NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroendocrine Tumors

Version 1.2015

NCCN.org
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Neuroendocrine Tumors

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NCCN Guidelines Panel Disclosures

¶ Surgery/Surgical oncology
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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.
Updates in Version 1.2015 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2014 include:

**Global**

- “Carcinoid tumors” was changed to “Neuroendocrine tumors of the gastrointestinal tract, lung and thymus (carcinoid tumors).”
- Details regarding biochemical evaluations are now listed in the Principles of Biochemical Testing (NE-B). Specific biochemical tests were removed from the algorithm where appropriate and replaced with: “Biochemical evaluation as clinically indicated (see NE-B).”
- The following footnotes were removed:
  - “Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.”
  - “Prior to evaluating ACTH, confirm hypercortisolemia using one of the following: Overnight 1 mg dexamethasone suppression test with 8 am plasma cortisol; Repeated (2–3) midnight salivary cortisols; 24-hour urine free cortisol.”
  - “For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.”
- The following footnote was moved from the algorithm to the Principles of Systemic Anti-Tumor Therapy (NE-D): “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.”

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

(Carcinoid Tumors)

**CARC-4**

- Hypergastrinemic patients, Tumor ≤2 cm:
  - The treatment for Zollinger-Ellison patients was revised to include lanreotide: “Octreotide or lanreotide for Zollinger-Ellison patients.” The “category 2B” recommendation was removed.
  - Surveillance recommendations were revised:
    - Removed separate surveillance recommendations for those treated with observation.
    - “No markers were removed: “H&P and markers.”
- Hypergastrinemic patients, Tumor >2 cm: Surveillance recommendations following the resection now match the surveillance recommendations for patients with normal gastrin.
- Footnote “n” was added: “See Principles of Systemic Anti-Tumor Therapy (NE-D).” (Also on CARC-6)

**CARC-5**

- Evaluation, bronchopulmonary and thymus: Under as appropriate: “ACTH/cortisol” was replaced by “Biochemical workup for Cushing’s syndrome if clinically indicated (See NE-B).”
- Thymus, locoregional disease: Treatment options after “incomplete resection” were revised: “RT +/- and/or chemotherapy (category 3 for addition of chemotherapy),”

**CARC-6**

- Under locoregional unresectable disease and/or distant metastases: 2nd bullet was revised: “Consider 24-hour urine 5-HIAA, if not already done.”
- For asymptomatic low tumor burden, clinically significant tumor burden, and carcinoid syndrome, lanreotide was added as a treatment option: “Octreotide or lanreotide.”
- Following clinically significant progressive disease:
  - The first option was revised: “Octreotide or lanreotide, if not already receiving.”
  - The following option was added: “Consider interferon alfa-2b (category 3).”
- Footnotes:
  - Footnote “b” was added: “See Principles of Biochemical Testing (NE-B).”
  - The following footnote was removed: “Anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon, oxaliplatin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. See Discussion for details.”

**Neuroendocrine Tumors of the Pancreas**

**PanNET-1**

- The following footnote was removed: “Risks and benefits of surgical resection should be carefully weighed in patients with small lesions.”
- Footnote “h” was revised: “Observation can be considered in select cases: tumors <1 cm, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities.”

Continued on next page
Updates in Version 1.2015 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2014 include:

**PanNET-2**
- For locoregional disease, lanreotide was added as an option: “Consider octreotide or lanreotide.”
- Footnote “j” was added: “See Principles of Systemic Anti-Tumor Therapy (NE-D).” (Also on PanNET-4, PanNET-5, and PanNET-7)

**PanNET-3**
- Footnote “m” was revised: “Somatostatin scintigraphy only if treatment with a somatostatin analog is planned. Octreotide somatostatin analogs should only be given if tumor demonstrates somatostatin receptors. In the absence of somatostatin receptors, somatostatin analogs can profoundly worsen hypoglycemia. (See Discussion for details).”

**PanNET-4**
- Locoregional disease:
  - First bullet was revised: “Stabilize glucose levels with IV fluids and octreotide or lanreotide.”
  - Second bullet was added: “Treat hyperglycemia and diabetes, as appropriate.”

**PanNET-5**
- Locoregional disease, first bullet was revised: “Stabilize with IV fluids and octreotide or lanreotide.”

**PanNET-6**
- 3–12 mo postresection, first bullet was revised: “H&P and consider biochemical markers from preoperative evaluation as clinically indicated.”
- >1 y postresection to a maximum of 10 y, second sub-bullet was revised: “Consider biochemical markers as clinically indicated.”

**PanNET-7**
- After asymptomatic, low tumor burden, and stable disease, a bullet was added: “Consider treatment with octreotide or lanreotide.”
- After manage clinically significant symptoms as appropriate, the first option was revised: “Consider octreotide or lanreotide if not already receiving (category 2B) and/or…”
- Footnote “j” was added: “See Principles of Systemic Anti-Tumor Therapy (NE-D).”
- The following footnote was removed: “The following agents have been used: capecitabine, dacarbazine, doxorubicin, 5-FU, streptozocin, and temozolomide.”

**Neuroendocrine Tumors of Unknown Primary**

**NUP-1**
- Footnote “a” was revised: “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 (See NE-B). Alpha blockade is required prior to biopsy or manipulation for suspected pheochromocytoma or paraganglioma (See PHEO-1). Octreotide premedication is required before biopsy in a suspected functioning carcinoid tumor.”

**Adrenal Gland Tumors**

**AGT-1**
- Evaluation: After functional evaluation, the list of biochemical tests was replaced with: “Biochemical workup as clinically indicated (See NE-B) for: Hyperaldosteronism, Cushings syndrome, Pheochromocytoma.”
- Clinical diagnosis
  - Multiple hormones” was added with a link to “See Primary Treatment (AGT-5).”
- The following footnote was removed: “For cervical paraganglioma, consider measuring dopamine.”

**AGT-2**
- History of prior or current malignancy with risk of or suspicion of adrenal metastasis
  - The second bullet was added: “Check plasma or 24-hour urine fractionated metanephrines.”
  - Additional evaluation recommendation was revised: “Consider image-guided needle biopsy if not pheochromocytoma.”
  - Hyperaldosteronism, suspect benign
  - Surgical candidate, additional evaluation recommendation was revised: “Consider adrenal vein sampling for aldosterone and cortisol.”

**AGT-3**
- Clinical diagnosis, the tumor size threshold was changed from “5 cm” to “4 cm.”
- The following primary treatment recommendations for ACTH-dependent Cushings’s syndrome were removed: “If ectopic, remove primary tumor if possible; or if primary tumor unresectable, then bilateral laparoscopic adrenalectomy or medical management (as described above).”
- Footnote “i” was revised: “Consider octreotide somatostatin analogs for symptom control if somatostatin scintigraphy is positive.”

**AGT-5**
- Follow-up schedule for localized disease was revised: “Every 3–12 mo up to 5 y (after 5 y as clinically indicated).”
Updates in Version 1.2015 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2014 include:

### Pheochromocytoma

**PHEO-1**

- **Evaluation**
  - Recommended, the second bullet was revised: “Chest/abdominal multiphasic CT, MRI, or FDG-PET.”
  - “Recommended” was added to “Genetic counseling.”
- **Footnotes**
  - Footnote “e” was revised: “Genetic counseling and genetic testing are recommended when appropriate. A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. (See Discussion).”
  - Footnote “g” was revised: “...Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. The calcium channel blocker nicardipine-Dihydropyridine calcium channel blockers may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The endpoint of alpha blockade is orthostasis.”

**PHEO-2**

- **Primary Treatment**
  - Treatment options for resectable was revised: “Alpha blockade with aggressive volume repletion ± alpha-methyltyrosine ± beta blockade preoperative (beta blockade only after alpha blockade) + Resection (laparoscopic preferred when safe and feasible).”
  - Locally unresectable, distant metastases: Treatment options were reorganized to list alpha/beta blockade options prior to resection options.

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

**HGNET-1**

- **Evaluation**
  - As appropriate, “Somatostatin scintigraphy” was added with the following footnote: “Consider somatostatin analogs if somatostatin scintigraphy is positive.”
- **Primary treatment**
  - After locoregional, unresectable and metastatic, the following bullet was removed: “Consider octreotide therapy if hormone secreting.”
  - For resectable, locoregional/unresectable, and metastatic disease, the chemotherapy recommendation was revised: “Chemotherapy with small cell lung-cancer regimens”
  - Footnote “c” was revised: “Small cell lung cancer regimens such as cisplatin or carboplatin and etoposide are generally recommended as primary treatment. However, evolving data...”

### Multiple Endocrine Neoplasia, Type 1

**MEN1-2**

- Footnote “f” was added: “A sestimibi scan may not accurately depict the total number of abnormal glands. Patients should receive 4-gland exploration regardless of sestamibi scan results.” (Also on MEN2-2, as footnote “g”)
- The following footnotes were removed:
  - “Gastrin levels need to be completed while fasting and off proton pump inhibitors for 1 week.”
  - “Potential hormones secreted include ACTH, FSH, LH, TSH, GH, and prolactin.” Link was added to NE-B for biochemical evaluation as clinically indicated.

### MEN1-3

- Under PanNET, the fourth bullet was revised: “Consider cross sectional imaging with multiphasic abdominal CT, MRI scan every 1–3 y.”
- For parathyroid and pituitary, the information regarding referrals was revised: “Consider referral to a specialist endocrinology.”

**MEN1-A**

- The last bullet was added: “Hyperparathyroidism is usually treated first in MEN-1 patients with hyperparathyroidism and pancreatic neuroendocrine tumors.”

**MEN1-B**

- The second bullet was revised: “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.”
Updates in Version 1.2015 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2014 include:

**Multiple Endocrine Neoplasia, Type 2**

**MEN2-1**
- The first sub-bullet was revised: “A clinical diagnosis of MEN2A includes two or more MEN2A-associated tumors (MTC, pheochromocytoma, or hyperparathyroidism) in a single individual or in close relatives.”
- **Footnotes**
  - Footnote “e” was added: “For the treatment of synchronous tumors, surgical resection of pheochromocytoma should take priority over thyroidectomy for medullary thyroid cancer.”
  - Footnote “l” was added: “For synchronous bilateral pheochromocytomas, a bilateral adrenalectomy is recommended.”

**MEN2-2**
- Treatment
  - Pheochromocytoma, the first treatment recommendation was revised: “Refer to endocrinology for Medical preparation with alpha + beta blockades for adrenalectomy and…”
- **Footnotes**
  - Footnote “e” was added: “For the treatment of synchronous tumors, surgical resection of pheochromocytoma should take priority over thyroidectomy for medullary thyroid cancer.”
  - Footnote “l” was added: “For synchronous bilateral pheochromocytomas, a bilateral adrenalectomy is recommended.”

**MEN2-A**
- The following sub-bullet was added to 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**

**NE-A 2 of 4**
- The first two bullets were revised and combined: “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. Functional status of a NET need not be included in the pathology report. However, if a specific clinical situation suggests that correlation with histologic evidence of peptide hormone may be helpful, then histochemical or immunohistochemical studies may be performed and included in the report. However, a note may be added with additional information of the immunoreactivity of specific peptide hormone.”

**Principles of Biochemical Testing (NE-B)**
- This section was revised significantly.

**Surgical Principles for Management of Neuroendocrine Tumors (NE-C)**
- The eighth bullet was revised: “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.”

**Principles of Systemic Anti-Tumor Therapy (NE-D)**
- This section was newly added to the algorithm.

**Discussion (MS-1)**
- The discussion section was updated to reflect the changes in the algorithm.
Neuroendocrine tumors of the gastrointestinal tract, lung and thymus (carcinoid tumors)\(^{b}\)
Clinical presentations:
- Jejunal, ileal, colon (See CARC-1)
- Duodenal (See CARC-1)
- Appendix (See CARC-2)
- Rectal (See CARC-3)
- Gastric (See CARC-4)
- Bronchopulmonary, thymus (See CARC-5)
- Atypical lung carcinoid
- Locoregional unresectable disease and/or distant metastases (See CARC-6)

Neuroendocrine tumors of the pancreas\(^{b}\)
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 (high-grade) neuroendocrine tumors/Large or small cell carcinoma other than lung (See HGNET-1)

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

\(^{b}\)Guidelines pertain to well-differentiated tumors. For poorly differentiated/high-grade/large or small cell carcinomas, see HGNET-1.

\(^{c}\)Includes adrenal cortical tumors and incidentalomas.
### CLINICAL LOCATION

#### Jejunal/ileal/colon

- **Recommended:**
  - Abdominal/pelvic multiphasic CT or MRI
  - As appropriate:
    - Somatostatin scintigraphy
    - Colonoscopy
    - Small-bowel imaging
    - Chest CT
    - Biochemical evaluation as clinically indicated
    - See NE-B

- **Locoregional disease**
  - Bowel resection with regional lymphadenectomy
de
  - Consider prophylactic cholecystectomy
echen when appropriate

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

- **Surveillance**
  - 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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#### Duodenal

- **Recommended:**
  - Abdominal/pelvic multiphasic CT or MRI
  - As appropriate:
    - Somatostatin scintigraphy
    - EGD/endoscopic ultrasound (EUS)
    - Chest CT
    - Biochemical evaluation as clinically indicated
    - See NE-B

- **Locoregional disease**
  - Bowel resection with regional lymphadenectomy
de
  - Consider prophylactic cholecystectomy
echen when appropriate

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

- **Surveillance**
  - 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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NCCN Guidelines Version 1.2015
Neuroendocrine Tumors of the Gastrointestinal Tract, Lung and Thymus (Carcinoid Tumors)

CLINICAL LOCATION

EVALUATION\(^a,b\) PRIMARY TREATMENT OF NON-METASTATIC DISEASE\(^c\)

SURVEILLANCE\(^g,h\)

Rectal

≤2 cm\(^k\) → Resection\(^c\) (transanal or endoscopic excision, if possible)

<1 cm: No follow-up required
1–≤2 cm: Endoscopy with rectal MRI or EUS at 6 and 12 mo, then as clinically indicated

3–12 mo postresection:
• H&P
• Consider 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)

Metastatic disease → Metastatic Disease (CARC-6)

>2 cm →

>2 cm →

\(^a\)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).
\(^g\)Earlier, if symptoms.
\(^h\)Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.
\(^k\)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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**Clinical Location**

Gastric →

**Evaluation**

- **Locoregional disease**
  - Recommended: EGD
  - Gastrin level
  - Multiphasic CT or MRI for patients with normal gastrin
  - As appropriate: EUS
  - Chest CT
  - Somatostatin scintigraphy for patients with normal gastrin
  - $B_{12}$ level if hypergastrinemia
  - Biochemical evaluation as clinically indicated (See NE-B)

- **Metastatic disease** → Metastatic Disease (CARC-6)
  - Hypergastrinemic patients
  - Tumor ≤ 2 cm
  - Solitary or multiple

**Primary Treatment of Non-Metastatic Disease**

- **Patient with normal gastrin**
  - Tumor > 2 cm
  - Solitary or multiple

- **Endoscopic resection**, if possible or Surgical resection
  - Radical gastric resection + lymph node removal
  - Consider endoscopic or wedge resection for tumors ≤ 2 cm

**Surveillance**

- **New lesion(s) or increasing tumors, consider antrectomy**
  - H&P
  - Years 1–3: every 6–12 mo with EGD
  - Years 4+:
    - Annually with EGD
    - Imaging studies as clinically indicated

- **3–12 mo postresection:**
  - H&P
  - Biochemical evaluation as clinically indicated (See NE-B)
  - Multiphasic CT or MRI

- **>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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### CLINICAL LOCATION

#### Broncho-pulmonary

<table>
<thead>
<tr>
<th>Recommended:</th>
<th>Localized disease</th>
<th>Metastatic disease</th>
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<tbody>
<tr>
<td>Chest CT and abdominal multiphasic CT or MRI</td>
<td></td>
<td>See NCCN Guidelines for Small Cell Lung Cancer; Lung Neuroendocrine Tumor algorithm</td>
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<tr>
<td>As appropriate:</td>
<td>Locoregional disease</td>
<td>Metastatic Disease (CARC-6)</td>
</tr>
<tr>
<td>• Somatostatin scintigraphy</td>
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<tr>
<td>• Bronchoscopy</td>
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<tr>
<td>• Biochemical workup for Cushing’s syndrome if clinically indicated (See NE-B)</td>
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<tr>
<td>• Other biochemical evaluation as clinically indicated (See NE-B)</td>
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#### Thymus

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<thead>
<tr>
<th>Recommended:</th>
<th>Localized disease</th>
<th>Resect⁴</th>
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<tbody>
<tr>
<td>Chest/mediastinal multiphasic CT and abdominal multiphasic CT or MRI</td>
<td>Complete Resection</td>
<td>Metastatic Disease (CARC-6)</td>
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<tr>
<td>As appropriate:</td>
<td>Locoregional disease</td>
<td>Metastatic Disease (CARC-6)</td>
</tr>
<tr>
<td>• Somatostatin scintigraphy</td>
<td>Incomplete Resection</td>
<td></td>
</tr>
<tr>
<td>• Bronchoscopy</td>
<td></td>
<td>RT and/or chemotherapy (category 3)</td>
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<tr>
<td>• Biochemical workup for Cushing’s syndrome if clinically indicated (See NE-B)</td>
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⁴Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

⁵Thymic carcinoids are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

⁶Consider 5-FU or capecitabine at radiosensitizing doses. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

Locoregional unresectable disease and/or distant metastases
- Imaging:
  - Multiphasic CT or MRI
  - Consider Somatostatin scintigraphy
- Consider 24-hour urine 5-HIAA, if not already done
- Consider chromogranin A (category 3)

If complete resection possible

- Resect primary + metastases

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

Locally symptomatic from primary tumor
- Consider resection of primary tumor

Clinically significant tumor burden
- Octreotide or lanreotide

Carcinoid Syndrome
- Octreotide or lanreotide
- Echocardiogram

Clinically significant progressive disease

Octreotide or lanreotide, if not already receiving and
- Consider hepatic regional therapy (arterial embolization, chemoembolization, radioembolization) [category 2B]
  - 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.
- Consider cytoreductive surgery/ablative therapy (category 2B)
  - Only if near complete resection can be achieved.
- Consider everolimus (10 mg/d) (category 3)
- Consider interferon alfa-2b (category 3)
- Consider cytotoxic chemotherapy (category 3), if no other options feasible

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For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway. Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy. 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. 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 Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Pancreatic Neuroendocrine Tumors (PanNET-2)

CLINICAL LOCATION

Gastrinoma (usually duodenal or head of pancreas)

Recommended:
- Gastrin levels (basal, stimulated as clinically indicated)
- Multiphasic CT or MRI
- As appropriate:
  - Somatostatin scintigraphy
  - EUS
  - Other biochemical evaluation as clinically indicated (See NE-B)

Locoregional disease

Exophytic or peripheral tumors by imaging

Enucleation of tumor + periduodenal node dissection

Distal pancreatectomy + splenectomy

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

Distal pancreatic resection ± spleenectomy

As appropriate:
- Manage gastric hypersecretion with proton pump inhibitors
- Consider octreotide or lanreotide
- Duodenectomy
- Duodenotomy and intraoperative ultrasound; local resection/enucleation of tumor(s) + periduodenal node dissection

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

Occult No primary tumor or metastases on imaging

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

Distal

Operative

See Surveillance (PanNET-6)

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.

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

cSee Principles of Biochemical Testing (NE-B).

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

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

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

gGastrin levels need to be completed while fasting and off proton pump inhibitors for 1 week.

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

iNot adjacent to the main pancreatic duct.

jThere is some disagreement among panel members regarding the role of splenectomy in all cases.
**CLINICAL LOCATION**

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

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

---

**Insulinoma**

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

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

**Metastatic disease**

**As appropriate:**
- Somatostatin scintigraphy\(^m\)

---

**Locoregional disease**

**Exophytic or peripheral tumors by imaging\(^k\)**

- Head
- Distal

**Stabilize glucose levels with diet and/or diazoxide**

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

- Head
- Distal

**Pancreateoduodenectomy\(^e\)**

**Tumor enucleation, consider laparoscopic resection\(^e\)**

---

**Distal disease**

**Metastatic disease**

**See Metastases (PanNET-7)**

---

**Head or Distal**

**See Surveillance (PanNET-6)**

---

\(^b\) 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).

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

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

\(^l\) Not adjacent to the main pancreatic duct.

\(^m\) Somatostatin scintigraphy only if treatment with a somatostatin analog is planned. Somatostatin analogs should only be given if tumor demonstrates somatostatin receptors. In the absence of somatostatin receptors, somatostatin analogs can profoundly worsen hypoglycemia. (See Discussion for details).

\(^n\) Splenectomy should be performed for larger tumors involving splenic vessels.

---

**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.
Glucagonoma (usually tail) →

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

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

Locoregional disease →

Recommended:
- Stabilize glucose levels with IV fluids and octreotide or lanreotide
- Treat hyperglycemia and diabetes, as appropriate

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

Distal pancreatectomy + peripancreatic lymph node dissection + splenectomy

Metastatic disease → See Metastases (PanNET-7)

Pancreatoduodenectomy + peripancreatic lymph nodes

Head (rare)

Distal

See Surveillance (PanNET-6)

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.

See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
See Principles of Biochemical Testing (NE-B).
For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
See Principles of Systemic Anti-Tumor Therapy (NE-D).
Small (<2 cm), peripheral glucagonomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.
Hypercoaguable state has been described. Perioperative anticoagulation can be considered.
VIPoma →

**EVALUATION**

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

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

- **Locoregional disease**
  - **Recommended:**
    - Stabilize with IV fluids and octreotide or lanreotide
    - Correct electrolyte imbalance (K⁺, Mg²⁺, HCO₃⁻)
  - **As appropriate:**
    - Somatostatin scintigraphy
    - EUS
    - Biochemical evaluation as clinically indicated (See NE-B)

- **Head**
  - Pancreatoduodenectomy + peripancreatic lymph nodes

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

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

**See Surveillance (PanNET-6)**

---

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

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

**References:**
- See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
- See Principles of Biochemical Testing (NE-B).
- For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
- See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
- Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
- See Principles of Systemic Anti-Tumor Therapy (NE-D).
- Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.
NCCN Guidelines Version 1.2015
Neuroendocrine Tumors of the Pancreas

SURVEILLANCE\textsuperscript{r,s}

RECURRENT DISEASE

MANAGEMENT OF RECURRENT DISEASE\textsuperscript{e}

\begin{itemize}
\item 3–12 mo postresection:
  \begin{itemize}
  \item H&P and consider biochemical markers from preoperative evaluation 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 \rightarrow Resection\textsuperscript{e}

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

Distant metastases \rightarrow 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 scintigraphy and FDG-PET 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\(^e,^t\) → Resect metastases + primary\(^u\) → Clinically significant progressive disease, see below

Locoregional unresectable disease and/or Distant metastases

Asymptomatic, low tumor burden, and stable disease

• Observe with markers and scans every 3–12 mo
• Consider treatment with octreotide\(^j,v\) or lanreotide\(^j,v\)

Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease

Manage clinically significant symptoms as appropriate (PanNET-1, PanNET-2, PanNET-3, PanNET-4, and PanNET-5)

Clinically significant progressive disease, see below

Consider octreotide\(^j,v\) or lanreotide\(^j,v\) if not already receiving and/or
• Everolimus\(^j\) (10 mg/d) or
• Sunitinib\(^j\) (37.5 mg/d) or
• Cytotoxic chemotherapy\(^j\) or
• Hepatic regional therapy (ie, arterial embolization, chemoembolization, radioembolization [category 2B]) or
• Cytoreductive surgery/ablative therapy\(^w\) (category 2B)

\(^e\)See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
\(^j\)See Principles of Systemic Anti-Tumor Therapy (NE-D).
\(^t\)Noncurative debulking surgery might be considered in select cases.
\(^v\)Somatostatin analogs should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).
\(^w\)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.

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.
**INITIAL WORKUP**

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

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

**Primary not discovered**

- Poorly differentiated
  - See Primary Treatment for poorly differentiated (high-grade) neuroendocrine tumor (*HGNET-1*)

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

**Primary found**

- See specific tumor type (*NE-1*)

---

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

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

**Clinical Presentation**
- History of prior or current malignancy with risk of or suspicion of adrenal metastasis

**Evaluation**
- Adrenal gland tumor on imaging
- Morphologic evaluation
- Adrenal protocol (CT scan or MRI) to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics
- Biochemical workup as clinically indicated (See NE-B) for:
  - Hyperaldosterism
  - Cushing’s syndrome
  - Pheochromocytoma
- Multiple hormones

**Clinical Diagnosis**
- Hyperaldosteronism
- Cushing’s syndrome
- Non-functioning tumor
- Pheochromocytoma
- See Primary Treatment (AGT-2)
- See Primary Treatment (AGT-3)
- See Primary Treatment (AGT-4)
- See Primary Treatment (AGT-5)

---

*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 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.)

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### NCCN Guidelines Version 1.2015

#### Adrenal Gland Tumors

**CLINICAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>History of prior or current malignancy with risk of or suspicion of adrenal metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rule out pheochromocytoma*</td>
</tr>
<tr>
<td>• Check plasma or 24-hour urine fractionated metanephrines* (See NE-B)</td>
</tr>
<tr>
<td>• Consider image-guided needle biopsy if not pheochromocytoma*</td>
</tr>
<tr>
<td>Metastasis from other site discovered</td>
</tr>
<tr>
<td>Adrenal cortical tissue</td>
</tr>
<tr>
<td>See Evaluation (AGT-1)</td>
</tr>
</tbody>
</table>

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

**ADDITIONAL EVALUATION**

- Consider adrenal vein sampling for aldosterone and cortisol

**PRIMARY TREATMENT**

- Not a surgical candidate
  - Medical management of hypertension and hypokalemia with spironolactone or eplerenone

- Surgical candidate
  - Adrenal vein sampling for aldosterone and cortisol
  - Adrenalectomy, laparoscopic preferred

- Hyperaldosteronism, suspect malignant
  - Open adrenalectomy

---

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

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

*fFalse negatives are possible; may consider proceeding directly to surgery in selected cases.

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

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

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 1.2015
Adrenal Gland Tumors

**CLINICAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>ACTH-independent Cushing’s syndrome</th>
<th>Tumor &lt;4 cm, benign imaging characteristics, and contralateral gland abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor &gt;4 cm or inhomogeneous, irregular margins, local invasion, or other malignant imaging characteristics</td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL EVALUATION**

- Adrenal vein sampling for cortisol

**PRIMARY TREATMENT**

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

- Unilateral adrenalectomy with removal of most active side, laparoscopic preferred
- Postoperative corticosteroid supplementation until HPA axis recovery

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

- Bilateral adrenalectomy if severe Cushing’s syndrome and medical failure

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

- Metastatic disease

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

- Adrenalectomy for suspected carcinoma (laparoscopic generally not appropriate)

- Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion

- See Adrenal Carcinoma (AGT-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.
Non-functioning tumor

- Benign-appearing adenoma (<4 cm) by CT or MRI criteria or myelolipoma by radiographic features (any size) without symptoms
  - Benign-appearing adenoma of intermediate size (4–6 cm) by CT or MRI criteria
  - Repeat imaging in 3–6 mo
  - Repeat imaging in 6–12 mo
- Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion

Suspected carcinoma
- Intermediate-size tumor (4–6 cm) with aggressive features
  - Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion
- Large tumor (>6 cm) with aggressive features
  - Consider adrenalectomy or short-interval follow-up
- Adrenalectomy for suspected carcinoma
  - See Adrenal Carcinoma (AGT-5)

Non-functioning tumor
- Enlarging (>1 cm in 1 y)
  - Consider adrenalectomy or short-interval follow-up
  - Repeat imaging in 6–12 mo

CLINICAL DIAGNOSIS
- Non-functioning tumor
- Suspected carcinoma

ADDITIONAL EVALUATION
- Repeat imaging in 3–6 mo
- Repeat imaging in 6–12 mo
- Imaging of chest, abdomen, and pelvis to evaluate for metastases and local invasion

PRIMARY TREATMENT
- No further follow-up
- Repeat imaging in 6–12 mo
- Adrenalectomy for suspected carcinoma
- Repeat imaging in 6–12 mo
- Adrenalectomy for suspected carcinoma

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

Localized disease

- Resect tumor and adjacent lymph nodes
  - Open adrenalectomy recommended

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

Metastatic disease

- Consider observation with imaging for clinically indolent disease every 3 mo and biomarkers (if tumor initially functional)
- Consider resection of primary tumor and metastases if >90% removable, particularly if functional
- Consider systemic therapy, preferably in clinical trial
  - Cisplatin or carboplatin + etoposide ± doxorubicin ± mitotane
  - Streptozocin ± mitotane
  - Mitotane monotherapy

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

ADRENAL CARCINOMA FOLLOW-UP

Localized disease

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

Metastatic disease

- Consider observation with imaging for clinically indolent disease every 3 mo and biomarkers (if tumor initially functional)
- Consider resection of primary tumor and metastases if >90% removable, particularly if functional
- Consider systemic therapy, preferably in clinical trial
  - Cisplatin or carboplatin + etoposide ± doxorubicin ± mitotane
  - Streptozocin ± mitotane
  - Mitotane monotherapy

Follow-up every 3–12 mo up to 5 y (after 5 y as clinically indicated)
- Consider imaging and biomarkers, if tumor initially functional

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.

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.
Cross-sectional imaging to stage disease.
Increased risk for local recurrence and peritoneal spread when done laparoscopically.
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.
Mitotane may have more benefit for control of hormone symptoms than control of tumor.
High-risk local recurrence features include: positive margins, rupture of capsule, large size, and high grade.
# NCCN Guidelines Version 1.2015
## Pheochromocytoma/Paraganglioma

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EVALUATION (^{a,b})</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma/paraganglioma</td>
<td><strong>Recommended:</strong>&lt;br&gt;- Plasma or 24-hour urine fractionated metanephrines (^{c,d})&lt;br&gt;- Chest/abdominal multiphasic CT, MRI, or FDG-PET&lt;br&gt;- Genetic counseling recommended (^{e})&lt;br&gt;&lt;br&gt;As appropriate:&lt;br&gt;- Bone scan, if bone symptoms&lt;br&gt;- MIBG scan/Somatostatin scintigraphy, if suspect multiple tumors or CT negative</td>
<td><strong>Alpha blockade(^{f}) with aggressive volume repletion</strong>&lt;br&gt;± alpha-methyltyrosine&lt;br&gt;± beta blockade preoperative (beta blockade only after alpha blockade)(^{g})&lt;br&gt;See Primary Treatment (PHEO-2)</td>
</tr>
</tbody>
</table>

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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).

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

\(^{d}\)For cervical paraganglioma, consider measuring dopamine.

\(^{e}\)Genetic counseling and genetic testing are recommended when appropriate. A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. ([See Discussion](#)).

\(^{f}\)Phenoxybenzamine or doxazosin can be considered.

\(^{g}\)Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room. Selective alpha1-blocking agents, such as prazosin, terazosin, and doxazosin, are alternative medications when long-term therapy is required for metastatic pheochromocytoma. Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. Dihydropyridine calcium channel blockers may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The endpoint of alpha blockade is orthostasis.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### NCCN Guidelines Version 1.2015

#### Pheochromocytoma/Paraganglioma

#### PRIMARy TREATMENT

<table>
<thead>
<tr>
<th>Resectable</th>
<th>Locally unresectable</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha blockade with aggressive volume repletion ± alpha-methyltyrosine ± beta blockade preoperative (beta blockade only after alpha blockade) + Resection (laparoscopic preferred when safe and feasible)</td>
<td>RT + alpha blockade ± alpha-methyltyrosine ± beta blockade ± cytoreductive (R2) resection, if possible</td>
<td>Continuous alpha blockade ± alpha-methyltyrosine ± beta blockade (optional) ± cytoreductive (R2) resection when possible or Clinical trial or Systemic chemotherapy (eg, dacarbazine, cyclophosphamide, vincristine) or 131I-MIBG (requires prior positive MIBG scan with dosimetry)</td>
</tr>
</tbody>
</table>

#### SURVEILLANCE

<table>
<thead>
<tr>
<th>3–12 mo postresection: • H&amp;P, blood pressure, and markers</th>
<th>&gt;1 y postresection up to 10 y: • H&amp;P, blood pressure, and markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider CT or MRI or FDG-PET scan</td>
<td>• Years 1–3: every 6–12 mo • Years 4+ up to 10 y: annually</td>
</tr>
<tr>
<td>• Consider CT or MRI or FDG-PET scan</td>
<td>• Genetic counseling and testing as clinically indicated</td>
</tr>
</tbody>
</table>

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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.

---

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

**f**Phenoxybenzamine or doxazosin can be considered.

**g**Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room. Selective alpha1-blocking agents, such as prazosin, terazosin, and doxazosin, are alternative medications when long-term therapy is required for metastatic pheochromocytoma. Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. Dihydropyridine calcium channel blockers may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The endpoint of alpha blockade is orthostasis.

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

**i**Earlier, if symptoms.
**TUMOR TYPE**

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

**EVALUATION**

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

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

**PRIMARY TREATMENT**

<table>
<thead>
<tr>
<th>Locoregional, unresectable</th>
<th>RT + chemotherapy&lt;sup&gt;c&lt;/sup&gt;</th>
<th></th>
<th>H&amp;P + appropriate imaging studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic</td>
<td>Chemotherapy&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Every 3 mo for 1 y, then every 6 mo</td>
</tr>
</tbody>
</table>

**SURVEILLANCE**

- H&P + appropriate imaging studies:
  - Every 3 mo for 1 y, then every 6 mo

---

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

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

<sup>c</sup>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 judgement should be used. See NCCN Guidelines for Small Cell Lung Cancer.

<sup>d</sup>Consider somatostatin analogs for symptom control, if somatostatin scintigraphy is positive.

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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.
A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors: multi-gland parathyroid hyperplasia; pancreatic NET; or pituitary tumors. 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. 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
- An at-risk relative of an individual with a known germline MEN1 mutation

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

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10% of cases have de novo MEN1 mutations.
**NCCN Guidelines Version 1.2015**

**Multiple Endocrine Neoplasia, Type 1**

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**Parathyroid:**
- Recommended
  - Serum calcium
  - Parathyroid hormone (PTH)
  - As appropriate
    - 24-hour urine calcium
    - 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 scintigraphy

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

---

**TREATMENT**

- Subtotal parathyroidectomy
- Cryopreservation of parathyroids ± thymectomy
- Total parathyroidectomy with autotransplantation
- Cryopreservation of parathyroids ± thymectomy

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

---

*For MEN1 genetic testing recommendations, see MEN1-1.*

*A sestamibi scan may not accurately depict the total number of abnormal glands. Patients should receive 4-gland exploration regardless of sestamibi scan results.*
MEN1 SURVEILLANCE

Parathyroid:  
- Calcium annually  
- If calcium rises:  
  - Serum PTH  
  - Reimage with neck ultrasound and/or parathyroid sestamibi scan  
  - Consider MRI neck  
  Consider referral to specialist

PanNET:  
- Serum gastrin annually  
- Serum chromogranin A and/or pancreatic polypeptide annually (category 3)  
- Follow other previously elevated serum hormones or as symptoms indicate  
- Consider cross-sectional imaging every 1–3 y  
- Consider serial EUS  
See appropriate sporadic PanNET workup and treatment (PanNET-1 through PanNET-5)

Pituitary:  
- MRI of pituitary every 3–5 y  
- Repeat prolactin, IGF-1, and other previously abnormal pituitary hormones annually or as symptoms indicate  
If tumor grows or hormones increase, consider referral to specialist

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 (Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97:2990-3011).

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.

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.
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 close relatives\(^a,b\)
  ◆ A clinical diagnosis of MEN2B includes the presence of MTC, pheochromocytoma, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, “marfanoid” body habitus, or inability to cry tears\(^a,b\)

• For patients known or suspected to have MEN2, a clinical evaluation includes: See MEN2 Clinical Evaluation and Primary Treatment (MEN2-2)
  1) Biochemical tests evaluating hormone levels;
  2) Imaging tests needed to localize MEN2-associated tumors; and
  3) Genetic counseling and testing

• Genetic counseling and RET genetic testing should be offered to the following:
  ◆ An individual with a diagnosis of MTC or clinical diagnosis of MEN2 or primary C-cell hyperplasia\(^a,b,c\)
  ◆ An at-risk relative of an individual with a known germline RET mutation\(^a,b\)
    ◊ Genetic testing of at-risk family members at a very early age.\(^a,b\) See NCCN Guidelines for Thyroid Carcinoma: Medullary Thyroid Cancer section.

• MEN2 clinical evaluation should be offered to the following:
  ◆ Individuals with a clinical diagnosis or suspicion of MEN2 even with negative RET genetic test
  ◆ At-risk relatives even if RET mutation has not been identified in the affected family member\(^b\) or if RET genetic testing has not been performed in the affected or at-risk family member

\(^c\)50% of cases have \textit{de novo} RET mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for RET mutations should still be performed on the affected individual.
# NCCN Guidelines Version 1.2015
## Multiple Endocrine Neoplasia, Type 2

## CLINICAL EVALUATION\(^d\)

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

**Parathyroid:**
- Recommended
  - Biochemical evaluation as clinically indicated \(\text{See NE-B}\)
  - As appropriate
    - 24-hour urine calcium
    - Neck ultrasound
    - Parathyroid sestamibi scan\(^g\)

**Pheochromocytoma:**\(^h, i\)
- Recommended:
  - Biochemical evaluation as clinically indicated \(\text{See NE-B}\)
  - MRI or multiphasic CT of abdomen
- As appropriate:
  - MIBG scan/somatostatin scintigraphy

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## TREATMENT\(^e\)

- See NCCN Guidelines for Thyroid Carcinoma

## SURVEILLANCE\(^f\)

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

---

\(\text{See NCCN Guidelines for Thyroid Carcinoma}\)

**Medical preparation with alpha + beta blockers for adrenalectomy and Adrenalectomy\(^l\)**
- Involved side only, laparoscopic procedure preferred as appropriate

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\(\text{See Pheochromocytoma Guidelines (PHEO-1)}\)

\(\text{Diagnosis of or clinical suspicion of MEN2 (See MEN2-1)}\)

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\(\text{Note: All recommendations are category 2A unless otherwise indicated.}\)

\(\text{Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.}\)

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\(\text{\(d\)For RET genetic testing recommendations, see MEN2-1.}\)

\(\text{\(e\)For the treatment of synchronous tumors, surgical resection of pheochromocytoma should take priority over thyroidectomy for medullary thyroid cancer.}\)

\(\text{\(f\)Earlier, if symptoms.}\)

\(\text{\(g\)A sestamibi scan may not accurately depict the total number of abnormal glands. Patients should receive 4-gland exploration regardless of sestamibi scan results.}\)

\(\text{\(h\)Evaluation of pheochromocytoma should be done before the administration of any anesthetic or invasive procedure.}\)

\(\text{\(i\)More likely to be multifocal.}\)

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

\(\text{\(k\)See Principles of Biochemical Testing (NE-B).}\)

\(\text{\(l\)For synchronous bilateral pheochromocytomas, a bilateral adrenalectomy is recommended.}\)
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%).

- 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%).

- 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.

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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 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).

See additional information on next page

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

Functional status
• 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.

Classification and grade
• Many classification schemes have been proposed for NETs. The most recent WHO classification system is suggested for GEP NETs and represents an attempt to unify European and American approaches. 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.

Continued on next page

See References on NE-A 4 of 4
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.4
- 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 (i.e., 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 where 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


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 BIOCHEMICAL TESTING (1 OF 3)\(^1\)\(^{-9}\)

- Some neuroendocrine tumors can secrete specific neuroendocrine hormones. Hormonal workup should be guided by the presence of symptoms of the excess hormone.
- 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.
- 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 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.\(^9\)

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Testing</th>
</tr>
</thead>
</table>
| **Carcinoid Tumor**       | Primary tumors in GI tract (ileum, appendix, rectum, pancreas) are usually non secreting unless extensive liver metastasis. More common to have carcinoid syndrome with extra-GI primary such as lung or bronchi. | May be non-secreting or may be associated with flushing, diarrhea, cardiac valvular fibrosis, bronchoconstriction.  
  • Chromogranin A (category 3)  
  • 24-hour urine 5-HIAA  
  ․ Foods to avoid for 48 hours prior to testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts.  
  ․ Additionally, patients should avoid coffee, alcohol, and smoking. |
| **Pancreatic NET**         | Pancreas                                                                 | Depends on hormone secreted, can be clinically silent.  
  • Serum pancreatic polypeptide (category 3)  
  • Chromogranin A (category 3)  
  • Calcitonin  
  • PTH-rp  
  • GHRH |
| **Insulinoma**             | Pancreas                                                                 | Hypoglycemia.  
  • Serum insulin, pro-insulin, c-peptide  
  • Consider 72-hour observed fast if diagnosis is in question |
| **VIPoma**                 | Most common in pancreas, can be extra pancreatic                        | Diarrhea, hypokalemia.  
  Serum VIP |
| **Glucagonoma**            | Pancreas                                                                 | Flushing, diarrhea, hyperglycemia.  
  Serum glucagon |
| **Gastrinoma**             | Pancreas                                                                 | Gastric ulcers.  
  Serum gastrin* |

*Basal, stimulated as indicated.

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**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 BIOCHEMICAL TESTING (2 OF 3)\(^{1-9}\)

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pheochromocytoma/Paraganglioma</strong></td>
<td>Adrenal or extra-adrenal sympathetic or parasympathetic chain</td>
<td><strong>Hypertension, tachycardia, sweating, syncope</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Plasma or 24-hour urine fractionated metanephrines</strong>**(^\star)**</td>
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<tr>
<td></td>
<td></td>
<td><strong>Cervical paragangliomas: consider serum or urine dopamine or methoxytyramine (the metabolite of dopamine)****(^\star)</strong></td>
</tr>
<tr>
<td><strong>Pituitary Tumor</strong></td>
<td>Pituitary (part of MEN1)</td>
<td><strong>May be asymptomatic, depends on the hormone secreted</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Serum IGF-1 (category 2B)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Serum prolactin</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>LH/FSH</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Alpha subunits</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>TSH</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ACTH</strong></td>
</tr>
<tr>
<td><strong>Cushing's Syndrome</strong></td>
<td>Adrenal, pituitary, or ectopic</td>
<td><strong>Central weight gain, striae, hypertension, hyperglycemia, depression, hirsutism</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hypercortisolemia should be confirmed with 1 of the following 3 tests:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 mg overnight dexamethasone suppression test</td>
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<tr>
<td></td>
<td></td>
<td>2–3 midnight salivary cortisols</td>
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<tr>
<td></td>
<td></td>
<td>24-hour urinary free cortisol</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>If hypercortisolemic, then serum ACTH should be done.</strong></td>
</tr>
<tr>
<td><strong>Hyperaldosteronism</strong></td>
<td>Adrenal</td>
<td><strong>Hypertension, hypokalemia</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Serum aldosterone/plasma renin activity ratio</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Confirmatory testing with saline suppression testing</strong></td>
</tr>
</tbody>
</table>


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PRINCIPLES OF BIOCHEMICAL TESTING (3 OF 3)1-9

References


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 pancreatoduodenectomy 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.
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: 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.

• For management of hormone-related symptoms, see CARC-6.

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.

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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: 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 somatostatin analogs, 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/Capecitabine⁷
    - 5-FU/Doxorubicin/Streptozocin (FAS)⁸
    - Streptozocin/Doxorubicin⁹
    - Streptozocin/5-FU¹⁰

*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.
PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

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.
### 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>Primary Tumor (T)</th>
<th>Staging</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

* For any T, add (m) for multiple tumors

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

#### Duodenum/Ampulla/Jejunum/Ileum

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Staging</th>
</tr>
</thead>
<tbody>
<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</td>
</tr>
</tbody>
</table>

* For any T, add (m) for multiple tumors

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

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

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Staging

American Joint Committee on Cancer (AJCC)

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

Colon or Rectum

TNM

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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 2 cm or less</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor size less than 1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor size 1–2 cm in greatest dimension</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>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades peritoneum or other organs</td>
</tr>
</tbody>
</table>

For any T, add (m) for multiple tumors

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**Distant Metastases (M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T-stage</th>
<th>N-stage</th>
<th>M-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
## Staging

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

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

### Pancreatic

**TNM**

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

* This also includes the “PanInIII” classification.

**Regional Lymph Nodes (N)**

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

**Distant Metastases (M)**

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

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# Staging

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

## Appendiceal Carcinoid

### TNM

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor 1 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 1 cm but not more than 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm or with extension to the cecum</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm or with extension to the ileum</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle*</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**Distant Metastases (M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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

**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.

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### Staging

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

#### Adrenal

**TNM**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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 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>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**Distant Metastases (M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</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>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
</tbody>
</table>

**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.
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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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. A recent independent analysis 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.

Histologic Classification and Staging of Neuroendocrine Tumors

Neuroendocrine tumors are generally subclassified by site of origin, stage, and histologic characteristics.
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/HPF and no necrosis) or atypical (2–10 mitosis/HPF and/or foci of necrosis).

Poorly-differentiated neuroendocrine carcinomas are of either small cell or large cell cytology, with greater than 10 mitoses/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. A comparable analysis based on 691 patients with jejunal-ileocecal neuroendocrine tumors similarly found that a threshold of 5 mitoses/10 HPF provided better prognostic information than one of 2 mitoses/10 HPF. The panel recommends that the current histologic grading system be used more as a general guide, in conjunction with clinical judgment, when treatment decisions are made.
Staging

Neuroendocrine tumors are staged according to the AJCC tumor (T), node (N), metastasis (M) staging system. The AJCC introduced its first TNM staging system for the classification of neuroendocrine tumors in its 7th edition of the AJCC Cancer Staging Manual. Carcinoids of the stomach, duodenum/ampulla/jejunum/ileum, colon/rectum, and appendix have separate staging systems. The association of tumor stage with prognosis has been confirmed in analyses of the SEER database and the National Cancer Data Base. A recent analysis of 691 patients with jejunal-ileocecal neuroendocrine tumors treated at the Moffitt Cancer Center between 2000 and 2010 revealed 5-year survival rates of 100%, 100%, 91%, and 72% for stages I through IV, respectively, further validating the TNM staging system. Of note, however, this analysis also suggested that, unlike other malignancies, primary tumor size and depth of invasion had little bearing on survival in early-stage disease.

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. 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

The molecular basis of neuroendocrine tumors remains poorly understood, and 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). Small bowel carcinoid tumors have been found to have recurrent mutations in the cyclin dependent kinase inhibitor, CDKN1B (p27), and loss of CDKN1B expression has been reported to be an adverse prognostic factor in gastroenteropancreatic neuroendocrine tumors. Circulating tumor cells (CTC) 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 varying pre-treated metastatic neuroendocrine tumors from various primary sites.

More research is required, however, before these and other new molecular assays are routinely used in the clinic.

**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. 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. 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. Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.

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, 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, radiolabeled somatostatin receptor scintigraphy,
performed using the radiolabeled somatostatin analog [\(^{111}\text{In-DTPA}\)-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 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. 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 hypercortisolism are suspected. Details of the evaluation and diagnosis of a patient with Cushing’s syndrome from a bronchial neuroendocrine tumor have recently been published.\(^{49}\)

### Management of Locoregional Disease

The management of locoregional neuroendocrine tumors of the GI tract, lung, and thymus depends on tumor size and 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 a somatostatin analog 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 generally recognized: type 1 (associated with chronic atrophic gastritis), type 2 (associated with antrum sparing type A Zollinger-Ellison syndrome), and type 3 (sporadic).\(^{50}\) 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).\(^{50}\)

For hypergastrinemic patients whose tumors are 2 cm or smaller and either solitary or multiple, options include: 1) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa; 2) observation; or 3) octreotide or lanreotide for symptom control in patients with gastrinoma and Zollinger-Ellison syndrome. For hypergastrinemic patients with solitary or multiple tumors larger than 2 cm, endoscopic resection (if possible) or surgical resection is indicated. Patients with nonmetastatic gastric neuroendocrine tumors and normal gastrin levels (type 3) have more aggressive tumors and are usually treated with radical resection of the tumor with regional lymphadenectomy. Alternatively, endoscopic or wedge resection can be considered for tumors ≤2 cm.\(^{51}\)
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 are recommended (category 3). If chemotherapy is offered, capecitabine or 5-FU at radiosensitizing doses may be considered. 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).

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 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. If future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy should be considered given the association between long-term treatment with somatostatin analogs and the development of biliary symptoms and gallstones.\(^5^2\)

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.\(^5^3,5^4\)

However, some controversy exists regarding the management of appendiceal neuroendocrine tumors measuring less than 2 cm with more aggressive histologic features. A recent population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal neuroendocrine tumors 2 cm or smaller.\(^5^5\) 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.

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).
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 less, 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. 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.

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. 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; \( P < .001 \)). 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 urine collection. Additionally, patients should avoid coffee, alcohol, and smoking for this period. Medications that can increase 5-HIAA include acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (an ingredient found in some cough medicines), and phenobarbital.

Somatostatin receptor scintigraphy 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.

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

Patients who have metastatic neuroendocrine tumors and carcinoid syndrome should be treated with a somatostatin analog (octreotide or lanreotide). 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.

Lanreotide has a similar mechanism of action as octreotide, but is administered as a deep subcutaneous injection. Studies have shown it to be effective at controlling symptoms in patients with carcinoid tumors, gastrinomas, or vasoactive intestinal peptide tumors (VIPomas). 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. Although the pre-defined difference in percentage of days the patient used rescue octreotide was not met, the panel believes that the difference seen (34% in the lanreotide arm vs. 49% in the placebo arm; \( P = .02 \)) was significant enough to warrant use of lanreotide for symptom control.

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

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 (\( P = .000072 \)). 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. Median OS for was not significantly different at 84 months in the placebo arm and not reached in the octreotide arm (HR, 0.85; 95% CI 0.46–1.56; \( P = .59 \)). 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; \( P < .001 \)). \(^{82}\)

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. \(^{83-86}\)

Cytoreductive surgery or ablative therapies such as radiofrequency ablation \(^{87}\) (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). \(^{88,89}\) For unresectable liver metastases, hepatic regional therapy (arterial embolization, \(^{90}\) chemoembolization, \(^{91-93}\) or radioembolization [category 2B]) \(^{93-100}\) 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. \(^{101}\) 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. \(^{102}\) 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. \(^{102}\) Other side effects have also been described. \(^{103-105}\)

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. \(^{106}\) 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. \(^{107}\)

Capecitabine was tested in patients with metastatic carcinoid tumors in a recent phase II trial; no objective responses were reported although 13 of 19 patients were reported to have experienced stable disease. \(^{108}\) 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. \(^{109}\) 5-FU was assessed in the phase III E1281 trial in
combination with streptozocin or doxorubicin.\textsuperscript{110} 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{111}

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{70,112-115} Because of its potential side effects,\textsuperscript{70,112-115} interferon is usually not initiated until failure of somatostatin analog treatment.\textsuperscript{107}

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

Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced carcinoid tumors.\textsuperscript{116-120} Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.\textsuperscript{121-123} However, patients pursuing this form of therapy are often highly selected. A prospective phase II study of radiopeptide therapy 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{124} At this time, this approach remains investigational. Randomized trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in advanced carcinoid tumors are needed.\textsuperscript{125}

**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.\textsuperscript{126-131} A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.\textsuperscript{132} 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.\textsuperscript{133} 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.\textsuperscript{133,134} 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.\textsuperscript{35} An estimated 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms.\textsuperscript{9,35} Consistent with these numbers, recent analysis of the NCCN Neuroendocrine Outcomes Database found that 22% of patients with pancreatic neuroendocrine tumors had a hormonal syndrome.\textsuperscript{46} Of these functioning tumors, up to 70% are insulinomas, and approximately 90% of these are benign. Approximately 15% are glucagonomas. Gastrinomas and somatostatinomas account for another 10%; most gastrinomas and somatostatinomas (80%-90%) are associated with a relatively high risk for metastases.\textsuperscript{134} The remaining rare pancreatic neuroendocrine...
tumors include VIPoma, pancreatic polypeptidoma (PPoma), 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. 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), chromogranin A (category 3), calcitonin, parathyroid hormone-related protein (PTHrp), and GHRH may also be tested as appropriate.  

Serum chromogranin A (category 3) may also be tested as clinically 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 levels also appear to be prognostic in 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 is often suspected in patients with severe gastroduodenal ulcer symptoms, such as dyspepsia, usually accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of basal and stimulated gastrin levels. 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. 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.143

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.

The New England Journal of Medicine recently published a case report outlining the diagnosis of gastrinoma in a patient presenting with severe, recurrent diarrhea.144

**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.145 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).146 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.147 If the diagnosis of insulinoma is uncertain, a 48- to 72-hour observed or inpatient observed fast may also be helpful. An insulin level greater than 3 mclU/mL (usually >6 mclU/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.147

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 scintography-positive, and patients with insulinoma should be carefully monitored when receiving somatostatin analogs because in some cases somatostatin analogs can profoundly worsen hypoglycemia (see Preoperative Management, below).148

The New England Journal of Medicine recently published a case report describing the diagnosis of insulinoma in a lactating patient presenting with periodic numbness and prolonged episodes of confusion and lethargy.149

**Evaluation of Glucagonomas and VIPomas**

For patients with recent-onset diabetes, cachexia, and/or a necrolytic erythematous skin rash, the panel recommends a blood test for glucagon and blood glucose 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{150}

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

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

**Preoperative Management**

Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. Octreotide or lanreotide can be considered for symptom control in most pancreatic neuroendocrine tumor subtypes.\textsuperscript{52} 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{148} Somatostatin analogues should generally not be used in patients with insulinoma in patients with 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{151} 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 in some cases be safely followed, depending on the site of the tumor.\textsuperscript{152,153} 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.\textsuperscript{154-156} Therefore, 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) 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.\textsuperscript{157,158}

**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 pancreatectoduodenectomy.

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, 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, can achieve lymph node retrieval comparable to distal pancreatectomy with en-bloc splenectomy.

Gastrinomas in the head of the pancreas are treated with duodenotomy and intraoperative ultrasound with enucleation or local resection of tumors and periduodenal node dissection.

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 pancreatectoduodenectomy 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.

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, pancreatectoduodenectomy with resection of the peripancreatic lymph nodes is recommended. Small (<2 cm) peripheral glucagonomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas. A hypercoagulable state has been reported in 10% to 33% of patients with glucagonoma. 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. Pancreatectoduodenectomy with dissection of peripancreatic nodes is recommended for tumors in the head of the pancreas. Small (<2 cm) peripheral VIPomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas.

Surgical Management of 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 pancreatectoduodenectomy if they are located in the head of the pancreas, and with distal pancreatectomy and splenectomy if they are distally localized. Resection for larger (>2 cm) or malignant-appearing tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

Surveillance 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{164-166} Higher lymph node ratio and Ki-67 status may indicate a higher chance of recurrence.\textsuperscript{164} 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 PET (FDG-PET) scan 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{167} Surgical resection is recommended for resectable locoregional or oligometastatic recurrence.

Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas
Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases. In patients with limited hepatic disease, surgical excision of both the primary tumor and liver metastases should be considered 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.\textsuperscript{66} 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.\textsuperscript{168} Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence.\textsuperscript{67,68} Additional resection or ablation may be possible. A recent study of 172 patients who had liver resection of metastatic neuroendocrine tumors (55 with the primary tumor in the pancreas) showed that significant long-term survival can be achieved after recurrence in many patients, with a 10-year overall survival rate of 50.4%.\textsuperscript{65}

Unfortunately, most patients 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 imaging 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, 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.

Biologically Targeted Therapies
The biologically targeted agents everolimus and sunitinib have recently 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 showed that the PFS effect of 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. A recent report highlights the outcomes of 169 pretreated patients with advanced neuroendocrine tumors of the pancreas (n=85) or other sites (n=84) who received everolimus through a compassionate use program. A higher risk of adverse events was noted in patients with previous radiolabeled peptide therapy and chemotherapy.

Sunitinib, administered orally at a dose of 37.5 mg once daily, was compared with placebo in a multicenter randomized study of patients with advanced progressive metastatic pancreatic neuroendocrine tumors. The study was designed to enroll 340 patients but was discontinued after enrollment of 171 patients, before the predefined efficacy analysis. At discontinuation, patients who received sunitinib had a median PFS duration of 11.4 months, compared with 5.5 months for patients receiving placebo (P < .001). The objective response rate seen with sunitinib was 9.3%. A large proportion of patients on the placebo arm subsequently received sunitinib at progression, and no significant
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. Streptozocin is FDA-approved for use in patients with advanced pancreatic neuroendocrine tumors. The combination of doxorubicin and streptozocin was initially reported to be associated with an overall response rate of 69% and a survival benefit in a relatively small randomized study of patients with advanced pancreatic neuroendocrine tumors. A more recent retrospective review from MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin. 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%. 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.

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%.

In addition, a recent phase II 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 with pancreatic neuroendocrine tumors had a radiographic response (with no responses in the 19 patients with carcinoid tumors), and the toxicity was acceptable. These results are consistent with prior studies of temozolomide-based therapy, and further support the activity of temozolomide in pancreatic neuroendocrine tumors. The added benefit of bevacizumab cannot be assessed from this single-arm study.

The combination of temozolomide with everolimus has also been studied. A recent phase 1/2 study found the combination to be safe with a partial response observed in 40% of patients.

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,\(^90\) radioembolization (category 2B),\(^94-100\) and chemoembolization.\(^189\) Whereas embolization in general is considered an effective approach in patients with hepatic-predominant disease,\(^83,84,86\) 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 analogues has been reported to result in tumor responses in patients with advanced pancreatic neuroendocrine tumors.\(^116-120\) Numerous large non-randomized cohort analyses have also reported encouraging survival rates with this approach.\(^122,123\) However, patients pursuing this form of therapy are often highly selected. At this time, this approach remains investigational, and randomized trials to further evaluate the relative benefit and potential toxicities of radiopptide therapy in patients with advanced pancreatic neuroendocrine tumors are needed.\(^125\)

**Liver Transplantation**

Several series have now reported the results of liver transplantation patients with patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver.\(^126-131,190\) A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.\(^132\) 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.\(^1\) 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.\(^191\)

**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.\(^192\) In addition, radionucleotide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. An FDG-PET scan and brain imaging 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.
Colonoscopy can also be considered, especially in cases of well-differentiated liver metastases, to identify possible primary tumors in the small intestine or colon. 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.

The possibility of functional adrenal neoplasms and carcinoid syndrome should be considered prior to biopsy or other invasive procedures. Functional adrenal neoplasms are diagnosed with plasma or 24-hour urine fractionated metanephrines (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 Tumors/Large or Small Cell Tumors, below. 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). 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. Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and MEN1. The underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated; however, inactivating somatic mutations of the p53 tumor suppressor gene (chromosome 17p13) and alterations at the 11p15 locus (site of the IGF-2 gene) seem to occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization. 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. 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.

**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. If the clinical suspicion for pheochromocytoma is low and plasma 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. Confirmation testing with the saline suppression test or salt loading test may be indicated, because both false positives and false negatives can occur. Electrolytes should also be measured, because excessive aldosterone production causes both retention of sodium and excretion of potassium. The Endocrine Society has developed detailed guidelines for the detection, diagnosis, and treatment of primary aldosteronism.

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**
When patients present with symptoms of Cushing’s syndrome, hypercortisolemia should be confirmed with: 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. Elevated levels of cortisol, confirmed with one of the above tests, 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. Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, and ectopic tumors in the lung, thyroid, pancreas, or bowel are probable sources. These patients should be assessed and treated for pituitary or ectopic sources of ACTH production. A recent 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.  

Cushing’s syndrome can 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. Imaging 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 individual drugs for management of Cushing’s disease are limited.  

Octreotide or lanreotide can also be considered for ectopic Cushing’s syndrome if the tumor is somatostatin scintography-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 more than 1 cm growth of the mass occurs in 1 year. Alternatively, these masses can be observed with short-interval follow-up. Larger tumors (4–6 cm) with benign-appearing features can also 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.²¹⁸ 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.²¹⁹ 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.²¹⁸ MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.²²⁰,²²¹ 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.

Imaging 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.²²²

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.²¹³,²¹⁴

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 adrenocorticoytic agent.²²³-²²⁵ The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany.²²⁶ 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, lifelong replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed to prevent adrenal insufficiency if it is used in this setting. 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 imaging 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 imaging 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 versus 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. Because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed to prevent adrenal insufficiency.

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.\textsuperscript{234} 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.\textsuperscript{235} In fact, a recent study showed that 87.5\% of patients presenting with these tumors prior to age 20 harbored a germline mutation in one of several genes tested if they also had metastatic disease.\textsuperscript{236} 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.\textsuperscript{237} Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see \textit{Surveillance of Pheochromocytomas/Paragangliomas}, below).

\textbf{Evaluation for Pheochromocytoma/Paragangliomas}  
A patient with possible pheochromocytoma should be evaluated with fractionated metanephrines in plasma or 24-hour urine; elevated levels of metanephrines are suggestive of pheochromocytoma.\textsuperscript{238} 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.\textsuperscript{239} Elevations in metanephrine levels that are 4 times above the upper limit for 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.\textsuperscript{240} Measurement of dopamine levels can be considered for cervical paragangliomas.

Imaging studies, including chest/abdominal CT scan or MRI or FDG-PET, are also recommended. A metaiodobenzylguanidine (MIBG) scan is highly effective for localizing pheochromocytomas (including extra-adrenal tumors) and is recommended as appropriate, especially when a tumor is not identified by either MRI or CT scan.\textsuperscript{241} Somatostatin scintography is optional and is used if multiple tumors are suspected or if CT results are negative. A bone scan should be performed if clinically indicated.

\textbf{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.\textsuperscript{234,242} 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, \textit{RET}, \textit{NF1}, \textit{VHL}, \textit{SMAD4}, \textit{ENG}, \textit{ALK1}), germline mutations in \textit{SDHB}, \textit{SDHA}, \textit{SDHAF2}, \textit{SDHD}, \textit{SDHC}, \textit{TMEM127}, \textit{MAX}, and \textit{HIF2A} have also been associated with an increased incidence of pheochromocytomas and paragangliomas.\textsuperscript{242-247} 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. Because a significant proportion of patients with a pheochromocytoma or paraganglioma have a heritable mutation, 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.

**Primary Treatment of Pheochromocytomas/Paragangliomas**

Surgical resection is the mainstay of treatment for both benign and malignant pheochromocytomas and paragangliomas. Surgery or stress can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Before surgery, the patient should receive preoperative treatment with alpha-adrenergic blockade (such as phenoxybenzamine or doxazosin) with aggressive volume repletion. Additional adrenergic blockade of alpha1 receptors with prazosin, terazosin, or doxazosin can also be performed when long-term therapy is required for metastatic pheochromocytoma. The tyrosine hydroxylase inhibitor, alpha-methyltyrosine, can also be administered prior to surgery to help prevent hypertensive crisis. Beta-adrenergic blockade may also be used after initiation of alpha-adrenergic blockade before surgery to prevent or treat tachyarrhythmias after correction of hypovolemia. Choices include non-cardioselective beta blockers, such as propranolol, nadolol, or labetalol, or cardioselective beta blockers, such as atenolol and metoprolol. Dihydropyridine calcium channel blockers may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The endpoint of alpha blockade is orthostasis. The panel acknowledges that other effective agents can be used for alpha and beta blockade. The panel also points out that rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room to control blood pressure.

A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas. If possible, cytoreductive resection is also recommended for the treatment of isolated distant metastases. Cytoreductive (R2) resection, if possible, is recommended for locally unresectable disease, together with RT. For metastatic disease, continuous alpha blockage with or without alpha-methyltyrosine and with or without beta blockade, together with cytoreductive resection when possible is the recommended initial treatment. Other options for treating unresectable, metastatic disease include: 1) clinical trial; 2) systemic chemotherapy with cyclophosphamide, vincristine, and/or dacarbazine, or 3) iodine-131-MIBG therapy after confirming dosimetrically that tumors take up MIBG.

A recent retrospective review of 52 evaluable patients treated with systemic chemotherapy 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 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.

**Survveillance 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. Patients with persistent disease need more frequent examination at intervals of every 3 to 4 months. In addition, CT, MRI, or FDG-PET scans can be considered. As mentioned previously, genetic counseling and testing are also recommended as clinically indicated. Timing for these surveillance events and procedures can be earlier if symptoms dictate.

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

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

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

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, somatostatin scintigraphy, or other scans and plasma ACTH or other biochemical markers are recommended as clinically indicated.

**Primary Treatment of Poorly Differentiated/Large or Small Cell Tumors**

For resectable poorly differentiated/small cell tumors, 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 Tumors**

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

**Multiple Endocrine Neoplasia**

The MEN syndromes are characterized by tumors that affect endocrine organs. The 2 most common syndromes are MEN1 and MEN2. MEN1 is an autosomal-dominant inherited syndrome mainly affecting the parathyroid glands (causing hyperparathyroidism), pituitary gland, and endocrine pancreas; 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. Of interest, somatic mutation of the MEN1 gene is the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids. Somatic RET mutations are also found in sporadic MTC.

**MEN1**

MEN1 (or Wermer syndrome), as previously mentioned, involves mainly the parathyroid glands, pituitary gland, and pancreas, but may also be associated with carcinoid tumors (eg, thymus, bronchial, 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. 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 peri-duodenal 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 is 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, a clinical evaluation includes biochemical tests evaluating hormone levels and imaging tests.
to localize the site of tumors or hyperplasias. 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 with parathyroid tumors is the most common component of MEN1. Parathyroid hormone (PTH) testing and measurement of serum calcium levels are recommended if hyperparathyroidism is suspected. An additional test that may be considered is a 24-hour urinary calcium test to rule out benign familial hypocalciuric hypercalcemia. The presence of elevated or high-normal levels of serum calcium and elevated levels of PTH confirm a diagnosis of primary hyperparathyroidism in a patient without hypocalciuria.

Imaging of the parathyroid glands using sestamibi scanning and/or neck ultrasound is optional but may aid in identifying ectopically situated parathyroids. The technetium 99m (Tc99m) sestamibi and ultrasound scanning are about 80% and 70% sensitive, respectively, for identifying solitary parathyroid adenomas found in most patients with sporadic hyperparathyroidism. However, these scans are only about 35% accurate in patients with familial hyperparathyroidism. Neither scan can distinguish between adenomatous and hyperplastic parathyroid glands. Because most patients with familial hyperparathyroidism have multiple abnormal parathyroid glands, preoperative localization studies are less accurate and abnormal parathyroid glands are best identified during surgery.264,265

**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. Elevated prolactin levels are indicative of prolactinoma, and increased IGF-1 occurs in acromegaly.

Additional biochemical tests can be performed as appropriate. These tests include ACTH for Cushing's syndrome. Patients with Cushing's disease and pituitary adenoma have moderately increased ACTH levels. In contrast, those with ectopic Cushing's syndrome have markedly elevated ACTH levels and usually a more dramatic onset and progressive clinical course, while those with Cushing's syndrome due to benign or malignant adrenal tumors have levels of ACTH that are suppressed by dexamethasone (see Adrenal Gland Tumors, above).

Other additional possible hormone tests include thyroid-stimulating hormone (TSH), produced by some adenomas, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to aid in the recognition of nonfunctioning tumors.
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.261,266 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.267,268

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.269 Removal of a single functioning tumor, although a reasonable approach for sporadic tumors, usually misses 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 somatostatin analog 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.

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 parathyroid carcinoma. The panel recommends annual calcium levels to screen for parathyroid tumors. If calcium levels rise, serum PTH should be measured and imaging with neck ultrasound and/or parathyroid sestamibi should be performed. MRI of the neck can also be considered.

Surveillance for MEN-1–associated pancreatic neuroendocrine tumors should include annual measurement of serum gastrin. Serum chromogranin A and/or PP can also be assessed annually (category 3).

It is important to note that gastrin and chromogranin A are elevated in patients using proton pump inhibitors. Other serum hormones should be followed as symptoms indicate or if they were previously elevated. Cross-sectional imaging every 1 to 3 years or serial EUS can also be considered in patients with MEN1.

Surveillance for pituitary tumors includes an MRI of the pituitary every 3 to 5 years. For patients with a history of pituitary tumors, prolactin, IGF-1, and other previously abnormal pituitary hormones should be followed annually or as symptoms indicate.

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. For patients at risk for bronchial or thymic carcinoid tumors, the panel suggests that chest imaging can be considered every 1 to 3 years.

All close family members of patients with MEN1 should be genetically counseled, and genetic testing should be considered as described above.

MEN2 and Familial MTC
MEN2 can be further subdivided into MEN2A (Sipple syndrome) and MEN2B based on the spectrum of accompanying endocrine tumors and disorders. MTC is seen in nearly all patients with MEN2A and MEN2B and is often the first manifestation of the syndrome. Patients with MEN2A may also have or develop pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%). Some patients with MEN2A have lichen planus amyloidosis or Hirschsprung’s disease. Most patients with MEN2B have mucosal neuromas or intestinal ganglioneuromas in addition to MTC; 50% of these patients have...
pheochromocytoma, but almost none have hyperparathyroidism (<1%). Nearly all patients with MEN2B have Marfanoid habitus and/or poor dentition. Some patients also have ectopic lenses in the eye or very flexible joints.

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, RET.

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 close 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 the inability to cry tears. 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 Evaluation for Pheochromocytoma/Paragangliomas, above) before administration of anesthetic or before any invasive procedure. Because patients with pheochromocytoma have persistent vasoconstriction, aggressive volume repletion is recommended preoperatively. Patients should also be treated preoperatively with alpha and beta blockade. Additional treatment with alpha methyltyrosine and a beta blocker can also be considered (see Primary Treatment of Pheochromocytomas/Paragangliomas, above).
A parathyroid workup is also recommended for patients with MEN2; it consists of serum calcium and PTH determinations. A 24-hour urine collection to assess both calcium and creatinine levels can be done as appropriate for primary hyperparathyroidism. A neck ultrasound or a sestamibi scan can also be performed as appropriate.

**Genetic Counseling/Testing in MEN2**

Genetic counseling and *RET* genetic testing should be offered to individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2 (see Evaluation of MEN2 Syndromes, above). Genetic counseling and testing should also be offered to at-risk relatives of an individual with a known germline *RET* mutation at a very young age. All patients with MTC should be tested for germline mutation of the *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 *de novo* germline mutation.

Even with negative *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. See MEN2 Surveillance, below.

**Primary Treatment of MEN2A, MEN2B, and Familial MTC**

In patients with a positive *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 *RET* mutation or at diagnosis, 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 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 normal. 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.

**MEN2 Surveillance**

Follow-up surveillance for patients with RET mutations treated for MTC are described in the NCCN Guidelines for Thyroid Carcinoma (available at www.NCCN.org). Follow-up for treatment of pheochromocytomas in these patients is similar to patients who have sporadic disease (see, Surveillance of Pheochromocytomas/Paraganglioma, above).

After subtotal or total parathyroidectomy, a routine H&P including blood pressure and markers should be performed 3 to 6 months after resection in patients with MEN2, then every 6 months during the first 3 years, and annually until 10 years postresection. Imaging studies (ie, CT or MRI) should be performed selectively, as clinically indicated.

**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 tumors 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.
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