NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroendocrine Tumors

Version 2.2014

NCCN.org
# NCCN Guidelines Version 2.2014 Panel Members

### Neuroendocrine Tumors

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### NCCN Guidelines Panel Disclosures

- ¶ Surgery/Surgical oncology
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- ≠ Pathology
- ‡ Internal medicine
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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.

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Updates in Version 2.2014 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2014 include:

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

Updates in Version 1.2014 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2013 include:

**Global**
- “24-hour urine 5-HIAA” replaced “5-HIAA”
- “Islet cell tumor” was removed from Neuroendocrine Tumors
- “Somatostatin scintigraphy” replaced “Octreoscan”

**Neuroendocrine Tumors**

**NE-1**
- Multiple endocrine neoplasia, type 1
  - List was revised to include only those tumor types described on MEN1-2
- Multiple endocrine neoplasia, type 2
  - List was revised to include only those tumor types described on MEN2-2

**Carcinoid Tumors**

**CARC-1**
- Footnote “d” was modified:
  - “Should include:
    - Careful examination of the entire bowel, as multiple synchronous lesions may be present.
    - Assessment of the proximity to or involvement of the superior mesenteric artery and superior mesenteric vein.”

**CARC-5**
- Footnote “q” was added:
  - “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”

**CARC-6**
- Footnote “s” was added: “Noncurative debulking surgery might be considered in select cases.”

**Neuroendocrine Tumors of the Pancreas**

**PanNET-1**
- Footnote “a” was revised: “For rare tumors secreting hormones such as somatostatin, ACTH, PTTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway.”

**PanNET-2**
- Footnote “n” was added: “There is some disagreement among panel members regarding the role of splenectomy in all cases.”

**PanNET-4**
- Management of Primary Non-Metastatic Disease
  - Footnote “r” was added to “Pancreatoduodenectomy + peripancreatic lymph nodes.”
  - Footnote
    - Footnote “r” was revised: “Hypercoaguable state has been described. Consider Perioperative anticoagulation can be considered.”

**PanNET-6**
- Surveillance: “>1 y postresection up to 10 y” was modified: “>1 y postresection up to a maximum of 10 y”

**PanNET-7**
- Footnote “v” was added: “Noncurative debulking surgery might be considered in select cases.”

**Neuroendocrine Tumors of Unknown Primary**

**NUP-1**
- Initial Workup
  - 4th bullet revised: “Consider FDG-PET scan, and brain imaging in poorly differentiated tumors only.”

**Adrenal Gland Tumors**

**AGT-1**
- Evaluation
  - Cushing’s syndrome was revised:
    - Serum ACTH, cortisol, and DHEA-s with 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
  - Pheochromocytoma was revised:
    - Plasma-free or 24-hour urine fractionated metanephrines
    - Fractionated urine metanephrines and catecholamines for confirmation
  - Clinical diagnosis
    - Bullet and text under Pheochromocytoma was removed: “Elevated plasma-free metanephrines or confirmed elevation of urine metanephrines and catecholamines.”

Continued on next page
Updates in Version 1.2014 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2013 include:

**Adrenal Gland Tumors**

**AGT-1** (Continued)

- Footnotes
  - Footnote “e” was added: “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”
- Footnote “g” was added: “For cervical paraganglioma, consider measuring dopamine.”
- Footnote was removed: “Chemical shift imaging demonstrating signal drop out.”

**Phaeochromocytoma**

**PHEO-1**

- Evaluation: 1st bullet was modified: “Plasma free or 24-hour urine fractionated metanephrine and normetanephrine or urine metanephrine”
- Footnote “d” was added: “For cervical paraganglioma, consider measuring dopamine.”

**PHEO-2**

- Surveillance: “FDG” was added to “PET scan.”

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

**HGNET-1**

- Footnote “b” was revised, “Cisplatin or carboplatin and etoposide are generally recommended as primary treatment. 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.”

**Multiple Endocrine Neoplasia, Type 1**

**MEN1-3**

- Footnote “h” was revised: “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).”

**MEN1-A**

- The table was removed and replaced with the following text:
  - 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.

**MEN1-B**

- 3rd bullet, 1st sub-bullet was revised: “Insulinoma causing symptomatic hypoglycemia Symptomatic functional tumors refractory to medical management.”

**Multiple Endocrine Neoplasia, Type 2**

**MEN2-1**

- First bullet was revised: “MEN2 is subdivided into MEN2A and MEN2B. Medullary thyroid cancer (MTC) occurs in ~100% of nearly all patients with MEN2A...”

**MEN2-2**

- Clinical Evaluation
  - Pheochromocytoma: Recommended, 1st sub-bullet was modified: “Plasma free or 24-hour urine fractionated metanephrine and normetanephrine or urine metanephrine”
  - Footnotes
  - Footnote “g” was added: “For cervical paraganglioma, consider measuring dopamine.”

**Pheochromocytoma**

**PHEO-1**

- Evaluation: 1st bullet was modified: “Plasma free or 24-hour urine fractionated metanephrine and normetanephrine or urine metanephrine”
- Footnote “d” was added: “For cervical paraganglioma, consider measuring dopamine.”

**PHEO-2**

- Surveillance: “FDG” was added to “PET scan.”

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

**HGNET-1**

- Footnote “b” was revised, “Cisplatin or carboplatin and etoposide are generally recommended as primary treatment. 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.”

**Multiple Endocrine Neoplasia, Type 1**

**MEN1-3**

- Footnote “h” was revised: “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).”
Updates in Version 1.2014 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2013 include:

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

**NE-A 1 of 4**
- Table 1 was significantly revised to reflect the grading classification systems for gastroenteropancreatic (GEP) neuroendocrine tumors and lung and thymus neuroendocrine tumors.
- Reference added below Table 1: Adapted from Bosman FT, Carneiro F, Hruban RH, Theise ND. World Health Organization Classification of Tumours of the Digestive System. IARC, Lyon, 2010; and Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC;2004.
- Footnotes
  - Text from footnote “a” was revised and relocated to a text box below Table 1: “Table 1 should be used as a general guide. Some tumors may not fall into a single category. 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.)”
- Footnotes
  - 2nd bullet revised: “Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, and CD56, although the last marker CD56 has recently proven to be less specific.”
  - Classification and grade
    - 1st bullet, 2nd sentence revised: “The most recent WHO classification system is suggested for GEP NETs and represents an attempt to unify European and American approaches.”

**NE-A 2 of 4**
- Immunohistochemistry and other ancillary techniques
  - 2nd bullet revised: “Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, and CD56, although the last marker CD56 has recently proven to be less specific.”

**NE-A 3 of 4**
- Ki-67 Index
  - 2nd bullet was revised: “If both mitotic rate and Ki-67 index are used and these are discordant, it is currently recommended that the higher grade be assigned used to assign classification.”
  - 3rd bullet was added: “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.”
  - 4th bullet was revised: “The pathologist should report the actual parameters used to assign grade (ie, mitotic rate and proliferation index) so that retrospective reviews may be done and clinicians have the necessary information to make informed treatment decisions. Clinical judgment must be applied in these circumstances.”
  - 5th bullet, reference “3” was added.

**NE-A 4 of 4**
- Reference “3” was updated: “Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC;2004.”

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

**NE-B**
- Pheochromocytoma/paraganglioma
  - Removed catecholamines and dopamine.
- Footnote
  - Footnote “2” was revised: “Should be considered with cervical paraganglioma. For cervical paraganglioma, consider measuring dopamine.”

**Surgical Principles for Management of Neuroendocrine Tumors**

**NE-C**
- 8th bullet was revised: “Octreotide therapy should be administered parenterally prior to induction of anesthesia in patients with functional carcinoid tumors to prevent carcinoid crisis.”
CLINICAL PRESENTATIONS AND DIAGNOsis

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

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

Neuroendocrine tumors of unknown primary (See NUP-1)

Adrenal gland tumors (See AGT-1)

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated (high grade) neuroendocrine tumors/
Large or small cell carcinoma other than lung (See HGNET-1)

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

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

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

See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
Guidelines pertain to well-differentiated tumors. For poorly differentiated/high-grade/large or small cell carcinomas, see HGNET-1.
Includes adrenal cortical tumors and incidentaloma.

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

#### Jejunal/ileal/colon

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

**As appropriate:**
- Somatostatin scintigraphy
- Colonoscopy
- Small-bowel imaging
- Chest CT

**EVALUATION**

- Locoregional disease
- Metastatic disease

**PRIMARY TREATMENT OF NON-METASTATIC DISEASE**

- Bowel resection with regional lymphadenectomy
- Consider prophylactic cholecystectomy when appropriate

**SURVEILLANCE**

- 3-12 mo postresection:
  - H&P
  - Consider 24-hour urine 5-HIAA
  - Consider chromogranin A (category 3)
  - Consider abdominal/pelvic multiphasic CT or MRI

- >1 y postresection up to 10 y:
  - Every 6-12 mo
    - H&P
    - Consider 24-hour urine 5-HIAA
    - Consider chromogranin A (category 3)
    - Consider multiphasic CT or MRI

#### Duodenal

**Recommended:**
- Abdominal/pelvic multiphasic CT or MRI

**As appropriate:**
- Somatostatin scintigraphy
- EGD/endoscopic ultrasound (EUS)
- Chest CT

**EVALUATION**

- Locoregional disease
- Metastatic disease

**PRIMARY TREATMENT OF NON-METASTATIC DISEASE**

- Endoscopic resection
- Local excision (transduodenal)
  - Lymph node sampling
  - Pancreatoduodenectomy

**SURVEILLANCE**

- 3-12 mo postresection:
  - H&P
  - Consider 24-hour urine 5-HIAA
  - Consider chromogranin A (category 3)
  - Consider abdominal/pelvic multiphasic CT or MRI

- >1 y postresection up to 10 y:
  - Every 6-12 mo
    - H&P
    - Consider 24-hour urine 5-HIAA
    - Consider chromogranin A (category 3)
    - Consider multiphasic CT or MRI

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Carcinoid Tumors

**CLINICAL LOCATION**

- **≤2 cm and confined to the appendix**
  - **EVALUATION**
    - Simple appendectomy
  - **PRIMARY TREATMENT OF NON-METASTATIC DISEASE**
  - **SURVEILLANCE**

- **>2 cm or incomplete resection (nodes, margins)**
  - **EVALUATION**
    - Recommended: Abdominal/pelvic multiphasic CT or MRI
    - As appropriate: Chest CT
  - **PRIMARY TREATMENT OF NON-METASTATIC DISEASE**
    - Re-exploration
    - Right hemicolectomy
  - **SURVEILLANCE**

**Metastatic disease**
- **EVALUATION**
  - **PRIMARY TREATMENT OF Non-METASTATIC DISEASE**
  - **SURVEILLANCE**

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**Appendix**
- **Metastatic disease**
  - **EVALUATION**
    - **PRIMARY TREATMENT OF Non-METASTATIC DISEASE**
    - **SURVEILLANCE**

**3-12 mo postresection:**
- H&P
- Consider 24-hour urine 5-HIAA
- Consider chromogranin A (category 3)
- Consider abdominal multiphasic CT/MRI

**>1 y postresection up to 10 y:**
- Every 6-12 mo
  - H&P
  - Consider 24-hour urine 5-HIAA
  - Consider chromogranin A (category 3)
  - Consider multiphasic CT or MRI

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Note: All recommendations are category 2A unless otherwise indicated.
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a See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
b See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).
c See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

dEarlier, if symptoms.
eSomatostatin scintigraphy and PET scan are not recommended for routine surveillance.
fSome appendiceal carcinoids will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. See NCCN Guidelines for Colon Cancer.
gSome institutions will consider more aggressive treatments for 1- to 2-cm tumors with poor prognostic features. See Discussion for details.
CLINICAL LOCATION | EVALUATIONa,b | PRIMARY TREATMENT OF NON-METASTATIC DISEASEc | SURVEILLANCEg,h

Rectal

≤2 cmk

Recommended:
• Colonoscopy
• Abdominal/
  Pelvic multi-phasic CT
  or MRI
• Endorectal MRI or EUS
  As appropriate:
• Somatostatin
  scintigraphy
• Chest CT

≥2 cm

Resection (transanal
  or endoscopic
  excision, if possible)

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

Metastatic disease

Metastatic Disease (CARC-6)

≥2 cm

• Low anterior resection
  • or
  • Abdominoperineal
    resection (APR)

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

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

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

**Clinical Evaluation a,b**

**Locoregional disease**

- Tumor ≤2 cm
- Solitary or multiple

- Hypergastrinemic patients m

- EGD
- Gastrin level l
- Multiphasic CT or MRI for patients with normal gastrin

As appropriate:
- EUS
- Chest CT
- Somatostatin scintigraphy for patients with normal gastrin
- B12 level if hypergastrinemia

**Metastatic disease**

- Tumor >2 cm
- Solitary or multiple

- Endoscopic resection, if possible or Surgical resection

**Primary Treatment of Non-Metastatic Disease c**

- Tumor >2 cm
- Solitary or multiple

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

**Surveillance g,h**

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

- H&P and markers b
  - Years 1-3: every 6-12 mo with EGD
  - Years 4+:
    - Annually with EGD
    - Imaging studies as clinically indicated

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

**Gastric**

- Recommended:
  - EGD
  - Gastrin level l
  - Multiphasic CT or MRI for patients with normal gastrin

- As appropriate:
  - EUS
  - Chest CT
  - Somatostatin scintigraphy for patients with normal gastrin

- B12 level if hypergastrinemia

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

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

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

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

- 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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# NCCN Guidelines Version 2.2014
## Carcinoid Tumors

### Clinical Location: Brochopulmonary

**EVALUATION**

- **Recommended:**
  - Chest CT and abdominal multiphasic CT or MRI
  - Somatostatin scintigraphy
  - Bronchoscopy
  - ACTH/cortisol

- **As appropriate:**
  - Somatostatin scintigraphy
  - Bronchoscopy
  - ACTH/cortisol

**Primary Treatment of Non-Metastatic Disease**

- **Localized disease**
  - See NCCN Guidelines for Small Cell Lung Cancer: Lung Neuroendocrine Tumor algorithm

- **Locoregional disease**
  - Resect
  - Complete Resection

**Metastatic Disease**

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

**Surveillance**

- **3-12 mo postresection:**
  - H&P
  - Consider chromogranin A (category 3)
  - Chest/mediastinal multiphasic CT or MRI

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

### Clinical Location: Thymus

**Recommended:**

- Chest/mediastinal multiphasic CT and abdominal multiphasic CT or MRI

**As appropriate:**

- Somatostatin scintigraphy
- Bronchoscopy
- ACTH/cortisol

**Primary Treatment of Non-Metastatic Disease**

- **Localized disease**
  - Resect

**Metastatic Disease**

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

**Surveillance**

- **3-12 mo postresection:**
  - H&P
  - Consider chromogranin A (category 3)
  - Chest/mediastinal multiphasic CT or MRI

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

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

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

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

*d 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

*e Consider 5-FU or capecitabine at radiosensitizing doses. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.

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

---

**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

Locoregional unresectable disease and/or distant metastases

- Imaging:
  - Multiphasic CT or MRI
  - Consider Somatostatin scintigraphy
- Consider 24-hour urine 5-HIAA
- Consider chromogranin A (category 3)

Asymptomatic, low tumor burden

If complete resection possible:
- Observe with markers and scans every 3-12 mo or Octreotide

Locally symptomatic from primary tumor

Consider resection of primary tumor

Clinically significant tumor burden

Octreotide

Clinically significant progressive disease

Carcinoid Syndrome

- Octreotide
- Echocardiogram

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

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).
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.
Octreotide is approved for symptom control in Europe. Octreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.
Noncurative debulking surgery might be considered in select cases.
Nonfunctioning pancreatic tumors

Recommended:
- Multiphasic CT or MRI
- Somatostatin scintigraphy
- EUS
- Pancreatic polypeptide (category 3)
- Chromogranin A (category 3)

As appropriate:
- Pancreatoduodenectomy ± regional nodes

EVALUATION

Small (<2 cm)

Locoregional disease

Larger (>2 cm), or invasive tumors

Head

Distal

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE

Enucleation ± regional nodes
or
Distal pancreatectomy ± regional nodes/splenectomy
or
Pancreatoduodenectomy ± regional nodes
or
Consider observation in selected cases

See Surveillance (PanNET-6)

See Metastases (PanNET-7)

Nonfunctioning pancreatic tumors

For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway.

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

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

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

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.

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

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

**EVALUATION**

- Recommended:
  - Gastrin levels\(^1\) (basal, stimulated as indicated)
  - Multiphasic CT or MRI
  - Somatostatin scintigraphy
  - EUS
  - Chromogranin A (category 3)

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

- Occult
  - No primary tumor or metastases on imaging

- Duodenum
  - Manage gastric hypersecretion with proton pump inhibitors
  - Consider octreotide\(^{k,l}\)

- Head
  - Exophytic or peripheral tumors by imaging\(^m\)
  - For deeper or invasive tumors and those in proximity to the main pancreatic duct

- Distal
  - Manage gastric hypersecretion with proton pump inhibitors

- Metastatic disease
  - See Metastases (PanNET-7)

- Locoregional disease

**CLINICAL LOCATION**

<table>
<thead>
<tr>
<th>Location</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>Recommended: Gastrin levels(^1) (basal, stimulated as indicated), Multiphasic CT or MRI, Somatostatin scintigraphy, EUS, Chromogranin A (category 3)</td>
<td>Occult: No primary tumor or metastases on imaging, Duodenum: Manage gastric hypersecretion with proton pump inhibitors, Consider octreotide(^{k,l}), Head: Exophytic or peripheral tumors by imaging(^m), Distal: Manage gastric hypersecretion with proton pump inhibitors, Metastatic disease: See Metastases (PanNET-7), Locoregional disease:</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

\(^{h}\)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.

\(^{i}\)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.

\(^{j}\)Not adjacent to the main pancreatic duct.

\(^{k}\)There is some disagreement among panel members regarding the role of splenectomy in all cases.
**CLINICAL LOCATION**

**EVALUATION**

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

<table>
<thead>
<tr>
<th>Location</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locoregional disease</strong></td>
<td>Stabilize glucose levels with diet and/or diazoxide</td>
<td>Tumor enucleation, consider laparoscopic resection</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td>As appropriate: Somatostatin scintigraphy</td>
<td>Pancreate-duodenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal pancreatectomy (spleen-preserving), consider laparoscopic resection</td>
</tr>
</tbody>
</table>

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

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

---

**References:**

- See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
- See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (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).
**CLINICAL LOCATION**

**EVALUATION**

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

**Glucagonoma (usually tail)**

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

**As appropriate:**
- Somatostatin scintigraphy
- EUS
- Chromogranin A (category 3)

**Locoregional disease**

**Stabilize glucose levels with IV fluids and octreotide**

**Head (rare)**

**Pancreatoduodenectomy + peripancreatic lymph nodes**

**Distal**

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

See [Surveillance (PanNET-6)]

**Metastatic disease**

See [Metastases (PanNET-7)]

---

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

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

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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.

**VIPoma**

**Recommended:**
- Electrolytes
- VIP levels
- Multiphasic CT or MRI

**As appropriate:**
- Somatostatin scintigraphy
- EUS
- Chromogranin A (category 3)

**Location**

**EVALUATION**

- **Locoregional disease**
  - Stabilize with IV fluids and octreotide
  - Correct electrolyte imbalance (K⁺, Mg²⁺, HCO₃⁻)

- **Metastatic disease**
  - Stabilize with IV fluids and octreotide

**MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE**

- Pancreatoduodenectomy + peripancreatic lymph nodes

**See Surveillance (PanNET-6)**

**Distal s**

- Distal pancreatectomy + peripancreatic lymph node dissection + splenectomy

**Pancreas**

- Head

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

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

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

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

**Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.**
**NCCN Guidelines Version 2.2014**
Neuroendocrine Tumors of the Pancreas

<table>
<thead>
<tr>
<th>SURVEILLANCE(^{t,u})</th>
<th>RECURRENT DISEASE</th>
<th>MANAGEMENT OF RECURRENT DISEASE(^{f})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locoregional disease</strong></td>
<td>Resectable</td>
<td>Resection</td>
</tr>
<tr>
<td></td>
<td>Unresectable</td>
<td>See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)</td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-12 mo postresection:
- H&P and consider markers from preoperative evaluation as indicated\(^{c}\)
- Multiphasic CT or MRI

>1 y postresection to a maximum of 10 y:
- Every 6-12 mo
  - H&P
  - Consider markers\(^{c}\)
  - Consider multiphasic CT or MRI

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

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

\(^{e}\)Earlier, if symptoms.

\(^{f}\)Somatostatin scintigraphy and PET scan are not recommended for routine surveillance.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

If complete resection possible

Resect metastases + primary

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

Clinically significant progressive disease, see below

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

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

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C). Noncurative debulking surgery might be considered in select cases.


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

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

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

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

<table>
<thead>
<tr>
<th>Tumor-directed localizing studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiphasic CT or MRI</td>
</tr>
<tr>
<td>• Consider somatostatin scintigraphy, ultrasound, or EUS</td>
</tr>
<tr>
<td>• Bone scan, if symptoms</td>
</tr>
<tr>
<td>• Consider FDG-PET scan, and brain imaging in poorly differentiated tumors only</td>
</tr>
<tr>
<td>• Consider EGD and/or colonoscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biopsy-proven neuroendocrine tumors (NET) of unknown primary\textsuperscript{a}</th>
<th>Primary not discovered\textsuperscript{d}</th>
<th>Poorly differentiated\textsuperscript{e,f}</th>
<th>Primary found</th>
<th>Well-differentiated\textsuperscript{e,f}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Primary Treatment for poorly differentiated (high-grade) neuroendocrine tumor (HGNET-1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See Carcinoid Tumors (CARC-6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See specific tumor type (NE-1)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

\textsuperscript{b}Sequence of initial workup may vary.

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

\textsuperscript{d}Consider small bowel primary tumor based on symptoms and associated radiologic findings.


\textsuperscript{f}See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).

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

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

CLINICAL PRESENTATION

Adrenal gland tumor on imaging

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

EVALUATIONa,b

Morphologic evaluation

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

See Additional Evaluation (AGT-2)

Functional evaluation

• Hyperaldosteronism
  ▪ Plasma aldosterone, renin activityd
  ▪ Electrolytes
  ▪ Cushing’s syndrome
  ▪ Serum ACTH, cortisol, and DHEA-se
  ▪ Pheochromocytoma
  ▪ Plasma or 24-hour urine fractionated metanephrinesg

CLINICAL DIAGNOSIS

Hyperaldosteronism → See Primary Treatment (AGT-2)

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

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

Pheochromocytoma → See Pheochromocytoma Guidelines (PHEO-1)

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

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a See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
bSee Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).
cIf 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.)
ePrior to evaluating ACTH, confirm hypercortisolism 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
fReview 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.
gFor cervical paraganglioma, consider measuring dopamine.
Adrenal Gland Tumors

CLINICAL DIAGNOSIS

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

Rule out pheochromocytoma

Consider image-guided needle biopsy

Adrenal cortical tissue

See Evaluation (AGT-1)

Metastasis from other site discovered

See NCCN disease-specific treatment guidelines

Hyperaldosteronism, suspect benign

Not a surgical candidate

Consider adrenal vein sampling for aldosterone

Bilateral aldosterone production

Medical management of hypertension and hypokalemia with spironolactone or eplerenone

Surgical candidate

Unilateral aldosterone production

Adrenalectomy, laparoscopic preferred

Hyperaldosteronism, suspect malignant

Open adrenalectomy

HY:

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

i:

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

j:

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

k:

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

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

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 DIAGNOSIS**

- Tumor <5 cm, contralateral gland normal, circumscribed tumor, and other benign imaging characteristics

**ADDITIONAL EVALUATION**

- Adrenal vein sampling for cortisol

**PRIMARY TREATMENT**

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

---

**ACTH-independent Cushing’s syndrome**

- Tumor <5 cm, benign imaging characteristics, and contralateral gland abnormal

**ADDITIONAL EVALUATION**

- Adrenal vein sampling for cortisol

**PRIMARY TREATMENT**

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

---

**ACTH-dependent Cushing’s syndrome**

- Tumor >5 cm or inhomogeneous, irregular margins, local invasion, or other malignant imaging characteristics

**ADDITIONAL EVALUATION**

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

**PRIMARY TREATMENT**

- Adrenalectomy for suspected carcinoma
- Laparoscopic generally not appropriate

---

**Metastatic disease**

**PRIMARY TREATMENT**

- If ectopic, remove primary tumor if possible or if primary tumor unresectable, then bilateral laparoscopic adrenalectomy or medical management (as described above)

---

**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.

---

*m* Consider octreotide if Somatostatin scintigraphy is positive.

*n* May require removal of adjacent structures (e.g., liver, kidney, pancreas, spleen, diaphragm) for complete resection.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Note: All recommendations are category 2A unless otherwise indicated.
### Adrenal Gland Tumors

#### Adrenal Carcinoma

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

**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
  - Consider imaging and biomarkers, if tumor initially functional

#### Treatment

1. Resect tumor and
   adjacent lymph nodes
2. If high risk for local recurrence:
   - Consider external-beam RT to tumor bed
   - Consider adjuvant mitotane therapy (category 3)

---

**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.
### Pheochromocytoma/Paraganglioma

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EVALUATION&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>TREATMENT</th>
<th>SEE Primary Treatment (PHEO-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pheochromocytoma/paraganglioma</strong></td>
<td><strong>Recommended:</strong>&lt;br&gt;• Plasma or 24-hour urine fractionated metanephrines&lt;sup&gt;c,d&lt;/sup&gt;&lt;br&gt;• Chest/abdominal multiphasic CT or MRI&lt;br&gt;• Genetic counseling&lt;sup&gt;e&lt;/sup&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&lt;sup&gt;f&lt;/sup&gt;</strong> with aggressive volume repletion&lt;br&gt;± alpha-methyltyrosine&lt;br&gt;± beta blockade preoperative (beta blockade only after alpha blockade)&lt;sup&gt;g&lt;/sup&gt;</td>
<td><strong>See Primary Treatment (PHEO-2)</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).  
<sup>b</sup> See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).  
<sup>c</sup> Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation. Elevations that are 4 times above the upper limit of normal are diagnostic.  
<sup>d</sup> For cervical paraganglioma, consider measuring dopamine.  
<sup>e</sup> Genetic counseling and genetic testing are recommended when appropriate (See Discussion).  
<sup>f</sup> Phenothiazine or doxazosin can be considered.  
<sup>g</sup> 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. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers.

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

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## Pheochromocytoma/Paraganglioma

### PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Resectable</th>
<th>Resect (laparoscopic preferred when safe and feasible)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Locally unresectable</th>
<th>Cytoreductive (R2) resection, if possible ± RT + alpha blockade ± alpha-methyltyrosine ± beta blockade</th>
</tr>
</thead>
</table>

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

### SURVEILLANCE

<table>
<thead>
<tr>
<th>3-12 mo postresection:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• H&amp;P, blood pressure, and markers</td>
</tr>
<tr>
<td>• Consider CT or MRI or FDG-PET scan</td>
</tr>
</tbody>
</table>

>1 y postresection up to 10 y:

| Years 1-3: every 6-12 mo |
| Years 4+ up to 10 y: annually |
| Consider CT or MRI or FDG-PET scan |
| Genetic counseling and testing as clinically indicated |

### Notes

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

---

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

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

*iEarlier, if symptoms.*
**TUMOR TYPE**

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

**EVALUATION**

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

**PRIMARY TREATMENT**

- Resection + chemotherapy with small cell lung cancer regimen ± RT or Consider definitive chemoradiation (See NCCN Guidelines for Small Cell Lung Cancer)
- RT + chemotherapy with small cell lung cancer regimen
  - Consider octreotide therapy c,d if hormone secreting
- Chemotherapy with small cell lung cancer regimen
  - Consider octreotide therapy c,d if hormone secreting

**SURVEILLANCE**

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

---

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

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

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

**b**Cisplatin or carboplatin and etoposide are generally recommended as primary treatment. 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.

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

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

**e**Earlier, if symptoms.
A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors: multi-gland parathyroid hyperplasia; pancreatic NET; or pituitary tumors.\textsuperscript{a,b} See Tumors in Patients with MEN1 (MEN1-A)

\begin{itemize}
  \item MEN1 may also be associated with carcinoid tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas.\textsuperscript{a,b}
  \item Patients with MEN1 are more likely to have multiple PanNETs than those with sporadic tumors.
\end{itemize}

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

\begin{itemize}
  \item 1) Biochemical tests evaluating hormone levels;
  \item 2) Imaging tests needed to localize the site of the tumor or hyperplasia; and
  \item 3) Genetic counseling and testing
\end{itemize}

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

\begin{itemize}
  \item An individual with a clinical diagnosis or suspicion of MEN1\textsuperscript{a,b,c,d}
  \item An at-risk relative of an individual with a known germline MEN1 mutation\textsuperscript{a}
\end{itemize}

MEN1 clinical evaluation should be offered to the following:

\begin{itemize}
  \item Individuals with a clinical diagnosis or suspicion of MEN1 even with a negative MEN1 genetic test
  \item 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
\end{itemize}


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

\textsuperscript{d}10% of cases have \textit{de novo} MEN1 mutations.

\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.
### CLINICAL EVALUATION

#### Parathyroid:
- **Recommended**
  - Serum calcium
  - Parathyroid hormone (PTH)
- **As appropriate**
  - 24-hour urine calcium
  - Neck ultrasound
  - Parathyroid sestamibi scan

#### Pancreatic neuroendocrine tumors (PanNET):**
- **Recommended**
  - Gastrin levels (basal, stimulated as indicated)
  - Pancreatic polypeptide (category 3)
  - Chromogranin A (category 3)
  - Multiphasic CT or MRI
- **As appropriate**
  - Glucagon, VIP, insulin, fasting glucose depending on symptoms
  - EUS
  - Somatostatin scintigraphy

#### Pituitary:
- **Recommended**
  - Pituitary MRI
  - Prolactin, IGF-1 (category 2B)
- **As appropriate**
  - Other pituitary hormones evaluating functioning pituitary tumors

### TREATMENT

- **Parathyroid:**
  - Subtotal parathyroidectomy
  - ± cryopreservation of parathyroids
  - ± thymectomy
  - or
  - Total parathyroidectomy with autotransplantation
  - ± cryopreservation of parathyroids
  - ± thymectomy

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

- **Pituitary:**
  - Consider referral to endocrinology for further workup

---

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For **MEN1** genetic testing recommendations, see [MEN1-1](#).

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

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 imaging with multiphasic abdominal CT, MRI scan every 1-3 y  
- Consider serial EUS  
- See appropriate sporadic PanNET workup and treatment (PanNET-1 through PanNET-5)

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

---

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

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

\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.}
Multiple Endocrine Neoplasia, Type 1

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.

In general, surgical management of patients with MEN1 is similar to those with sporadic tumors. Refer to the relevant site-specific recommendations earlier in these guidelines. (See PanNET-1 through PanNET-5)

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

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

- 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 cancers (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives\(^a,b\)
  - A clinical diagnosis of MEN2B includes the presence of MTC, pheochromocytoma, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, “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 de novo \(RET\) mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for \(RET\) mutations should still be performed on the affected individual.

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### CLINICAL EVALUATION\(^d\)

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

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

**Pheochromocytoma:**\(^e,f\)
- Recommended:
  - Plasma or 24-hour urine fractionated metanephrines\(^g\)
  - MRI or multiphasic CT of abdomen
- As appropriate:
  - MIBG scan/somatostatin scintigraphy

### TREATMENT

**Refer to endocrinology for medical preparation for adrenalectomy and Adrenalectomy**
- Involved side only, laparoscopic procedure preferred as appropriate

### SURVEILLANCE\(^i\)

<table>
<thead>
<tr>
<th>Time frame</th>
<th>Surveilllance Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 mo postresection</td>
<td>H&amp;P, blood pressure, and markers</td>
</tr>
<tr>
<td>&gt;6 mo postresection up to 10 y</td>
<td>H&amp;P, blood pressure, and markers</td>
</tr>
<tr>
<td>Years 1-3: every 6 mo</td>
<td></td>
</tr>
<tr>
<td>Years 4+: annually</td>
<td>Consider CT or MRI</td>
</tr>
</tbody>
</table>

\(^d\)For RET genetic testing recommendations, see MEN2-1.

\(^e\)Evaluation of pheochromocytoma should be done before the administration of any anesthetic or invasive procedure.

\(^f\)More likely to be multifocal.

\(^g\)For cervical paraganglioma, consider measuring dopamine.

\(^h\)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.

\(^i\)Earlier, if symptoms.

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

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Multiple Endocrine Neoplasia, Type 2

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)

---

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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

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

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

Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gastroenteropancreatic (GEP) NETs</th>
<th>Lung and Thymus</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade (G1)</td>
<td>&lt;2 mitoses/10 HPF AND/OR &lt;3% Ki-67 index</td>
<td>&lt;2 mitoses/10 HPF AND 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

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Functional status

• Functional status of a NET need not be included in the pathology report. However, if a specific clinical situation suggests that correlation with histologic evidence of peptide hormone may be helpful, then histochemical or immunohistochemical studies may be performed and included in the report.

• Functioning NETs should have the same pathologic diagnosis as the non-functioning NETs at the same anatomic site, since the functional status is based upon clinical findings and should not alter the pathologic diagnosis. However, a note may be added with additional information of the immunoreactivity of specific peptide hormone.

Immunohistochemistry and other ancillary techniques

• Immunohistochemistry and other ancillary techniques may not be required to diagnose well-differentiated NETs when sufficient tumor material is available for histologic review.

• Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, and CD56, although CD56 has recently proven to be less specific. In less well-differentiated tumors or tumors of unknown origin, it may be helpful (or required in the case of poorly differentiated neuroendocrine carcinomas) to utilize immunohistochemistry panels.

• Although not entirely specific, lung origin is favored by thyroid transcription factor 1 (TTF-1); intestinal or pancreatic origin by CDX2; and pancreatic and rectal NETs by Isl1 and PAX8.\(^1,2\)

Classification and grade

• Many classification schemes have been proposed for NETs.\(^3-9\) The most recent WHO classification system is suggested for GEP NETs and represents an attempt to unify European and American approaches.\(^8\) Multiple site-specific grading systems also exist.

• Therefore, the specific classification and grading scheme being utilized should be reported in parentheses after the diagnosis to avoid confusion with overlapping terminology and criteria used in other systems.

• The raw data used to derive the grade should be reported.

• Regardless of the system used, it is most important to realize that the term “neuroendocrine tumor” or “neuroendocrine carcinoma” without any further qualification as to grade is inadequate for prognostication and therapy and is inappropriate for pathology reporting.\(^1,10\)

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 (ie, mitotic rate, proliferation index) so clinicians have the necessary information to make informed treatment decisions.
- Although the 2004 WHO3 does not utilize Ki-67 as part of its grading system for thymus and lung NETs, it may be quite useful in the setting of small biopsies and cytology specimens when there is insufficient tissue for an accurate mitotic count. The Ki-67 index cut-points are not currently well-defined but tend to parallel those proposed in GEP-NETs, and generally the data suggest that Ki-67 proliferation rates of <20% exclude small cell lung carcinoma.12

Neuroendocrine Tumors

PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

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

# NCCN Guidelines Version 2.2014
## Neuroendocrine Tumors

### SERUM HORMONE EVALUATION POTENTIALLY INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS

#### HORMONE-RELATED STUDIES (blood markers)

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

---

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

2. For cervical paraganglioma, consider measuring dopamine.

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<table>
<thead>
<tr>
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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 prior to induction of anesthesia in patients with functional carcinoid tumors to prevent carcinoid crisis.

• All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C).

• In general, laparoscopic resection is preferable for patients suspected to have small (<6 cm), clinically benign, functional adrenal tumors. An open exploration is recommended for tumors that have a high risk of being malignant.

• For MEN1-related surgical principles, see MEN1-B.
Staging

American Joint Committee on Cancer (AJCC)

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

Stomach

TNM

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ/dysplasia (tumor size less than 0.5 mm), confined to mucosa
T1 Tumor invades lamina propria or submucosa and 1 cm or less in size
T2 Tumor invades muscularis propria or more than 1 cm in size
T3 Tumor penetrates subserosa
T4 Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures
For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

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

Duodenum/Ampulla/Jejunum/Ileum

TNM

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor invades lamina propria or submucosa and size 1 cm or less* (small intestinal tumors); tumor 1 cm or less (ampullary tumors)
T2 Tumor invades muscularis propria or size > 1 cm (small intestinal tumors); tumor > 1 cm (ampullary tumors)
T3 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
T4 Tumor invades visceral peritoneum (serosa) or invades other organs
For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

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

* 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</th>
<th>N</th>
<th>M</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>
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<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>

### Continuation

Continued on next page
Staging

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

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

Pancreatic

TNM

Primary Tumor (T)

<table>
<thead>
<tr>
<th>T</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>Tis</td>
<td>Carcinoma in situ*</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the pancreas, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to the pancreas, more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
</tr>
</tbody>
</table>

Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>N</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>M</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>

* This also includes the “PanInIII” classification.

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

Continued on next page
Staging

American Joint Committee on Cancer (AJCC)

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

### Appendiceal Carcinoid

#### TNM

**Primary Tumor (T)**

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

**Regional Lymph Nodes (N)**

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

**Distant Metastases (M)**

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

### ANATOMIC STAGE/PROGNOSTIC GROUPS

<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, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
</tbody>
</table>

#### pTNM Pathologic Classification

- **pTNM** Pathologic Classification. The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 does not exist as a category.
- **pN0**. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

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

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

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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>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
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<tr>
<td>III</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</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.
Neuroendocrine Tumors

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview...
Histologic Classification and Staging of Neuroendocrine Tumors...
Histologic Classification...
Staging...
Pathologic Reporting...
Other Potential Prognostic Markers...
Sporadic Neuroendocrine Tumors...
Carcinoid Tumors...
Evaluation of Carcinoid Tumors...
Management of Locoregional Disease...
Surveillance of Carcinoid Tumors...
Management of Locoregional Unresectable and/or Metastatic Carcinoid Tumors...
Neuroendocrine Tumors of the Pancreas...
Evaluation of Neuroendocrine Tumors of the Pancreas...
Primary Treatment of Locoregional Resectable Neuroendocrine Tumors of the Pancreas...
Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas...
Neuroendocrine Tumors of Unknown Primary...
Evaluation of Neuroendocrine Tumors of Unknown Primary...
Primary Treatment of Neuroendocrine Tumors of Unknown Primary...
Adrenal Gland Tumors...
Evaluation and Treatment of Adrenal Gland Tumors...
Pheochromocytomas/Paragangliomas...
Evaluation for Pheochromocytoma/Paragangliomas...
Genetic Counseling/Testing in Pheochromocytomas/Paragangliomas...
Primary Treatment of Pheochromocytomas/Paragangliomas...
Surveillance of Pheochromocytomas/Paragangliomas...
Poorly Differentiated Neuroendocrine Tumors/Large or Small Cell Tumors...
Evaluation of Poorly Differentiated/Large or Small Cell Tumors...
Primary Treatment of Poorly Differentiated/Large or Small Cell Tumors...
Surveillance of Poorly Differentiated/Large or Small Cell Tumors...
Multiple Endocrine Neoplasia...
MEN1...
Evaluation of MEN1 Syndromes...
Genetic Counseling/Testing in MEN1...
Primary Treatment of MEN1 Syndromes...
MEN1 Surveillance...
MEN2 and Familial MTC...
Evaluation of MEN2A, MEN2B, and Familial MTC...
Genetic Counseling/Testing in MEN2...
Primary Treatment of MEN2A, MEN2B, and Familial MTC...
MEN2 Surveillance...
Future Trial Design...
References...
Overview

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

An analysis of the SEER database estimated that the incidence of neuroendocrine tumors in the United States was 5.25 cases per 100,000 people in the year 2004. This analysis suggested that the diagnosed incidence of neuroendocrine tumors is increasing, and that the prevalence of individuals with neuroendocrine tumors in the United States may exceed 100,000. A recent independent analysis of the SEER database also found that the incidence of gastrointestinal neuroendocrine tumors increased from 1975 to 2008.

Most neuroendocrine tumors seem to be sporadic; risk factors for sporadic neuroendocrine tumors are poorly understood. Neuroendocrine tumors may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia (MEN) types 1 and 2. Multiple endocrine neoplasia type 1 (MEN1), associated with mutations in the menin gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands. Multiple endocrine neoplasia type 2 (MEN2), associated with mutations in the RET proto-oncogene, is characterized by the development of medullary thyroid cancer, pheochromocytoma (often bilateral), and hyperparathyroidism. Neuroendocrine tumors have also been associated with von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.

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

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

These guidelines discuss the diagnosis and management of both sporadic and hereditary neuroendocrine tumors and are intended to assist with clinical decision-making. Most of the guideline sections pertain to well-differentiated, low- to intermediate-grade tumors, although poorly differentiated/high-grade/large or small cell carcinomas are also addressed (see Poorly Differentiated Neuroendocrine Tumors/Large or Small Cell Tumors, below). Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

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 judgement 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 cytotology, with >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 gastrointestinal neuroendocrine carcinoma suggested that platinum-based chemotherapy is most active in those with a Ki-67 index of ≥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 judgement, 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 Database. A recent analysis of 691 patients with jejunal-ileocecal neuroendocrine tumors treated at the Moffitt Cancer Center between 2000 and 2010 validated this system, with 5-year overall survival rates of 100%, 100%, 91%, and 72% for stages I through IV, respectively. 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. Similar results were reported in a recent analysis of 6792 small intestine neuroendocrine tumors in the SEER database, which found that outcomes were similar for patients with T1 and T2 tumors.

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

The TNM staging system for the classification of pancreatic neuroendocrine tumors in the 7th edition of the AJCC Cancer Staging Manual is the same as for exocrine pancreatic carcinoma. The primary tumor (T) is differentiated based on size and involvement of major vessels or other organs (see Staging in the guidelines). A recent retrospective analysis of 425 patients with pancreatic neuroendocrine tumors treated at the Moffitt Cancer Center between 1999 and 2010 validated this system, with 5-year overall survival rates of 92%, 84%, 81%, and 57% for stages I through IV, respectively ($P < .001$). Although the trends of this analysis are consistent with population-based studies, the survival rates from this analysis were significantly higher than those seen in population-based studies. For example, in the SEER database analysis of pancreatic neuroendocrine tumors, the 5-year survival rate for patients with metastatic disease was only 19.5%.

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, because they may also have prognostic significance.

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 gastrointestinal carcinoids). 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 ≥1 CTC in 7.5 mL of blood was independently associated with worse PFS and overall survival in patients with varyingly pre-treated metastatic neuroendocrine tumors from various primary sites.
More research is required before these and other new molecular assays are routinely used in the clinic.

**Sporadic Neuroendocrine Tumors**

**Carcinoid Tumors**

Approximately one-third of carcinoid tumors arise in the lungs or thymus, and two-thirds arise in the gastrointestinal tract. Sites of origin within the gastrointestinal tract include the stomach, small intestine, appendix, and rectum.¹ The prognosis for patients with carcinoid tumors varies according to the stage at diagnosis, histologic classification, and primary site of the tumor (see *Histologic Classification and Staging of Neuroendocrine Tumors*, above).

Carcinoid tumors may secrete various hormones and vasoactive peptides. Bronchial and thymic carcinoids have been associated with adrenocorticotropic hormone (ACTH) production and are a cause of Cushing’s syndrome.³⁸,³⁹ Carcinoid tumors arising in the small intestine or appendix are more commonly associated with carcinoid syndrome, related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation causing episodic flushing and diarrhea.⁴⁰ Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.⁴¹

The metabolic products released by intestinal carcinoid tumors are rapidly destroyed by liver enzymes in the portal circulation. Thus, the classical syndrome, occurring in approximately 8% to 28% of patients with carcinoid tumors,⁴²,⁴³ 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 Carcinoid Tumors

Patients who present with suspected carcinoid tumors should be evaluated with imaging studies to assess disease burden and possible primary location. Commonly used techniques include CT and MRI. Carcinoid tumors 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 carcinoid tumors express high-affinity receptors for somatostatin,⁴⁰,⁴⁴ radiolabeled somatostatin receptor scintigraphy, performed using the radiolabeled somatostatin analog \([^{111}\text{In-DTPA}]-\text{octreotide}\) may also be used in the initial evaluation of patients with carcinoid tumor. Additional recommendations vary by disease site and include colonoscopy and small bowel imaging as appropriate for jejunal, ileal, and colon carcinoids; endoscopic ultrasound (EUS) and/or esophagogastroduodenoscopy (EGD) as appropriate for duodenal and gastric carcinoids; proctoscopic examination for rectal carcinoids; and bronchoscopy as appropriate for bronchopulmonary and thymic carcinoids.

Details of the evaluation and diagnosis of a patient with Cushing’s syndrome from a bronchial carcinoid tumor have recently been published.⁴⁵

### Management of Locoregional Disease

The management of locoregional carcinoid tumors 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 Carcinoid Tumors, below). Specific recommendations for management of carcinoid tumor subtypes are described here.

**Gastric Carcinoid Tumors**

Three types of gastric carcinoid tumors are generally recognized: type 1 (associated with chronic atrophic gastritis), type 2 (associated with Zollinger-Ellison syndrome), and type 3 (sporadic). Types 1 and 2 gastric carcinoids are both associated with hypergastrinemia; the major difference between them is that patients with type 1 gastric carcinoids generally have atrophic gastritis and absent acid secretion, whereas those with type 2 gastric carcinoids have evidence of acid hypersecretion secondary to gastrinoma (Zollinger-Ellison syndrome).

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 for symptom control in patients with gastrinoma and Zollinger-Ellison syndrome (category 2B recommendation). 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 carcinoid 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.

**Thymic Carcinoid Tumors**

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

**Bronchopulmonary Carcinoid Tumors**

For localized or locoregional bronchopulmonary tumors, please refer to the Lung Neuroendocrine Tumors algorithm 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).

**Carcinoid Tumors of the Duodenum, Small Intestine, and Colon**

For localized lesions arising in the duodenum, endoscopic resection is recommended if feasible. Transduodenal local excision with or without lymph node sampling and pancreatoduodenectomy are other options for primary treatment of nonmetastatic duodenal carcinoid 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 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.\textsuperscript{48}

**Appendiceal Carcinoid Tumors**

Most appendiceal carcinoid tumors are identified incidentally, during appendectomy performed for appendicitis. Most appendiceal carcinoid tumors have well-differentiated histology, and for most appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient because metastases are uncommon.\textsuperscript{49,50}

However, some controversy exists regarding the management of appendiceal carcinoids 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 carcinoids 2 cm or smaller.\textsuperscript{51}

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 carcinoids may also contain evidence of adenocarcinoma (ie, “adenocarcinoid” or “goblet cell carcinoid”). These tumors should be managed according to the NCCN Guidelines for Colon Cancer (available at [www.NCCN.org](http://www.NCCN.org)).

**Carcinoid Tumors of the Rectum**

The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumors, examination under anesthesia and/or EUS before the procedure should be considered for tumors 1 to 2 cm in size. 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.\textsuperscript{52}

**Surveillance of Carcinoid Tumors**

Surveillance of carcinoid 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 carcinoid tumors of the jejunum/ileum/colon, duodenum, rectum, and thymus, and type 3 gastric carcinoid lesions 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.

Chromogranin A may be used as a tumor marker (category 3); although not diagnostic, elevated levels have been associated with recurrence.\textsuperscript{53} 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; \( P < .001 \)).\textsuperscript{54} 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 small-intestinal carcinoid 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 carcinoid tumor even if the concentration of 5-HIAA is normal. Diet and a variety of drugs can affect the 5-HIAA test. Therefore, patients should be advised not to eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, 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 carcinoid tumors differ from the above general recommendations. For rectal tumors smaller than 1 cm, prognosis is excellent and no follow-up is usually required. Follow-up endoscopies 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 carcinoids 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 carcinoid tumors. Patients with type 1 or 2 gastric carcinoid tumors measuring less than 2 cm may, in some cases, simply be followed up with H&P every 6 to 12 months or as symptoms indicate. More commonly, patients with type 1 or type 2 gastric carcinoid tumors are managed with endoscopic resection of larger lesions, and 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 carcinoids. If clinically indicated, imaging studies should also be performed. Antrectomy to remove the source of gastrin production can be considered in patients with type 1 gastric carcinoids if new lesions or increasing tumor burden is observed.

Management of Locoregional Unresectable and/or Metastatic Carcinoid Tumors

Baseline imaging recommendations for patients suspected to have distant metastatic disease include 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 is being considered. The most common sites of metastases from intestinal carcinoids 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. A recent 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%. However, most patients with metastatic disease 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 Symptom Control**

Patients who have metastatic carcinoid tumors and carcinoid syndrome should be treated with a somatostatin analog. 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 is a somatostatin analog approved for symptom control in Europe and for acromegaly in the United States that has a similar mechanism of action as octreotide. Studies have shown it to be effective at controlling symptoms in patients with carcinoid tumors, gastrinomas, or vasoactive intestinal peptide tumors (VIPomas). Because it is injected via a deep subcutaneous injection, it may be preferable in patients who have difficulty tolerating an intramuscular injection.

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, initiation of octreotide LAR 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 carcinoid 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
Cytoreductive surgery or ablative therapies such as radiofrequency ablation\textsuperscript{78} (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B).\textsuperscript{79,80} For unresectable liver metastases, hepatic regional therapy (arterial embolization,\textsuperscript{81} chemoembolization,\textsuperscript{82-84} or radioembolization [category 2B])\textsuperscript{84-90} is recommended.

**Systemic Therapy for Advanced Carcinoid Tumors**

**Cytotoxic chemotherapy:** The benefits associated with cytotoxic chemotherapy in advanced carcinoid appear, at best, to be modest. Tumor response rates are generally low, and no PFS benefit has been clearly demonstrated.\textsuperscript{91}

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.\textsuperscript{92} The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23\% in patients with poorly differentiated neuroendocrine tumors and 30\% in well-differentiated disease.\textsuperscript{93} 5-FU was assessed in the phase III E1281 trial in combination with streptozocin or doxorubicin.\textsuperscript{94} Response rates in both arms were around 16\%. Dacarbazine was given as salvage therapy, with a response rate of 8\%. Responses to temozolomide in advanced carcinoid are rare.\textsuperscript{95} The panel lists cytotoxic chemotherapy for carcinoid tumors 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:** Interferon alpha has been shown in several large, non-randomized series to be associated with an antitumor effect in patients with advanced carcinoid.\textsuperscript{63,96-99} Because of its potential side
effects, interferon is usually reserved as a salvage therapy after failure of octreotide.

**Everolimus for Advanced Carcinoid Tumors**
For patients with progressive metastatic carcinoid tumors, everolimus can also be considered (category 3). Everolimus is an inhibitor of mTOR, which has been the subject of recent trials in patients with advanced neuroendocrine tumors. It was well tolerated and showed promising antitumor effects in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial. In the randomized phase III RADIANT-2 trial, 429 patients with advanced carcinoid tumors and carcinoid syndrome were randomized to receive octreotide LAR with everolimus or placebo. Based on central review, patients receiving octreotide plus everolimus had a median 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. Other side effects have also been described.

**Radiolabeled Somatostatin Analogs for Advanced Carcinoid Tumors**
Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced carcinoid tumors. Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach. 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 radiopeptide therapy in advanced carcinoid are needed.

**Liver Transplantation for Liver Metastases of Carcinoid Tumors**
Liver transplantation has been performed in patients with carcinoid tumors whose metastases are confined to the liver. Although some highly selected patients have experienced long-term survival, the panel acknowledged the considerable associated risks and a high rate of tumor recurrence, 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 endocrine tumors account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence. Although the peak incidence of occurrence is between ages 40 and 69 years, a significant number of patients diagnosed with pancreatic neuroendocrine tumors are younger than 35 years. Based on an analysis of pancreatic neuroendocrine tumors in the SEER database from 1973 to 2000, the annual incidence per 1 million was 1.8 in women and 2.6 in men. An estimated 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms. Consistent with these numbers, recent analysis of the NCCN Neuroendocrine Outcomes Database found that 22% of patients with pancreatic neuroendocrine tumors had a hormonal syndrome. Of these functioning tumors, up to 70% are insulinomas, and approximately 90% of these are benign. Approximately 15% are glucagonomas. Gastrinomas and somatostatinomas account for another 10%; most (80%–90%) of these are associated with a relatively high risk for metastases. The remaining rare pancreatic neuroendocrine tumors include VIPoma, pancreatic polypeptidoma (PPoma), and the recently described cholecystokininoma (CCKoma).
The major clinical symptoms associated with functional neuroendocrine tumors of the pancreas depend on the hormone secreted. Insulinomas secrete insulin, resulting in fasting or nocturnal hypoglycemia. Gastrinomas secrete gastrin, and patients often present with recurrent peptide ulcers. The glucagon secreted by glucagonomas results in diabetes mellitus and/or migratory necrotic 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).

Pancreatic neuroendocrine tumors occurring in patients with MEN1 are typically multiple and require different treatment strategies from those used for patients with sporadic pancreatic endocrine 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). For nonfunctioning pancreatic neuroendocrine tumors, the recommended evaluation includes multiphasic CT or MRI scan. Serum chromogranin A (category 3) and pancreatic polypeptide (PP; category 3) may be tested as clinically appropriate. Functional tumors may give significant clinical symptoms even when very small, and lesion identification can therefore be difficult. Multiphasic, contrast-enhanced CT or MRI is recommended, and somatostatin scintography and EUS can also be considered.

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.

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 >10 times elevated and a gastric pH <2 is diagnostic of a gastrinoma. Patients who have clinical manifestations suspicious for a gastrinoma and a gastric pH <2 but with <10 times elevation of serum gastrin levels require further testing.

In addition, imaging studies (multiphasic CT/MRI scan) often aid not only in localizing the tumor but also in confirming the diagnosis. Other
tests, such as somatostatin scintography, EUS, and chromogranin A levels (category 3), may be performed as appropriate. Approximately 70% of patients with MEN1 and gastrinoma have tumors situated in the duodenum.

The *New England Journal of Medicine* recently published a case report outlining the diagnosis of gastrinoma in a patient presenting with severe, recurrent diarrhea.\(^{130}\)

**Insulinomas**

Insulinomas are generally small tumors that are best localized with EUS, which has been shown to localize approximately 82% of pancreatic endocrine tumors.\(^{131}\) 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).\(^{132}\) Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative.

If the diagnosis of insulinoma is uncertain, determining the insulin/glucose ratio after a 48- to 72-hour observed or inpatient observed fast may also be helpful. An insulin level greater than 3 mU/mL (usually >6 mU/mL) when blood glucose is less than 40 to 45 mg/dL, with an insulin-to-glucose ratio of 0.3 or greater reflecting the inappropriate secretion of insulin at the time of hypoglycemia, indicate the presence of these tumors.\(^{133-135}\) Patients with insulinoma also have elevated levels of C-peptide.\(^{133}\) Testing for urinary sulfonylurea helps rule out factitious hypoglycemia.

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 scintography should be performed only if octreotide is being considered as a treatment. Octreotide should only be administered to patients whose tumors are somatostatin scintography-positive, because in the absence of somatostatin receptors, octreotide can profoundly worsen hypoglycemia (see *Preoperative Management*, below).\(^{136}\)

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.\(^ {137}\)

**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 scintography 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 scintography and EUS can also be considered as appropriate. A recent case report describes the diagnosis and treatment of a patient with VIPoma.\(^ {138}\)
Primary Treatment of Locoregional Resectable Neuroendocrine Tumors of the Pancreas

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

Preoperative Management

Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. Octreotide can be considered for symptom control in most pancreatic neuroendocrine tumor subtypes. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Octreotide should be used with caution in patients with insulinoma because it can also suppress counterregulatory hormones, such as growth hormone (GH), glucagon, and catecholamines. In this situation, octreotide can precipitously worsen hypoglycemia, and can result in fatal complications in some cases. In each instance where octreotide is recommended for symptom control, lanreotide is an acceptable alternative, as discussed in more detail in Management of Locoregional Unresectable and/or Metastatic Carcinoid Tumors, above.

For gastrinomas, gastrin hypersecretion may be treated with proton pump inhibitors. VIPomas and glucagonomas are generally sensitive to octreotide. Because severe weight loss is common in patients with glucagonoma, total parenteral nutrition may also be considered. 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. Other studies, including an analysis of the SEER database, suggest that some small tumors (measuring less than 2 cm in size in these studies), can pursue a more aggressive course. 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.

Surgical Management of Gastrinomas

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

Gastrinomas in the head of the pancreas that are exophytic or peripheral as determined by imaging and are not immediately adjacent to the pancreatic duct should be enucleated. The periduodenal nodes should also be removed. Gastrinomas in the pancreatic head that are deeper or invasive and those with proximity to the main pancreatic duct should be managed with pancreatoduodenectomy.

Gastrinomas in the distal pancreas are treated with distal pancreatectomy. The role of routine splenectomy in such cases is debated. Gastrinomas in some cases may be associated with lymph node metastases, 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.

Surgical Management of Insulinomas
The primary treatment for exophytic or peripheral insulinomas, because they are primarily benign, is enucleation. This procedure can be performed laparoscopically for localized solitary tumors within the body and tail of the pancreas. Sporadic tumors are usually solitary, whereas familial tumors are multiple. If enucleation is not possible because of invasion or the location of the tumor within the pancreas, then pancreatoduodenectomy for tumors in the head of the pancreas or distal pancreatectomy with preservation of the spleen for smaller tumors not involving splenic vessels may be considered. Distal pancreatectomy can be performed laparoscopically.

Surgical Management of Glucagonomas
Most glucagonomas are malignant and calcified and located in the tail of the pancreas, with regional node involvement. The recommended treatment is distal pancreatectomy with splenectomy and resection of the peripancreatic lymph nodes. For tumors in the pancreatic head, pancreatoduodenectomy with resection of the peripancreatic lymph nodes is recommended. Small (<2 cm) peripheral glucagonomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas. A hypercoagulable state has been reported in 10% to 33% of patients with glucagonoma. Therefore, perioperative anticoagulation can be considered because of the increased risk of pulmonary emboli.

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

Surgical Management of Other Pancreatic Neuroendocrine Tumors
The treatment recommendations for tumors secreting hormones such as somatostatinoma, ACTH, parathyroid hormone-related protein (PTHrP), and PP are similar to those for nonfunctioning tumors. Tumors that are small (<2 cm) and peripheral can be enucleated with or without removal of regional nodes, or distal pancreatectomy can be performed with or without removal of regional nodes and with or without splenectomy. Deeper, larger (>2 cm), or invasive tumors are treated with pancreatoduodenectomy if they are located in the head of the pancreas.
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 Pancreatic Neuroendocrine Tumors**

Disease recurrence has been observed in 21% to 42% of patients with pancreatic neuroendocrine tumors and can occur after many years.\(^{150-152}\)

Higher lymph node ratio and Ki-67 status may indicate a higher chance of recurrence.\(^{153}\) 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 tumor 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.\(^{154}\) 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. Noncurative debulking surgery can also be considered in select cases. When performing staged pancreatoduodenectomy and liver resection, hepatectomy should be considered before pancreatic resection to reduce the risk of perihepatic sepsis from the contaminated biliary tree.\(^{155}\) Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence.\(^{60,61}\) 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%.\(^{59}\)

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

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

**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.

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 difference in overall survival was observed between the arms. Adverse events associated with sunitinib include fatigue and, in rare cases, congestive heart failure. Other side effects have also been described.

Somatostatin Analogs
Patients with pancreatic neuroendocrine tumors and symptoms of hormone secretion should, in most cases, receive treatment with a somatostatin analog 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 (category 2B). Although no randomized studies to date have 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. Preliminary results from the CLARINET study, in which 204 patients with gastroenteropancreatic 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; $P = .0002$).

Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced pancreatic neuroendocrine tumors. Numerous large non-randomized cohort analyses have also reported encouraging survival rates with this approach. 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 radiopeptide therapy in patients with advanced pancreatic neuroendocrine tumors are needed.

Cytotoxic Chemotherapy for Advanced Pancreatic Neuroendocrine Tumors
Cytotoxic chemotherapy is another option for patients with unresectable or metastatic pancreatic neuroendocrine tumors (category 2A). 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.
tumors.\textsuperscript{164} 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.\textsuperscript{165} The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23\% in patients with poorly differentiated neuroendocrine tumors and 30\% in well-differentiated disease.\textsuperscript{93}

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.\textsuperscript{95,166-169} 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.\textsuperscript{169} Another retrospective review of the temozolomide and capecitabine combination reported a 61\% response rate in 18 patients, with 1 surgically proven complete pathologic response.\textsuperscript{170} A small recent retrospective study (7 patients) found a response rate of 43\%.\textsuperscript{171}

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).\textsuperscript{166} 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 NET. 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.\textsuperscript{172}

**Hepatic-Directed Therapies**

Hepatic-directed therapies may be considered in patients with progressive hepatic-predominant disease, mainly with the palliative goals of extending life and relieving hormonal symptoms. The panel lists cytoreductive surgery or ablative therapy (RFA\textsuperscript{78}, cryotherapy, microwave\textsuperscript{79,80}) as category 2B recommendations for these patients. Although some groups report that the risks of cytoreductive surgery outweigh its benefits,\textsuperscript{173} others have reported good outcomes.\textsuperscript{174,175}

Additional options include hepatic regional therapies such as arterial embolization,\textsuperscript{81} radioembolization (category 2B),\textsuperscript{85-90} and chemoembolization.\textsuperscript{176} While embolization in general is considered an effective approach in patients with hepatic-predominant disease,\textsuperscript{75-77} no randomized clinical trials have yet compared bland, chemo, or radioembolization, so the optimal embolization approach remains uncertain.

**Liver Transplantation**

Liver transplantation has been performed in patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver.\textsuperscript{113-118,177} Although some highly selected patients have experienced long-term survival, the panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

**Neuroendocrine Tumors of Unknown Primary**

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

Evaluation of Neuroendocrine Tumors of Unknown Primary

The initial evaluation of a patient with biopsy-proven neuroendocrine tumors of unknown primary includes patient family history, clinical manifestations, laboratory studies, imaging studies, and/or immunohistochemical studies. Family history is particularly relevant as it may identify affected relatives and patients who are at increased risk for multiple endocrine tumors, such as patients with MEN1 or MEN2.

Given the differences in systemic treatment approaches for carcinoid and pancreatic neuroendocrine tumors, establishing whether or not a patient has a primary pancreatic neuroendocrine tumor can have important treatment implications. Potential primary sites may be investigated with imaging studies, such as multiphasic CT or MRI. Ultrasound or EUS of the pancreas is useful for patients with possible insulinomas or other neuroendocrine tumors of the pancreas. Many neuroendocrine tumors express specific receptors for amines or peptides (eg, somatostatin receptors), and somatostatin scintigraphy may also be helpful in localizing certain neuroendocrine tumors. In addition, 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. If a small bowel primary tumor is suggested by symptoms and radiologic findings and if metastases are completely resectable, exploratory surgery can be considered.

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

Primary Treatment of Neuroendocrine Tumors of Unknown Primary

If the primary tumor is not identified, poorly differentiated neuroendocrine tumors should be treated as described for Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors, 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). A bimodal age distribution is seen, 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\textsuperscript{190,191}) and alterations at the 11p15 locus (site of the \textit{IGF-2} gene\textsuperscript{192,193}) seem to occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.\textsuperscript{181,194-196} Signs and symptoms associated with hypersecretion of cortisol, called \textit{Cushing's syndrome}, include weight gain, weakness (primarily in proximal muscles), hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae, buffalo hump, supraclavicular fat pad enlargement, hyperglycemia, and hypokalemia. Aldosterone-secreting tumors may present with hypertension, weakness, and hypokalemia. Androgen-secreting tumors in women may induce hirsutism, deepening of the voice, and oligo/amenorrhea.\textsuperscript{194} In men, estrogen-secreting tumors may induce gynecomastia and testicular atrophy. Hormonally inactive ACCs typically produce symptoms related to tumor burden, including abdominal pain, back pain, early satiety, and weight loss.\textsuperscript{194,197}

\textbf{Evaluation and Treatment of Adrenal Gland Tumors}

Evaluation of patients with adrenal gland tumors should take into account whether patients have a history of prior malignancy, which may raise suspicion that the tumor is metastatic. In these patients, an image-guided needle biopsy can be considered. Usually, a functioning adrenal neoplasm (in particular pheochromocytoma) should be ruled out before biopsy. However, 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 \url{www.NCCN.org}). If biopsy reveals adrenal cortical tissue, than 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, \textit{Cushing's syndrome}, and pheochromocytoma, as described here and below.

\textbf{Evaluation and Treatment of Hyperaldosteronism}

When hyperaldosteronism (also called \textit{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.\textsuperscript{198} Confirmatory 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.\textsuperscript{199}

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.\textsuperscript{200,201}

Benign hyperaldosteronism is much more common and can be caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia.
Adrenal vein sampling for aldosterone 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. Levels of serum ACTH, cortisol, and the sex steroid dehydroepiandrosterone sulfate (DHEA-S) should then be assessed. Elevated levels of cortisol are indicative of Cushing’s syndrome. Patients who experience symptoms secondary to increased adrenocortical steroid levels may require treatment for palliation of symptoms, such as hypertension, hyperglycemia, hypokalemia, and muscle atrophy.

Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, and ectopic tumors in the lung, thyroid, pancreas, or bowel are probable sources. If an ectopic tumor is found, it should be removed if possible. If the primary tumor is unresectable, a bilateral laparoscopic adrenalectomy or medical management (see below) is recommended. 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.\(^4\)

Cushing’s syndrome can also be caused by a benign adrenal tumor (adrenal adenoma) or a malignant adrenal tumor, neither of which produces ACTH. Malignancy should be suspected if the tumor is larger than 5 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. For malignant disease, see later discussion of adrenal carcinoma. Benign adrenal tumors are removed through 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 multinodal hyperplasia. When the tumor appears benign and the contralateral gland appears abnormal, adrenal vein sampling of cortisol production determines treatment. If cortisol production is asymmetric, the laparoscopic unilateral adrenalectomy with removal of the most active side is recommended, again with postoperative corticosteroid supplementation. If cortisol production is symmetric, medical management is indicated.

Medical management of hypercortisolism is achieved with adrenostatic agents, including ketoconazole and mitotane. Ketoconazole is most commonly used (at doses of 400–1200 mg/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 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 recommended when medical management of severe 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 and are thus sometimes called *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. On CT scans with intravenous contrast, adjacent lymph nodes or liver metastases may be present. On unenhanced CTs, the Hounsfield unit (HU) number is typically higher in carcinomas than in adenomas, and a threshold value of 10 HU has been proposed as a means of distinguishing benign from malignant adrenal tumors. If the HU attenuation value is greater than 10 on unenhanced CT, then enhanced CT and washout at 15 minutes is recommended. If the enhancement washout value is greater than 60% at 15 minutes, the tumor is likely benign. MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans. Whether CT or MRI scans are performed, they should be performed using an adrenal protocol to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics.

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.

**Treatment and Surveillance of Nonmetastatic Adrenal Carcinoma**
Surgical resection of the tumor with removal of adjacent lymph nodes is recommended in patients with localized adrenal carcinoma, and may require removal of adjacent structures such as the liver, kidney, pancreas, spleen, and/or diaphragm for complete resection. Open adrenalectomy is preferred in tumors with a high risk of being malignant because of increased risk for local recurrence and peritoneal spread when performed laparoscopically.

Because of the rarity of ACCs, no randomized, prospective trials of adjuvant therapy have been published. Most retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticolytic agent. The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany. In the Italian
cohort, nearly half of the patients received adjuvant mitotane (47/102 patients) at doses ranging from 1 to 5 g/d, whereas none of the 75 German patients received adjuvant mitotane. The median duration of treatment was 29 months. In follow-up, disease-free and overall survivals were significantly longer in those treated with mitotane versus the controls, suggesting that adjuvant mitotane may be an effective postoperative strategy. The randomized phase III ADIUVÒ 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. Recurrences after this time 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. Pheochromocytomas release catecholamines and their metabolites norepinephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. About 40% of paragangliomas also secrete catecholamines.

The peak incidence of occurrence for pheochromocytomas is between the third and fifth decade of life, but they generally occur at a younger age and are more likely to be bilateral in patients with familial disease. Paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% vs. 10%). Pheochromocytomas and paragangliomas associated with a familial syndrome tend to be more aggressive and more likely to metastasize than sporadic tumors. In fact, a recent study showed that 87.5% of patients presenting with these tumors prior to age 20 harbored a germline mutation in one of several genes tested if they also had metastatic disease. For those without metastases, the rate of identification of these mutations was still high, at 64.7%. Delays as long as 30 years between presentation and metastasis have been reported in patients with familial paragangliomas, and many such patients survive long term after treatment of metastatic disease. Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see Surveillance of Pheochromocytomas/Paragangliomas, below).

### Evaluation for 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. Concurrent medications should be reviewed before metanephrine testing for those that interfere with plasma metanephrines evaluation, including acetaminophen, certain beta- and alpha-adrenergic blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors. 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. Measurement of dopamine levels can be considered for cervical paragangliomas.

Imaging studies, including chest/abdominal CT scan or MRI, 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. 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.

**Genetic Counseling/Testing in Pheochromocytomas/Paragangliomas**

Although 59% to 90% of patients with pheochromocytomas are thought to have sporadic disease, pheochromocytomas frequently 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 (i.e., RET, NF1, VHL, SMAD4, ENG, ALK1), germline mutations in SDHB, SDHA, SDHAF2, SDHD, SDHC, TMEM127, MAX, and HIF2A have been associated with increased incidence of pheochromocytomas and paragangliomas. Patients under the age of 45 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 up to 41% 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 blockage of alpha receptors with prazosin, terazosin, or doxazosin can also be performed when long-term therapy is required for metastatic pheochromocytoma. The tyrosine hydroxylase inhibitor, alphamethyltyrosine, 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. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The panel acknowledges that other effective agents can be used for alpha and beta blockade. The panel also points out that rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room to control blood pressure.

A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas. If possible, cytoreductive resection is also recommended for the treatment of isolated distant metastases. Cytoreductive resection is also recommended for locally unresectable or metastatic disease, if possible, with or without RT. Symptoms can be
controlled using alpha blockade with or without alpha-methyltyrosine and with or without beta blockade with an R2 resection. In addition, other options for distant metastases include: 1) clinical trial; 2) systemic chemotherapy with cyclophosphamide, vincristine, and/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 an improved median survival (6.4 years versus 3.7 years for non-responders). Approximately 33% of patients exhibited a response.

**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 or other scans and plasma ACTH or other biochemical markers are recommended as indicated.

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

For resectable poorly differentiated/small cell tumors, surgical resection and chemotherapy with a small cell lung cancer regimen with or without radiotherapy are advised (see NCCN Guidelines for Small Cell Lung Cancer, available at [www.NCCN.org](http://www.NCCN.org)). In general, cisplatin or carboplatin and etoposide are recommended as primary treatment. Alternatively, definitive chemoradiation can be considered, also according to the NCCN Guidelines for Small Cell Lung Cancer.

For unresectable locoregional disease, radiotherapy in combination with chemotherapy (again, with a small cell lung cancer regimen) is recommended. If metastatic tumors are present, chemotherapy alone (with a small cell lung cancer regimen) is recommended. Octreotide therapy can be considered for symptom control in the rare cases of hormone-secreting tumors that are unresectable or metastatic. Lanreotide, which is approved for symptom control in Europe, has a similar mechanism of action as octreotide. Because it is injected subcutaneously, it may be preferable in patients who have difficulty tolerating an intramuscular injection. See *Management of Locoregional*
Unresectable and/or Metastatic Carcinoid Tumors, above, for a detailed discussion on lanreotide.

Evolving data suggest that patients with intermediate Ki-67 levels (in the 20%–50% range) may not respond as well to platinum/etoposide as patients with small cell histology or those with extremely high Ki-67. Clinical judgement should be used in selecting chemotherapy regimens for patients with Ki-67 levels in this intermediate range.

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 two main types of MEN 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
MEN1 (or Wermer syndrome), as previously mentioned, involves mainly the parathyroid glands, pituitary gland, and pancreas, but may also be associated with carcinoid tumors (e.g., 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 a sporadic parathyroid adenoma, or of a thymic or bronchial carcinoid tumor, or of a pheochromocytoma.

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.
result of an excess of several hormones from more than one gland, such as hyperparathyroidism and a simultaneous gastrinoma, insulinoma, or a functioning pituitary tumor. However, in most patients, a single hormonal syndrome dominates the clinical picture.

About 80% of patients with MEN1 and hypoglycemia related to insulinoma have multiple islet cell neoplasms. Patients with MEN1 and Zollinger-Ellison syndrome also frequently have more than one tumor. Of these tumors, 70% are gastrin-secreting carcinoids in the duodenum and/or periduodenal lymph nodes. Nonfunctioning pancreatic neuroendocrine tumors are usually larger when clinically detected and are more likely to be malignant. Overall, about 10% of insulinomas and up to 90% of gastrinomas are malignant.120,250 Malignant pancreatic neuroendocrine tumors and 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 (Tc$^{99m}$) sestamibi and ultrasound scanning are about 80% and 70% sensitive, respectively, for identifying solitary parathyroid adenomas found in most patients with sporadic hyperparathyroidism. However, these scans are only about 35% accurate in patients with familial hyperparathyroidism. Neither scan can distinguish between adenomatous and hyperplastic parathyroid glands. Because most patients with familial hyperparathyroidism have multiple abnormal parathyroid glands, preoperative localization studies are less accurate and abnormal parathyroid glands are best identified during surgery.251,252

Evaluation for Pancreatic Tumors in MEN1
Approximately 75% of patients with MEN1 and pancreatic neuroendocrine tumors have functioning tumors. 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, and includes determination of basal gastrin levels. Other biochemical tests, including stimulated gastrin levels, are performed as indicated. 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 prolactin and IGF-1 levels as category 2B recommendations. 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; luteinizing hormone (LH) and follicle-stimulating hormone (FSH), to aid in the recognition of nonfunctioning tumors; and GH for acromegaly.

**Genetic Counseling/Testing in MEN1**

Genetic counseling and MEN1 genetic testing should be offered to individuals with suspicion or a clinical diagnosis of MEN1 (see Evaluation of MEN1 Syndromes, above) and to at-risk relatives of individuals with known germline MEN1 mutations. It should be noted that a germline MEN1 mutation is seldom found in individuals with a single MEN1-associated tumor and no family history. Approximately 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 MEN1 patients focuses on treatment of the specific hormonal syndrome and/or treatment of the underlying hyperplasia or tumor. A consultation with an endocrinologist for all patients with MEN1 should be considered. In most instances, surgical excision by an experienced surgeon is the initial treatment of choice for functioning tumors, whereas asymptomatic tumors (such as pituitary tumors) may be treated medically or with observation if no local mass effects are present. All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus 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 MEN1 patients is treated as in patients with neuroendocrine tumors arising sporadically, according to the appropriate tumor type.

**Primary Treatment of Parathyroid Tumors in MEN1**

Treatment options for parathyroid hyperplasia in patients with MEN1 include subtotal parathyroidectomy with or without thyomectomy (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.\textsuperscript{254,255} 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.\textsuperscript{256} Removal of a single functioning tumor, although a reasonable approach for sporadic tumors, usually misses additional (possibly malignant) tumors in the setting of MEN1. Therefore, 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.

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

**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.\textsuperscript{257} 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 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. Imaging with multiphasic abdominal CT or MRI scan 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’s 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 MEN2A patients 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 MEN2B patients 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 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.

The initial symptoms associated with MEN2A and MEN2B include a mass in the thyroid gland (with or without adjacent central or lateral cervical lymph node adenopathy) and, less frequently, symptoms of excess hormone production related to MTC (such as diarrhea and facial flushing), pheochromocytoma (headaches, increased perspiration, and rapid heart rate), or hyperparathyroidism.

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

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

A clinical diagnosis of MEN2A includes findings of 2 or more MEN2A-associated cancers (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia) 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.\textsuperscript{259,260} 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.

MEN2 patients should be evaluated for a coexisting pheochromocytoma (see \textit{Evaluation for Pheochromocytoma/Paraganglioma}, 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 blockade. Additional treatment with alpha methyltyrosine and a beta blocker can also be considered (see \textit{Primary Treatment of Pheochromocytomas/Paragangliomas}, above).

A parathyroid workup is also recommended for MEN2 patients; 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 \textit{RET} genetic testing should be offered to individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2 (see \textit{Evaluation of MEN2 Syndromes}, above).\textsuperscript{259,260} Genetic counseling and testing should also be offered to at-risk relatives of an individual with a known germline \textit{RET} mutation at a very young age.\textsuperscript{259,260} All patients with MTC should be tested for germline mutation of the \textit{RET} oncogene even if the family history is not suggestive of a hereditary syndrome, because about 50% of patients with presumed sporadic MTC have a \textit{de novo} germline mutation.\textsuperscript{260}

Even with negative \textit{RET} genetic test results, individuals with clinical diagnosis or suspicion of MEN2 should undergo regular surveillance for MEN2-associated tumors. Similarly, at-risk relatives should have MEN2 surveillance even if the affected relative had a negative test result or no genetic testing.\textsuperscript{259} See \textit{MEN2 Surveillance}, below.

Primary Treatment of MEN2A, MEN2B, and Familial MTC

In patients with a positive \textit{RET} oncogene test who are otherwise asymptomatic, prophylactic thyroidectomy is performed during the first 5 years of life depending on the aggressiveness of the inherited \textit{RET} mutation or at diagnosis,\textsuperscript{259,261-263} as detailed in the NCCN Guidelines for Thyroid Carcinoma (available at 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). However, patients with familial disease are much more likely to have bilateral thyroid carcinomas.

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 identification and selective resection of abnormal parathyroid glands, and for leaving normal parathyroid glands in place (marked with a clip or stitch during thyroid surgery) when possible. Subtotal parathyroidectomy is recommended when all glands appear abnormal. Some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC, while others believe the risk of hypoparathyroidism with this approach (about 6%) is too high to warrant the procedure. If a normal parathyroid gland is not preserved in situ in patients with MEN2A, it can be autotransplanted to the forearm, since recurrent primary hyperparathyroidism occurs in almost 20% of these patients. If hyperparathyroidism recurs with a documented elevated PTH level in the ipsilateral basilic vein, the tumor can be removed or subtotally resected.

Management of patients with pheochromocytoma and RET mutations 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.

**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](http://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 MEN2 patients, 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. The NCI recently convened a task force to set priorities for future studies and to recommend appropriate standards for trials in neuroendocrine tumors. Among their recommendations are the following:

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