
Pheochromocytomas/Paragangliomas

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla in 80% to 90% of cases. Ectopic/extra-adrenal pheochromocytomas that arise from para-aortic sympathetic ganglia are called paragangliomas. Pheochromocytomas and paragangliomas occur in 0.05% to 0.1% of hypertensive patients, and their combined annual incidence in the United States is estimated to be between 500 and 1600 cases. Pheochromocytomas release catecholamines and their metabolites norepinephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. About 40% of paragangliomas also secrete catecholamines.

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% vs. 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 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 after treatment of metastatic disease. Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see Surveillance of Pheochromocytomas/Paragangliomas, below).

Evaluation for Pheochromocytomas/Paragangliomas

A patient with possible pheochromocytoma should be evaluated with fractionated metanephrines in 24-hour urine or free metanephrines in plasma; elevated levels of metanephrines are suggestive of pheochromocytoma. Concurrent medications should be reviewed before metanephrine testing for those that interfere with plasma metanephrines evaluation, including acetaminophen, certain beta- and alpha-adrenoreceptor blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors. Elevations in metanephrine levels that are 4 times above the upper limit of normal are diagnostic. Urine or plasma catecholamines are no longer routinely recommended for the evaluation of pheochromocytoma: 15% to 20% of patients with pheochromocytoma have normal levels of urine catecholamines, due to intermittent secretion in some tumors and insignificant secretion by others. Measurement of serum and/or 24-hour urine fractionated catecholamines for dopamine levels can be considered for cervical paragangliomas.

Contrast-enhanced chest/abdominal/pelvic CT or MRI are also recommended. Other imaging studies, including FDG-PET/CT, metaiodobenzylguanidine (MIBG) scan somatostatin scintography, and bone scan, should be performed as appropriate if metastatic disease is suspected.

Genetic Counseling/Testing in Pheochromocytomas/Paragangliomas

While many pheochromocytomas are thought to be sporadic, increasing evidence shows that a number of pheochromocytomas are in fact associated with inherited genetic syndromes. Pheochromocytomas occur in patients with MEN2A, MEN2B, and other familial diseases such as neurofibromatosis, von Hippel-Lindau syndrome, and Osler-Weber-Rendu syndrome. In addition to germline mutations associated with these syndromes (ie, RET, NF1, VHL, SMAD4, ENG,
ALK1), germline mutations in SDHB, SDHA, SDHAF2, SDHD, SDHC, TMEM127, MAX, HIF2A, and MDH2 have also been associated with an increased incidence of pheochromocytomas and paragangliomas.\textsuperscript{267-273} Patients less than age 45 years or those with multifocal, bilateral, or recurrent lesions are more likely to have a heritable mutation, although many individuals with a hereditary syndrome present with solitary disease and no family history.\textsuperscript{270} Because a significant proportion of patients with a pheochromocytoma or paraganglioma have a heritable mutation,\textsuperscript{267} genetic counseling is recommended in patients with such a diagnosis and in those with a family history of these tumors, with genetic testing when appropriate. The Endocrine Society has published guidelines that include a genetic testing decision algorithm.\textsuperscript{264}

Individuals with known germline mutations associated with pheochromocytomas and paragangliomas should undergo lifelong biochemical and clinical surveillance, beginning at age 10 years or ≥10 years before the earliest age of diagnosis in the family.\textsuperscript{270} The type and timing of the surveillance should be based on which gene is affected and take into account known genotype-phenotype relationships. MRI may be the preferable imaging modality for tumor detection in these individuals in order to limit radiation exposure.

**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. Therefore, patients with pheochromocytomas or paragangliomas should receive preoperative alpha-adrenergic blockade with aggressive volume repletion and high-salt diet for 7 to 14 days or until stable. Alpha 1-selective receptor blockers include terazosin, doxazosin, prazosin, and non-selective receptors include phenoxybenzamine. If additional blood pressure control is needed after alpha blockade, the addition of dihydropyridine calcium channel blockers can be considered. Calcium channel blockers are not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Methyltyrosine can be used in addition to alpha blockade to control blood pressure. Beta blockade (B1-selective blockers or non-selective beta blockers) can also be added to alpha blockade to control tachycardia. Generally, alpha and beta blockers should be administered independently, and use of combination beta,alpha blockers is not recommended. Non-selective alpha blockade phentolamine (IV) can be used intraoperatively for additional blood pressure control.

Resection is the recommended treatment for patients with resectable tumors. A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas.\textsuperscript{274-276} For locally unresectable tumors, RT can be considered, with cytoreductive resection, when possible. In addition, medical therapy should be continued for unresectable secreting tumors.

When distant metastases are present, cytoreductive resection is also recommended when possible, and medical therapy should be continued for secreting tumors. Other options for treating unresectable, metastatic disease include: 1) clinical trial; 2) systemic chemotherapy (eg, cyclophosphamide/vincristine/dacarbazine [CVD] or temozolomide)\textsuperscript{202,277-280}; or 3) iodine-131-MIBG therapy after confirming dosimetrically that tumors take up MIBG.\textsuperscript{281,282}

A retrospective review of 52 evaluable patients treated with various systemic chemotherapy regimens for metastatic pheochromocytomas or paragangliomas showed that patients with a response to chemotherapy (reduction in symptoms, antihypertensive medications, or tumor size) had a median survival of 6.4 years and non-responders had a median
survival of 3.7 years. Approximately 33% of patients exhibited a tumor response.

A review of 48 patients with pheochromocytoma or paraganglioma treated with iodine-131-MIBG therapy at 4 centers showed that, while partial responses were rare, stable disease was achieved after 83.1% of treatments. A meta-analysis of 17 studies that included a total of 243 patients with malignant paraganglioma or pheochromocytoma found a stable disease rate of 52% (95% CI, 0.41–0.62) after iodine-131-MIBG therapy. Partial and complete responses were seen in 27% and 3%, respectively.

**Survival 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 for up to 10 years. In addition, CT, MRI, or FDG-PET/CT scans can be considered. Timing for these surveillance events and procedures can be earlier if symptoms dictate. In addition, individuals with hereditary paraganglioma/pheochromocytoma may require more frequent follow-up.

**Poorly Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas**

Although rare, extrapulmonary, poorly differentiated neuroendocrine carcinomas occur in a wide variety of organs. They are characterized by a high mitotic index and high proliferative index (Ki-67); the most aggressive of these tumors histologically resemble classic small cell carcinoma of the lung. 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 poorly differentiated neuroendocrine carcinomas are aggressive and require combined multimodality treatment, usually following a treatment paradigm that parallels the treatment of small cell lung cancer. These tumors are rarely associated with a hormonal syndrome.

**Evaluation of Poorly Differentiated/Large or Small Cell Carcinomas**

CT scans of the chest, abdomen, and pelvis are recommended as baseline staging studies. 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. FDG-PET/CT, somatostatin scintigraphy, and/or plasma ACTH or other biochemical markers are recommended as clinically indicated.

**Primary Treatment of Extrapulmonary Poorly Differentiated/Large or Small Cell Neuroendocrine Carcinomas**

For resectable poorly differentiated/large or small cell neuroendocrine carcinomas, surgical resection and chemotherapy with or without radiotherapy are advised (see NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org). Alternatively, definitive chemoradiation can be considered, according to the NCCN Guidelines for Small Cell Lung Cancer. For unresectable locoregional disease, radiotherapy in combination with chemotherapy is recommended. If metastatic tumors are present, chemotherapy alone is recommended.

Small cell lung regimens, such as cisplatin or carboplatin with etoposide, are generally used as primary treatment. Evolving data, however, suggest that patients with intermediate Ki-67 levels (in the 20%–55% range) may not respond as well to platinum/etoposide as patients with higher Ki-67 (>55%). Clinical judgment should be used in selecting systemic therapy regimens for patients with Ki-67 levels in this intermediate range. Some panel members believe that treatments used...
for lower grade tumors may be reasonable in this population. Octreotide or lanreotide therapy can still be considered for symptom control in the rare cases of hormone-secreting, poorly differentiated tumors that are unresectable or metastatic if somatostatin scintigraphy is positive.

**Surveillance of Poorly Differentiated/Large or Small Cell Carcinomas**

After surgery, surveillance consists of a routine H&P along with appropriate imaging studies (MRI, CT, or FDG-PET/CT) 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**

The MEN syndromes are characterized by tumors that arise from endocrine organs and cells throughout the body. The 2 most common syndromes are MEN1 and MEN2. MEN1 is an autosomal-dominant inherited syndrome characterized by parathyroid adenomas (causing hyperparathyroidism), pituitary adenomas, and pancreatic neuroendocrine tumors; MEN1 may also be associated with carcinoid tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas. MEN2 is also an autosomal-dominant inherited syndrome and is associated with MTC (98%); pheochromocytoma (50%), often bilateral; and hyperparathyroidism (25%). In addition, familial MTC occurs in patients without MEN2 and is also inherited as an autosomal dominant disease.

MEN1 is associated with the germline mutation or inactivation of the tumor suppressor gene *MEN1* (chromosomal locus 11q13 encoding the menin protein), whereas MEN2 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*. Somatic mutation of the *MEN1* gene is also the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids. Somatic *RET* mutations are found in sporadic MTC.

**MEN1**

MEN1 (or Wermer syndrome), is typically characterized by tumors of the parathyroid and pituitary glands and neuroendocrine tumors of the pancreas, but may also be associated with carcinoid tumors (eg, thymus, bronchial, gastric), adrenal tumors, and multiple lipomas and skin angiomas. Over 98% of patients with MEN1 either have or will develop primary hyperparathyroidism, and about 50% will develop symptoms from functioning benign or malignant neoplasms of the pancreas. About 35% of patients have functioning tumors of the pituitary, and an additional 20% to 55% of patients also have or will develop nonfunctioning pancreatic neuroendocrine tumors. Approximately 2% and 5% of patients with MEN1 develop thymic and bronchial neuroendocrine tumors, respectively. A recent study has documented the natural history of this disease, finding that approximately two-thirds of patients die from an MEN1-related cause, most commonly pancreatic neuroendocrine tumors or thymic carcinoid tumors.

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 neuroendocrine 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 more than one gland,
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 MEN1 and hypoglycemia related to insulinoma have multiple islet cell neoplasms. Patients with MEN1 and Zollinger-Ellison syndrome also frequently have more than one tumor. Of these tumors, 70% are gastrin-secreting carcinoids in the duodenum and/or periduodenal lymph nodes. Nonfunctioning pancreatic neuroendocrine tumors are usually larger when clinically detected, and are more likely to be associated with metastases at the time of presentation. The development of metastatic pancreatic neuroendocrine tumors or metastatic carcinoid tumors of the thymus are the most common causes of death associated with MEN1. The clinical characteristics of pancreatic endocrine tumors are summarized under Neuroendocrine Tumors of the Pancreas, above.

**Evaluation of MEN1 Syndromes**

A clinical diagnosis for MEN1 can be made when a patient has 2 or more MEN1-associated tumors (ie, multi-gland parathyroid hyperplasia, multifocal pancreatic neuroendocrine tumors, pituitary tumors). For patients known or suspected to have MEN1, clinical evaluation includes biochemical evaluation of hormone levels and imaging to localize the site of tumors. In particular, patients should be evaluated for pancreatic neuroendocrine, parathyroid, and pituitary tumors (see below). In addition, genetic counseling and testing should be provided (see Genetic Counseling/Testing in MEN1, below).

**Evaluation for Parathyroid Tumors in MEN1**

Primary hyperparathyroidism associated with parathyroid adenomas is the most common manifestation of MEN1. Measurement of serum calcium levels and 25-OH vitamin D are recommended if hyperparathyroidism is suspected. Other biochemical evaluation should be done as clinically indicated.

Imaging of the parathyroid glands using sestamibi scanning and/or neck ultrasound is optional but may aid in identifying ectopically situated parathyroids. The technetium 99m (Tc\textsuperscript{99m}) 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.\textsuperscript{292,293}

**Evaluation for Pancreatic Tumors in MEN1**

Approximately 75% of patients with MEN1 and pancreatic neuroendocrine tumors have associated symptoms of hormone hypersecretion. The various characteristics of endocrine tumors of the pancreas (eg, gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma) are summarized under Neuroendocrine Tumors of the Pancreas, above. The workup for pancreatic neuroendocrine tumors in the context of MEN1 is similar to that for sporadic pancreatic neuroendocrine tumors. Imaging with EUS and somatostatin scintography can be used as appropriate. In particular, EUS is recommended if resection is being considered to preoperatively assess and localize tumors. For details on the evaluation for pancreatic tumors, see the section on Neuroendocrine Tumors of the Pancreas, above.
Evaluation for Pituitary Tumors in MEN1
Pituitary MRI is recommended when evaluating for pituitary tumors. Various laboratory tests are also used to evaluate for suspected pituitary tumors. The panel lists serum prolactin and IGF-1 levels among recommended tests (category 2B). Elevated prolactin levels are indicative of prolactinoma, and increased IGF-1 occurs in acromegaly.

Additional biochemical evaluation that can be considered includes measurement of thyroid-stimulating hormone (TSH [free T4]), produced by some adenomas, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Evaluation for Bronchial/Thymic Tumors in MEN1
Multiphasic CT or MRI is recommended to evaluate for bronchopulmonary or thymic tumors in patients with MEN1. Other biochemical evaluation should be done as clinically indicated.

Genetic Counseling/Testing in MEN1
Genetic counseling and MEN1 genetic testing should be offered to individuals with suspicion of or a clinical diagnosis of MEN1 (see Evaluation of MEN1 Syndromes, above) and to at-risk relatives of individuals with known germline MEN1 mutations. It should be noted that a germline MEN1 mutation is uncommon in individuals with a single MEN1-associated tumor and no family history. Only 10% of patients with MEN1 have a de novo germline mutation in MEN1, and thus no family history of MEN1-associated tumors.

Even with a negative MEN1 genetic test result, individuals with clinical diagnosis or suspicion of MEN1 should undergo regular surveillance for MEN1-associated tumors. Similarly, at-risk relatives should have MEN1 surveillance even if the affected relative had a negative test result or no genetic testing. See MEN1 Surveillance, below.

Primary Treatment of MEN1 Syndromes
Primary therapy of locoregional disease in patients with MEN1 focuses on treatment of the specific hormonal syndrome and/or treatment of the underlying hyperplasia or tumor. When a patient presents with hyperparathyroidism and pancreatic neuroendocrine tumors, the hyperparathyroidism is usually treated first. A consultation with an endocrinologist for all patients with MEN1 should be considered.

Primary Treatment of Parathyroid Tumors in MEN1
Treatment options for parathyroid hyperplasia in patients with MEN1 include subtotal parathyroidectomy with or without thymectomy (the bilateral upper thymus 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 thymectomy, and with or without cryopreservation of parathyroids, is another recommended option.

A randomized, prospective trial compared these surgical approaches in 32 patients with MEN1 and hyperparathyroidism. No significant differences were observed in outcomes including recurrent hyperparathyroidism. 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.

Primary Treatment of Pancreatic Tumors in MEN1
Treatment of pancreatic neuroendocrine tumors associated with MEN1 is similar to sporadic pancreatic neuroendocrine tumors and focuses on surgical excision preceded by medical management if necessary (see relevant site-specific recommendations in Neuroendocrine Tumors of the Pancreas, above). However, in contrast to patients with sporadic
disease where a tumor is usually solitary, pancreatic neuroendocrine tumors associated with MEN1 are frequently multiple. Removal of a single functioning tumor, although a reasonable approach for sporadic tumors, may miss additional tumors in the setting of MEN1. MEN1-associated metastatic pancreatic neuroendocrine tumors are often slower growing than metastatic sporadic tumors. Observation can be considered for non-functioning, indolent tumors. Surgical resection should be considered in cases of: 1) symptomatic functional tumors refractory to medical management; 2) a tumor larger than 1 to 2 cm in size; or 3) a tumor with a relatively rapid rate of growth over 6 to 12 months. The panel recommends endoscopy with EUS prior to pancreatic surgery to preoperatively assess and localize tumors.

For clinically significant progressive disease or symptomatic patients, treatment options are as for metastatic disease in the sporadic setting (see Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas, above).

All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C) preoperatively. Furthermore, in patients undergoing abdominal surgery in whom octreotide or lanreotide treatment is planned, prophylactic cholecystectomy can be considered, due to a higher risk of cholelithiasis in patients receiving somatostatin analogs. Metastatic disease in patients with MEN1 is treated as in patients with neuroendocrine tumors arising sporadically, according to the appropriate tumor type.

Primary Treatment of Pituitary Tumors in MEN1
The panel recommends consultation with endocrinology for the treatment of patients with pituitary tumors associated with MEN1, including those with prolactinoma, Cushing’s disease, acromegaly, and nonfunctioning tumors.

Primary Treatment of Bronchial/Thymic Tumors in MEN1
The recommendations for the workup and treatment of bronchopulmonary and thymic tumors are the same as for patients with sporadic disease (see Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus [Carcinoid Tumors]).

MEN1 Surveillance
All patients with MEN1 should be followed for the development or progression of MEN1-associated tumors, regardless of previous tumors or treatments. In contrast to sporadic hyperparathyroidism, patients with familial hyperparathyroidism (including MEN1), isolated familial hyperparathyroidism, or hyperparathyroidism associated with jaw tumor syndrome are more likely to develop recurrent disease. The patients are also more likely to have or develop new parathyroid carcinomas, pancreatic neuroendocrine tumors, pituitary tumors, and/or bronchial/thymic tumors. Carcinoid tumors occur in approximately 3% of patients with MEN1. Bronchial carcinoids occur more frequently in women, while thymic carcinoids occur more frequently in men. In addition, smokers appear to be at increased risk for the development of thymic carcinoids.

The panel recommends annual calcium levels to screen for parathyroid tumors. If calcium levels rise, serum PTH and 25-OH vitamin D should be measured and imaging with neck ultrasound and/or parathyroid sestamibi should be performed. Cross-sectional CT or MRI of the neck can also be considered.

Surveillance for MEN-1–associated pancreatic neuroendocrine tumors is accomplished by following serum hormones as symptoms indicate or
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 MEN2 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 the least aggressive, whereas MTC associated with MEN2B is the most aggressive. MEN2A, MEN2B, and familial MTC are all autosomal-dominant inherited diseases and are associated with germline mutations of the proto-oncogene, \textit{RET}.\textsuperscript{6,300}

The initial symptoms associated with MEN2A and MEN2B 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.

For a full discussion of the management of MTC, consult the NCCN Guidelines for Thyroid Cancer (available at www.NCCN.org). The following discussion focuses on the presentation of MEN2 and on the issues unique to MTC in this setting.

**Evaluation of MEN2A, MEN2B, and Familial MTC**

A clinical diagnosis of MEN2A includes findings of 2 or more MEN2A-associated tumors (MTC, pheochromocytoma, or hyperparathyroidism) in a single individual or in first-degree relatives.\textsuperscript{301,302} 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, Marfanoid body habitus, or the inability to cry tears.\textsuperscript{301,302} For patients known or suspected to have MEN2A or MEN2B, a clinical evaluation includes: 1) biochemical tests evaluating hormone levels; 2) imaging tests to localize MEN2-associated tumors; and 3) genetic counseling and 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. Neck ultrasound of thyroid and cervical lymph nodes should also be performed to document intrathyroidal tumors and to possibly identify cervical lymph node metastases.

Patients with MEN2 should be evaluated for a coexisting pheochromocytoma (see \textit{Evaluation for Pheochromocytoma/Paragangliomas}, above) before administration of anesthetic or before any invasive procedure. Because patients with pheochromocytoma have persistent vasoconstriction, medical therapy (ie, alpha blockade with volume repletion, high salt diet, and additional therapy as needed) is required preoperatively (see \textit{Primary Treatment of Pheochromocytomas/Paragangliomas}, above).

A parathyroid workup is also recommended for patients with MEN2; it consists of serum calcium and 25-OH vitamin D determinations. A neck ultrasound or a sestamibi scan can also be performed as appropriate.

\textbf{Genetic Counseling/Testing in MEN2}

Genetic counseling and \textit{RET} genetic testing should be offered to individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2 (see \textit{Evaluation of MEN2 Syndromes}, above).\textsuperscript{301,302} Genetic counseling and testing should also be offered to at-risk relatives of an individual with a known germline \textit{RET} mutation at a very young age.\textsuperscript{301,302} All patients with MTC should be tested for germline mutation of the \textit{RET} oncogene even if the family history is not suggestive of a hereditary syndrome, because about 50% of patients with presumed sporadic MTC have a \textit{de novo} germline mutation.\textsuperscript{302}

Even with negative \textit{RET} genetic test results, individuals with clinical diagnosis or suspicion of MEN2 should undergo regular surveillance for MEN2-associated tumors. Similarly, at-risk relatives should have MEN2 surveillance even if the affected relative had a negative test result or no genetic testing.\textsuperscript{301} See \textit{MEN2 Surveillance}, below.

\textbf{Primary Treatment of MEN2A, MEN2B, and Familial MTC}

In patients with a positive \textit{RET} oncogene test who are otherwise asymptomatic, prophylactic thyroidectomy is performed during the first 5 years of life depending on the aggressiveness of the inherited \textit{RET} mutation or at diagnosis,\textsuperscript{301,303-305} as detailed in the NCCN Guidelines for Thyroid Carcinoma (available at [www.NCCN.org](http://www.NCCN.org)). The treatment of MTC associated with MEN2 is similar to the management of its sporadic counterpart (see the NCCN Guidelines for Thyroid Carcinoma, available at [www.NCCN.org](http://www.NCCN.org)). However, patients with familial disease are much more likely to have bilateral thyroid carcinomas. In addition, patients may have synchronous pheochromocytoma and medullary thyroid cancer. In these cases, resection of pheochromocytoma should take priority over thyroidectomy.

Patients with MEN2 and familial MTC may be prone to hypoparathyroidism because the thyroid gland is often already removed prophylactically or for treatment of C-cell hyperplasia or MTC. The consensus of the panel is for 4-gland exploration (regardless of
The sestamibi scan results, which are frequently misleading or uninformative with regard to the number of abnormal glands) and selective resection of abnormal parathyroid glands, and for leaving normal parathyroid glands in place (marked with a clip or stitch during thyroid surgery) when possible. Subtotal parathyroidectomy is recommended when all glands appear abnormal. Some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC, while others believe the risk of hypoparathyroidism with this approach (about 6%) is too high to warrant the procedure. If a normal parathyroid gland is not preserved in situ in patients with MEN2A, it can 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.

Management of patients with pheochromocytoma and MEN2 is similar to that of pheochromocytoma in other settings, although the possibility of multiple (ie, bilateral) pheochromocytomas should be considered if surgical resection is being planned. A bilateral adrenalectomy may be necessary. An interesting retrospective, population-based, observational study of 563 patients with MEN2 and pheochromocytoma from 30 centers across 3 continents found that adrenal-sparing resections led to similar rates of recurrence with lower rates of adrenal insufficiency or steroid dependency (43% vs. 86%). More studies are needed, however, before this approach can be routinely recommended.

Future Trial Design
Recent successes have shown that large randomized controlled trials studying treatments for neuroendocrine tumors can provide practice-changing results. Current recommendations for clinical trials in neuroendocrine tumors include the following:

- Pancreatic neuroendocrine tumors should be studied separately from tumors in other locations.
- Well-differentiated and poorly differentiated neuroendocrine carcinomas should be studied in separate trials.
- PFS 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.


119. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or...
NCCN Guidelines Version 2.2016 Neuroendocrine Tumors


194. Raymond E, Niccoli P, Raoul J, et al. Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients (Pts) with advanced unresectable pancreatic neuroendocrine tumors (NET) [abstract]. J Clin Oncol 2011;29 (suppl):4008. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/4008?sid =af3f1a6a7-a6a3-41fa-907e-6be57ae28b63.


Neuroendocrine Tumors


Cancer Institute Neuroendocrine Tumor clinical trials planning meeting.
J Clin Oncol 2011;29:934-943. Available at: