National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroendocrine Tumors

Version 3.2017 — June 13, 2017

NCCN.org

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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 3.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2017 include:

NET-9
- Pathway for carcinoid syndrome has been removed from this page. See NET-10.

NET-10
- This page has been added to expand the recommendations for the treatment of carcinoid syndrome.
- Telotristat has been added as an option to consider in combination with octreotide or lanreotide, for persistent diarrhea from poorly controlled carcinoid syndrome.
- Footnote "ee" added: "Telotristat is not indicated for flushing due to poorly controlled carcinoid syndrome."

NE-D (1 of 3)
- Row added to include the systemic therapy options for carcinoid syndrome:
  - Octreotide or lanreotide ± therapy for poorly controlled carcinoid syndrome, including:
    - ◊ Telotristat 250 mg orally, three times daily (for persistent diarrhea), and/or
    - ◊ Additional therapy for disease control (for any persistent symptoms [ie. flushing, diarrhea])
- Reference: Kulke MH, Hörsch D, Caplin ME, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol. 2017; 35(1):14-23.

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

Updates in Version 2.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2017 include:

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

Updates in Version 1.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2016 include:

Global
- "Somatostatin receptor scintigraphy" has been changed to "somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT)." The following footnote has also been added: "PET/CT of skull base to mid-thigh."
- Footnote has been revised: "Somatostatin receptor- ~~scintigraphy~~ based imaging and FDG-PET/CT scans are not recommended for routine surveillance."
- Footnote has been added: "Multiphasic imaging studies are performed with contrast."
- The target anatomy of imaging, and recommended imaging modalities have been clarified throughout the guidelines.

Neuroendocrine Tumors of the GI Tract, Lung, and Thymus

General
- Where indicated, surveillance recommendations for GI, lung, and thymus neuroendocrine tumors have been relocated to page NET-7.
- The following footnotes that apply to the surveillance recommendations have been relocated to NET-7:
  - "Earlier, if symptoms."
  - "Somatostatin receptor-based imaging and FDG-PET/CT scan are not recommended for routine surveillance."

NET-1
- Under evaluation, "Chest CT" has been changed to "Chest CT *with or without contrast*." (Also on NET-2 and NET-3)
- Duodenal: After endoscopic resection of locoregional disease, surveillance recommendations have been clarified. Routine endoscopic surveillence is recommended for noninvasive tumors. For invasive tumors, see surveillance on NET-7.

NET-2
- Language in footnote "h" has been revised: "Some appendiceal *neuroendocrine tumors* ~~carcinoids~~ will have mixed histology..."

NET-3
- A pathway has been added to clarify that no additional follow-up is recommended for small (<1 cm) incidental rectal tumors that were completely resected.
- For "all other rectal tumors," recommended evaluation options are "endorectal MRI or EUS." Additional evaluation applies only to T2-T4 disease.

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Updates in Version 1.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2016 include:

NET-4

- Primary treatment option has been added for Type 1 gastric tumors: "Endoscopic resection of prominent tumors."
- For type 2 gastric tumors, primary treatment options have been clarified.
  - For primary gastrinomas that are not resected, options revised: "Consider endoscopic surveillance and endoscopic resection of prominent tumors and/or *consider* octreotide or lanreotide *and Manage gastric hypersecretion with high-dose proton pump inhibitors."*
- Following primary treatment for type 3 gastric tumors, for surveillance a link has been added to NET-7.
- Line added to footnote "k": "However, PPI should be continued in patients with overt clinical symptoms of gastrinoma and/or risks of complications."
- Footnote "m" has been added: "For rare, >2 cm, type 1 gastric tumors, workup should include multiphasic CT or MRI of the abdomen. Primary tumor resection and antrectomy should be perfomed as clinically indicated. For metastatic disease, see NET-9."
- The following footnotes have been removed:
  - "If gastric pH is low or there is clinical or radiographic evidence, see gastrinoma on PanNET-2."
  - "Patients with metastatic, unresectable gastrinoma are unlikely to require surveillance of type 2 gastric NET."

NET-5

- Separate pathways included for low grade (typical) and intermediate grade (atypical) unresectable or incompletely resected locoregional disease.
  - Options for low grade: Consider RT (category 3)
  - Options for intermediate grade: RT ± cisplatin/etoposide or carboplatin/etoposide.
- Footnote "r" revised: "~~Consider 5-FU or capecitabine at radiosensitizing doses.~~ Cisplatin/etoposide or carboplatin/etoposide may be appropriate for patients with atypical or poorly differentiated carcinomas. *Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67).*"

NET-6

- The algorithm for bronchopulmonary neuroendocrine tumors has been significantly revised and expanded.

NET-7

- Page added to include the surveillance recommendations for most GI, lung, and thymus neuroendocrine tumors.

NET-8

- Page has been added to include recommendations for metastatic bronchopulmonary/thymus neuroendocrine tumors.

NET-9

- "Chest CT as clinically indicated" added where imaging is recommended.
- For progressive disease, reorganized algorithm and treatment with octreotide or lanreotide is recommended (if not already receiving). If disease progression while on octreotide or lanreotide, additional therapy options that are listed may be considered.
- "Consider everolimus" has been changed from a category 3 recommendation to a category 2A recommendation.
- Hepatic-directed therapies for hepatic-predominant disease have been regrouped. (Also on PanNET-7)
- The following footnotes have been added:
  - "cc": "Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive."
  - "dd": "If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options."

Neuroendocrine Tumors of the Pancreas

PanNET-1

- Footnote has been removed: "For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway."
- Footnote "f" has been revised: "Observation can be considered in select cases: *small* tumors ~~<1 cm~~, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities. *(Sadot E, et al. Ann Surg Oncol 2016;23:1361-70.) Follow surveillance recommendations on PanNET-6.*"

PanNET-2

- Recommended evaluation option has been revised: "*Serum* gastrin level ~~(basal, stimulated as clinically indicated)~~."
- Footnote "j" has been revised: "Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. It should ideally be checked when fasting and off PPI for >1 week. *However, PPI should be continued in patients with overt clinical symptoms of gastrinoma and/or risks of complications."*

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Updates in Version 1.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2016 include:

PanNET-3
- Serum insulin, pro-insulin, and c-peptide levels have been added as recommended evaluation options for insulinoma.

PanNET-5
- Management of locoregional disease, the first bullet has been revised: "Stabilize *glucose levels* ~~with IV fluids~~."

PanNET-6
- This page has been simplified.
- Footnote "u" has been added: "Surveillance recommendations also apply to cases where observation has been chosen."
- Footnote "v" has been added: "In select cases, resection may be considered."

PanNET-7
- The following evaluation options have been added for locoregional, unresectable and/or metastatic pancreatic neuroendocrine tumors:
  - Abdominal/pelvic multiphasic CT or MRI and chest CT (± contrast) as clinically indicated
  - Consider somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT)
  - Biochemical evaluation as clinically indicated
- For progressive disease, consider octreotide or lanreotide (if not already receiving). If disease progression while on octreotide or lanreotide, additional therapy options that are listed may be considered.
- Footnote "z" has been added: "If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options."

Neuroendocrine Tumors of Unknown Primary

NUP-1
- The following footnote has been removed: "Consider possibility of functioning adrenal neoplasms and suspected carcinoid tumor syndrome prior to biopsy. Evaluate plasma or 24-hour urine fractionated metanephrines prior to biopsy or maniplulation of adrenal masses (See NE-B). Alpha blockade is required prior to biopsy or manipulation for suspected pheochromocytoma or paraganglioma (See PHEO-1). Octreotide premedication is required before biopsy in a suspected functioning carcinoid tumor."

Adrenal Gland Tumors

AGT-3
- Mifepristone has been added as one of the medical management options for hypercortisolism from presumed multinodular hyperplasia of the adrenal, for tumors <4 cm with symmetric cortisol production, for those with symmetric cortisol production after adrenal vein sampling.

AGT-5
- Footnote "n" has been revised: "*Chest CT with or without contrast and abdominal/pelvic CT or MRI with contrast to evaluate for metastases and local invasion to stage disease, if not previously done.* ~~*Cross-sectional imaging to stage disease*~~."

Pheochromocytoma

PHEO-1
- Footnote "f" has been revised: "~~Genetic counseling and genetic testing are recommended when appropriate.~~ A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. Certain genetic variants may require more frequent follow-up. (See Discussion)"

PHEO-2
- For locally unresectable disease, the following treatment options have been revised:
  - "Continue medical therapy for secreting tumors *and consider referral to multidisciplinary center."*
  - "Radiation therapy ± cytoreductive (R2) resection, when possible or *131I-MIBG (requires prior positive MIBG scan with dosimetry)"*
- Palliative RT has been added as an option for bone metastases.
- Footnote "l" has been added: "CVD = cyclophosphamide, vincristine, and dacarbazine."

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Updates in Version 1.2017 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2016 include:

Poorly Differentiated Carcinomas/Large or Small Cell

PDNEC-1

- Somatostatin receptor imaging has been removed from the recommended evaluation options.
- The following footnotes have been added:
  - "a": Not all high-grade neuroendocrine cancers are poorly differentiated. NETs with ki-67 index >20% may be characterized by relatively well-differentiated histology, particularly tumors with ki-67 index between 20%–50%. Tumors that fall into the "well-differentiate/high-grade" category may respond relatively poorly to cisplatin/etoposide or carboplatin/etoposide, and respond more favorably to treatments described for well-differentiated NETs, see NET-8 or NET-9.
  - "b": Somatostatin scintigraphy is not part of the routine evaluation of poorly differentiated neuroendocrine tumors, but may be considered for morphologically well-differentiated tumors with higher proliferation index, as appropriate. For options for well differentiated tumors, see NET-8 or NET-9.
- Footnote "e" has been added: "See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A)."
- Footnote removed: "Consider octreotide or lanreotide for symptom control, if somatostatin receptor scintigraphy is positive."

Multiple Endocrine Neoplasia, Type 1

MEN1-1

- Content from former MEN1-A has been incorporated. MEN1-A has been removed.

MEN1-A

- Reference added: "Yates CJ, Newey PJ, Thakker RV. Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1. Lancet Diabetes Endocrinol 2015;3:895-905."

Multiple Endocrine Neoplasia, Type 2

MEN2-1

- Content from former MEN2-A has been incorporated. MEN2-A has been removed.

MEN2-2

- Surveillance for parathyroid has been simplified: "*Calcium evaluation*" and "*Additional evaluation if clinically indicated.*"
- Options for pheochromocytoma have been replaced by a link to page PHEO-1.

Principles of Biochemical Testing

NE-B (1 of 3)

- GI tract, lung, and thymus (carcinoid tumors)
  - Under clinical symptoms, first bullet revised: "Primary tumors in the GI tract usually are not associated with symptoms of hormone secretion unless extensive ~~liver~~ metastasis."
  - Under clinical symptoms, third bullet revised: "Bronchial/thymic tumors may be associated with *classic carcinoid syndrome as well as* Cushing's syndrome."
  - Under testing, the last bullet has been revised: "~~ACTH~~ *Test for Cushing's syndrome (see next page).*"
- Insulinoma: Under testing, "See Workup for insulinoma (PanNET-3)" has been added.
- Glucagonoma: "hypercoaguable state" has been added to the list of clinical symptoms.

Principles of Systemic Anti-Tumor Therapy

NE-D (2 of 3)

- Footnote "†" has been revised: "~~Although no randomized studies to date have directly shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors,~~ *The PROMID trial showed an antitumor effect of octreotide* ~~improvement in primary endpoint of time to tumor progression~~ in advanced neuroendocrine tumors of the midgut. *The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 gastroenteropancreatic NETs.* ~~Lanreotide and octreotide share the same mechanism of action, and the panel believes that either lanreotide or octreotide are appropriate options for tumor control in this setting.~~"

Staging

ST-6

- AJCC staging tables for lung neuroendocrine tumors have been added.

CLINICAL PRESENTATIONS AND DIAGNOSIS[a]

Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus (carcinoid tumors)[b]
Clinical presentations:
- Jejunal, ileal, colon (See NET-1)
- Duodenal (See NET-1)
- Appendix (See NET-2)
- Rectal (See NET-3)
- Gastric (See NET-4)
- Thymus (See NET-5)
- Bronchopulmonary, atypical lung carcinoid (See NET-6)
- Locoregional unresectable disease and/or distant metastases
  - Bronchopulmonary/thymus (See NET-8)
  - GI Tract (See NET-9)

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

Neuroendocrine tumors of unknown primary (See NUP-1)[b]

Adrenal gland tumors (See AGT-1)[c]

Pheochromocytoma/paraganglioma (See PHEO-1)

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

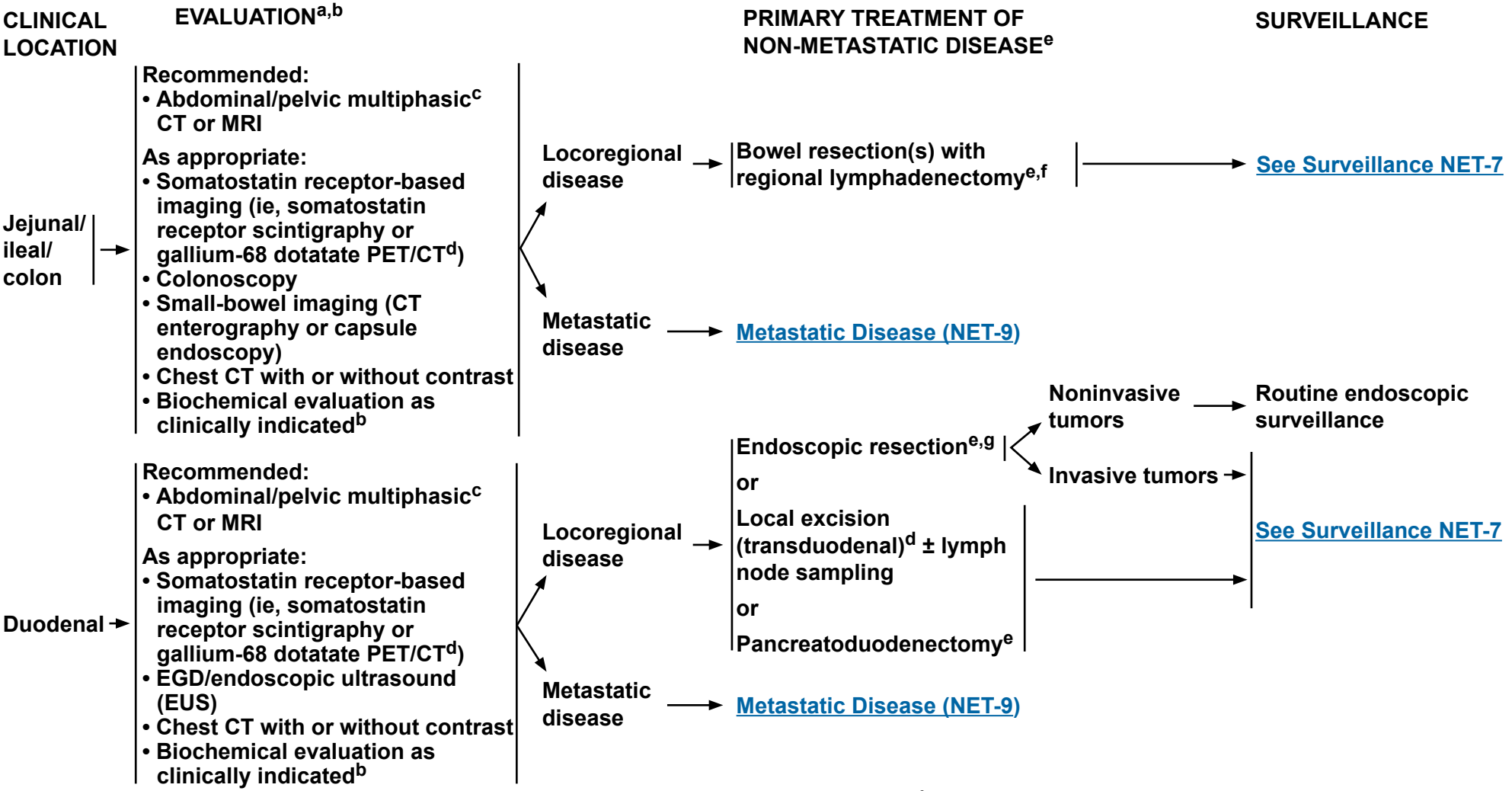
Multiple endocrine neoplasia, type 1 (See MEN1-1)
- Parathyroid
- Pancreatic neuroendocrine tumors (PanNETs)
- Pituitary tumor

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

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

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] Guidelines pertain to well-differentiated tumors. For poorly differentiated/large or small cell carcinomas, see PDNEC-1.
[c] Includes adrenal cortical tumors and incidentalomas.

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



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[f] 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.

[g] If endoscopic resection performed, follow-up EGD as appropriate.

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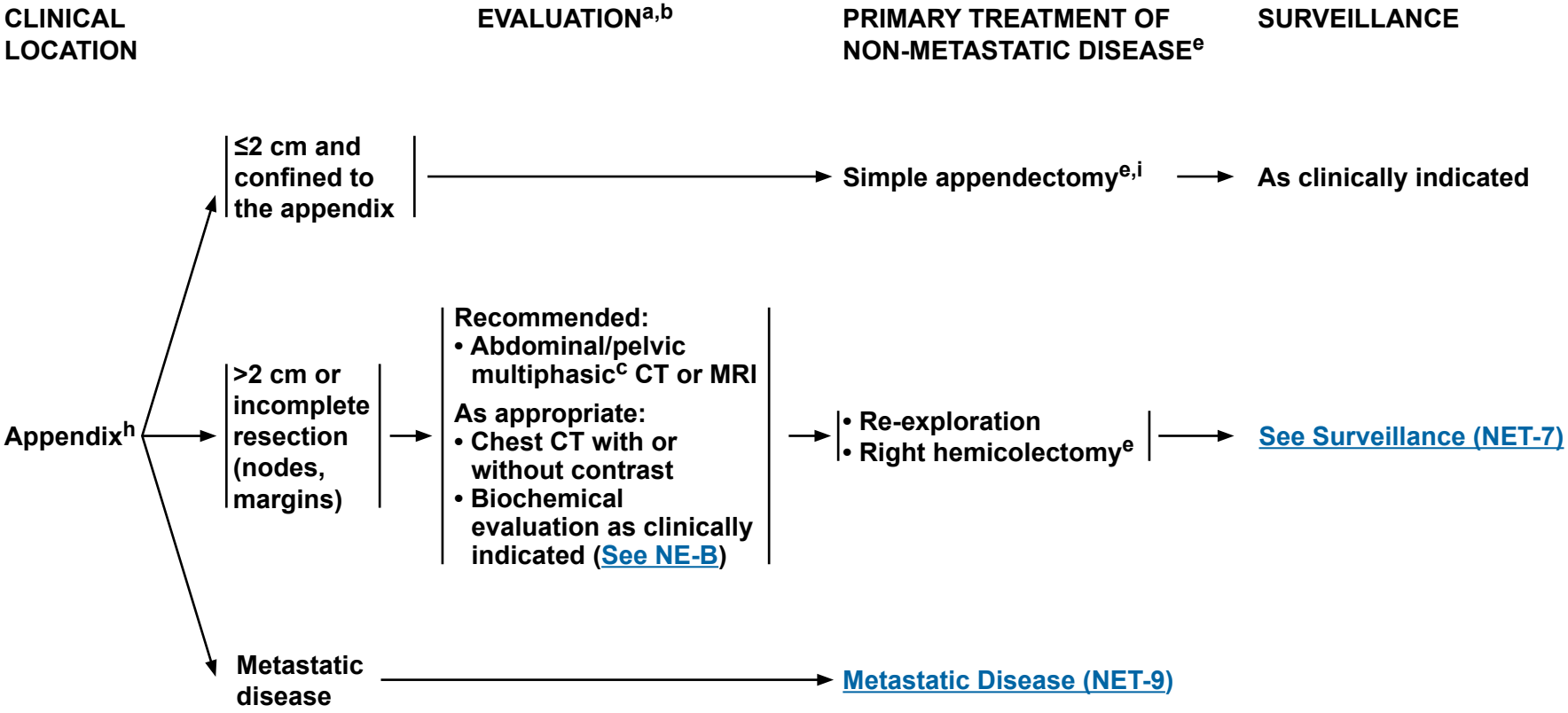

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h] Some appendiceal neuroendocrine tumors will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. See NCCN Guidelines for Colon Cancer.
[i] Some institutions will consider more aggressive treatments for 1- to 2-cm tumors with poor prognostic features. See Discussion for details.

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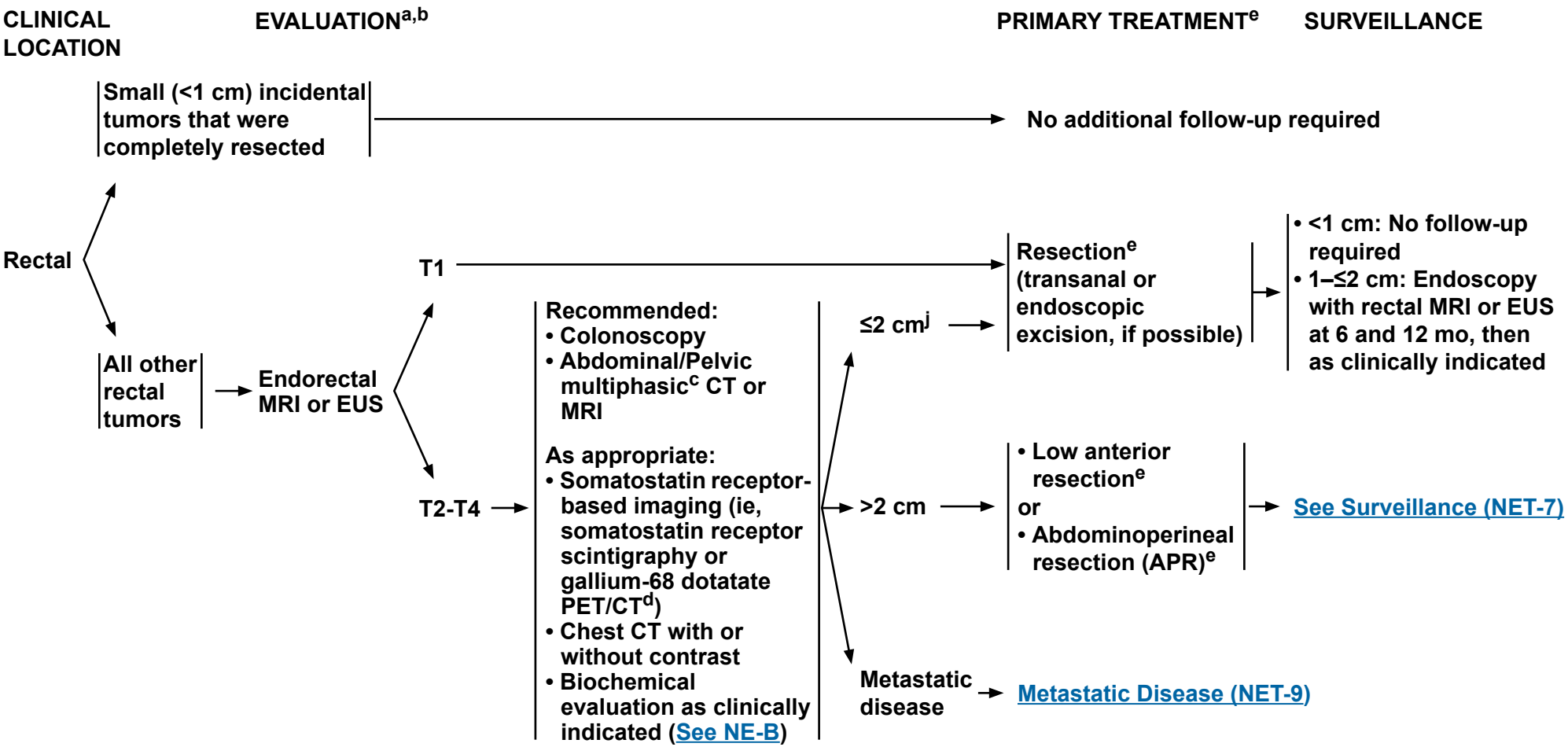

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[j] 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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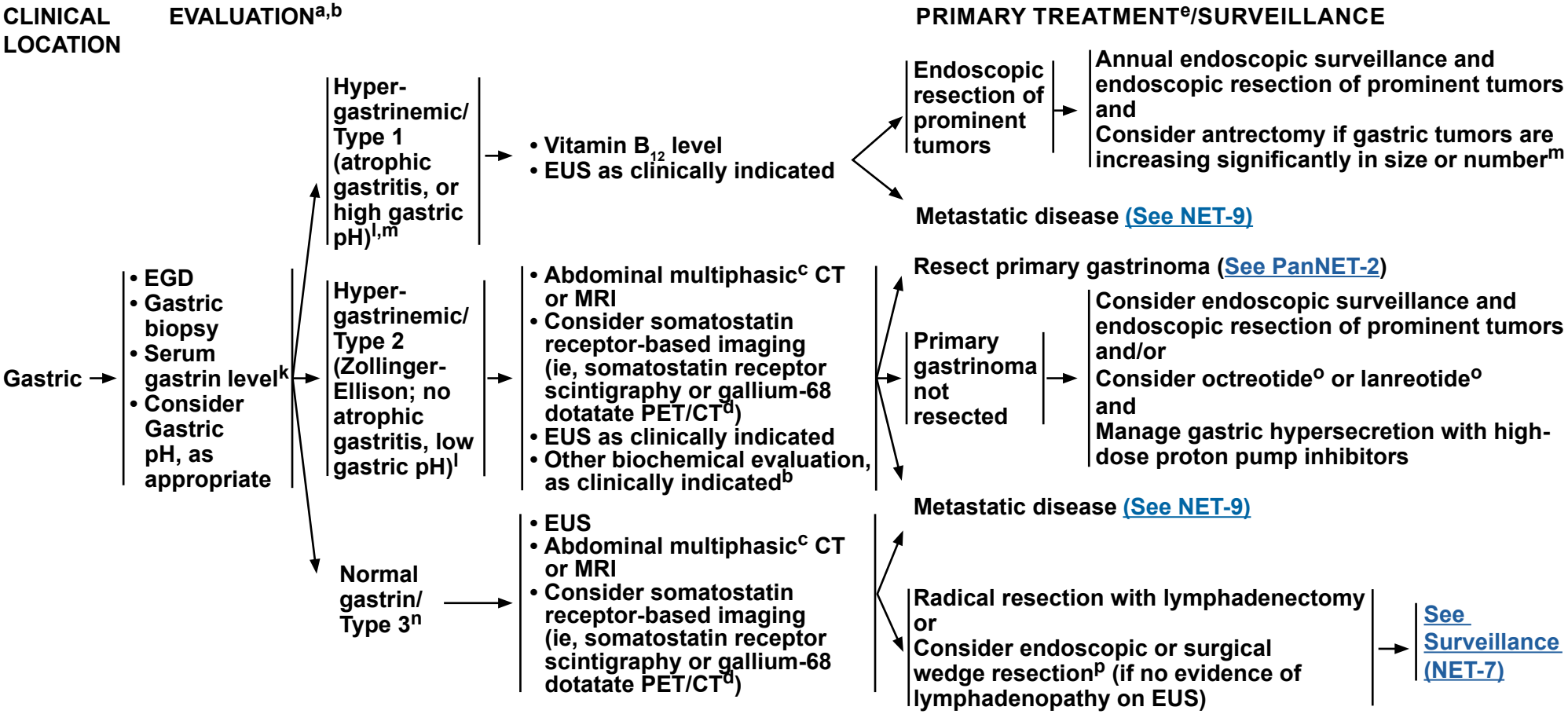

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[k] Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. It should ideally be checked when fasting and off PPI for >1 week. However, PPI should be continued in patients with overt clinical symptoms of gastrinoma and/or risks of complications.
[l] Elevated gastrin levels are usually diagnostic of type 1 or type 2 tumors.
[m] For rare, >2 cm, type 1 gastric tumors, workup should include multiphasic CT or MRI of the abdomen. Primary tumor resection and antrectomy should be perfomed as clinically indicated. For metastatic disease, see NET-9.
[n] Type 3 gastric neuroendocrine tumors tumors are sporadic, unifocal, and unassociated with either atrophic gastritis or Zollinger-Ellison syndrome.
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[p] Endoscopic resection should be reserved for small (<1 cm), superficial, low-grade tumors.

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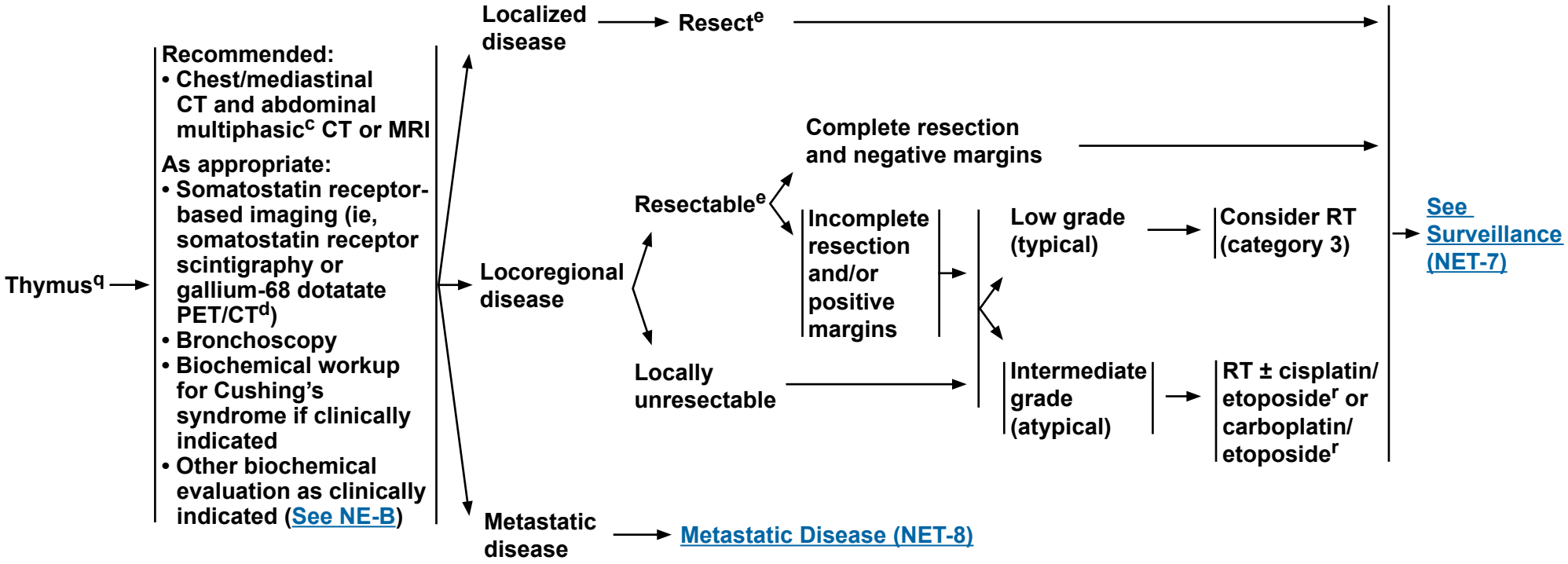

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)..
[q] Thymic neuroendocrine tumors are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1)
[r] Cisplatin/etoposide or carboplatin/etoposide may be appropriate for patients with atypical or poorly differentiated carcinomas.Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67).

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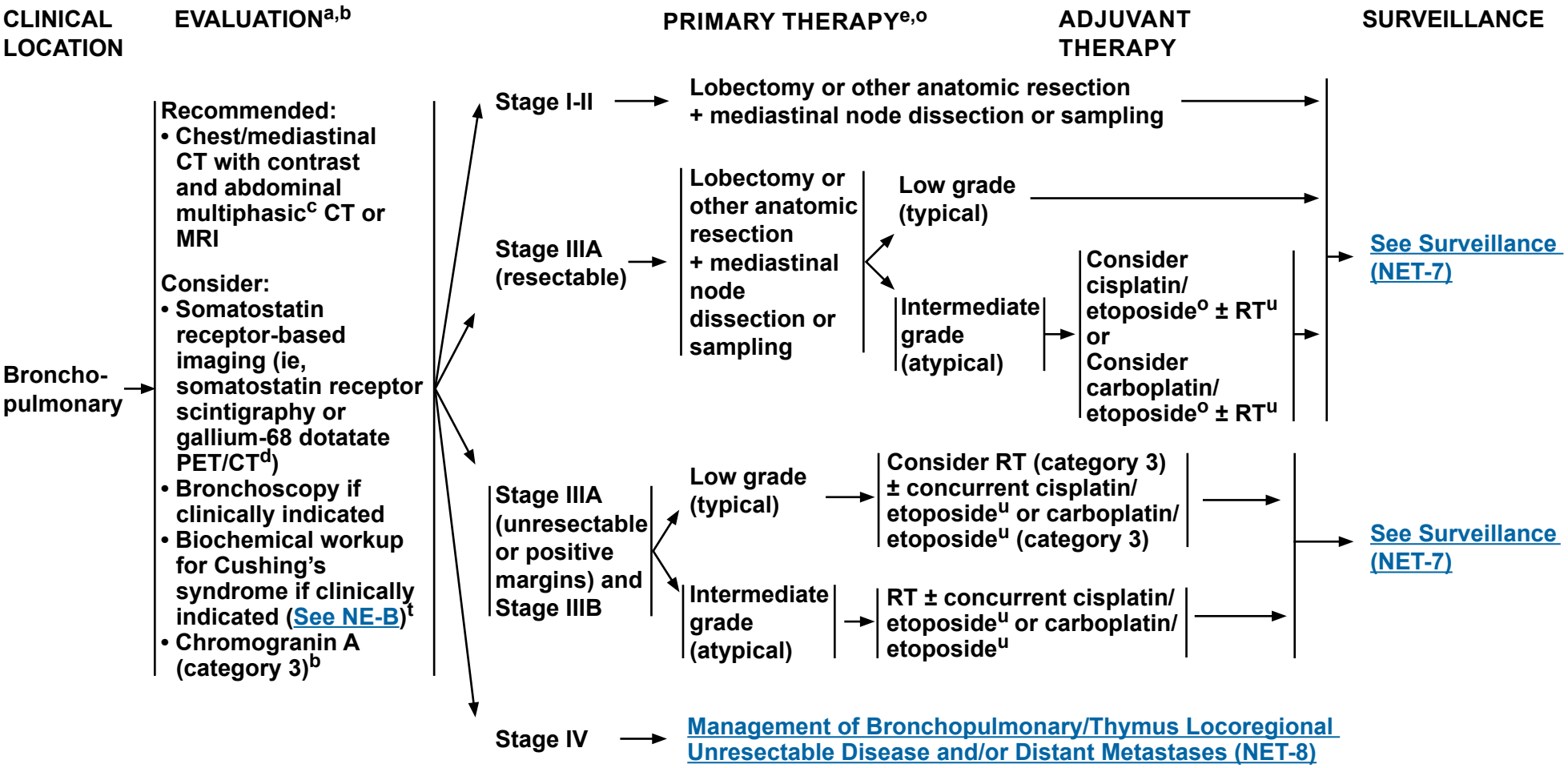

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[t] If Cushing's syndrome is suspected, assess for and treat ectopic sources of ACTH production.
[u] Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67). There is limited data on the efficacy of chemoradiation for unresectable IIIA or IIIB low grade lung neuroendocrine tumors; however some panel members consider chemoradiation in this situation.

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SURVEILLANCE[c,v,w]
GI TRACT, LUNG, AND THYMUS

3–12 mo postresection:
- H&P
- Consider biochemical markers as clinically indicated (See NE-B)[b]
- Abdominal ± pelvic multiphasic[c] CT or MRI as clinically indicated
- Chest CT with or without contrast for primary lung/thymus tumors (as clinically indicated for primary GI tumors)

>1 y postresection to a maximum of 10 y:
- Every 6–12 mo
  - H&P
  - Consider biochemical markers as clinically indicated (See NE-B)[b]
  - Consider abdominal ± pelvic multiphasic[c] CT or MRI
  - Consider chest CT with or without contrast for primary lung/thymus tumors (as clinically indicated for primary GI tumors)

→ **Disease recurrence[x]** →

RECURRENT DISEASE

MANAGEMENT OF RECURRENT DISEASE[e]

See Management of Bronchopulmonary/Thymus Locoregional Unresectable Disease and/or Distant Metastases (NET-8)
or
See Management of Gastrointestinal Tract Locoregional Unresectable Disease and/or Distant Metastases (NET-9)
or
See Management of Carcinoid Syndrome (NET-10)

[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[v] Earlier, if symptoms.
[w] Somatostatin receptor-based imaging and FDG-PET/CT scan are not recommended for routine surveillance.
[x] In select cases, resection may be considered.

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

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[e,o]

BRONCHOPULMONARY OR THYMUS

EVALUATION[b,c]

- Locoregional unresectable bronchopulmonary/thymic disease and/or distant metastases
- Recommended:
  - Chest CT with contrast and abdominal/pelvic multiphasic[c] CT or MRI
- Consider:
  - Somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT[d])
  - FDG-PET/CT for atypical histology
  - Biochemical workup for Cushing's syndrome if clinically indicated (See NE-B)[s]

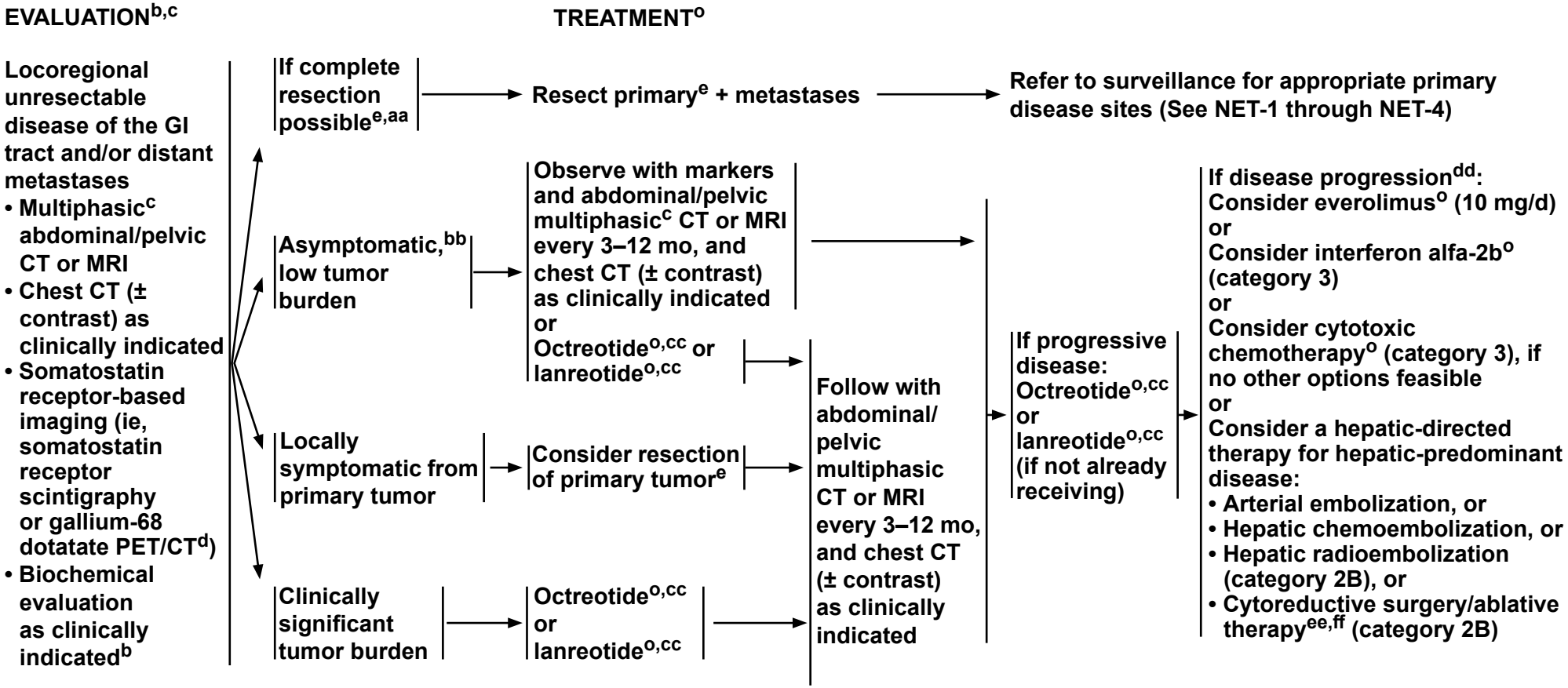
TREATMENT[o,x,y]

Asymptomatic, low tumor burden and low grade (typical)	Observe with chest CT with contrast and abdominal/pelvic multiphasic[c] CT or MRI every 3–6 mo or Octreotide or lanreotide
Clinically significant tumor burden and low grade (typical)	Consider: Octreotide or lanreotide or Everolimus ± octreotide or lanreotide or Temozolomide ± octreotide or lanreotide
Intermediate grade (atypical)	Consider: Octreotide or lanreotide or Everolimus ± octreotide or lanreotide or Temozolomide ± octreotide or lanreotide or Cisplatin/etoposide[z] ± octreotide or lanreotide or Carboplatin/etoposide[z] ± octreotide or lanreotide
Multiple lung nodules and evidence of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)	Observe with chest CT (without contrast) every 12 mo or for new symptoms ± Octreotide or lanreotide (if symptomatic)

[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[s] If Cushing's syndrome is suspected, assess for and treat ectopic sources of ACTH production.
[y] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[z] Cisplatin/etoposide or carboplatin/etoposide can be considered for intermediate grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

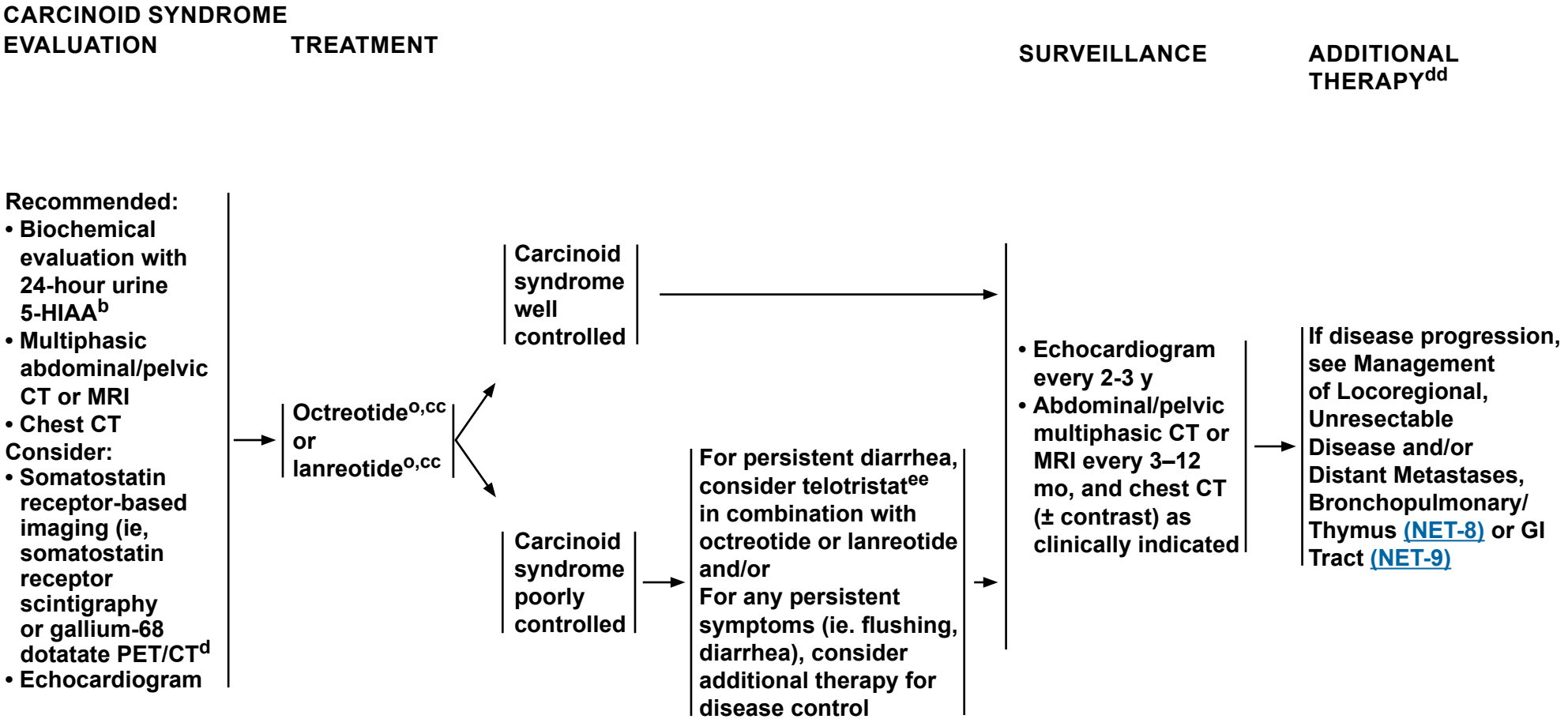
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT



[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with contrast.
[d] PET/CT of skull base to mid-thigh.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] Noncurative debulking surgery might be considered in select cases.
[bb] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[ee] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.
[ff] Only if near complete resection can be achieved.

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



[b] See Principles of Biochemical Testing (NE-B).
[d] PET/CT of skull base to mid-thigh.
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[cc] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[dd] If disease progression, treatment with octreotide, lanreotide or telotristat may be continued in combination with any of the subsequent options.
[ee] Telotristat is not indicated for flushing due to poorly controlled carcinoid syndrome.

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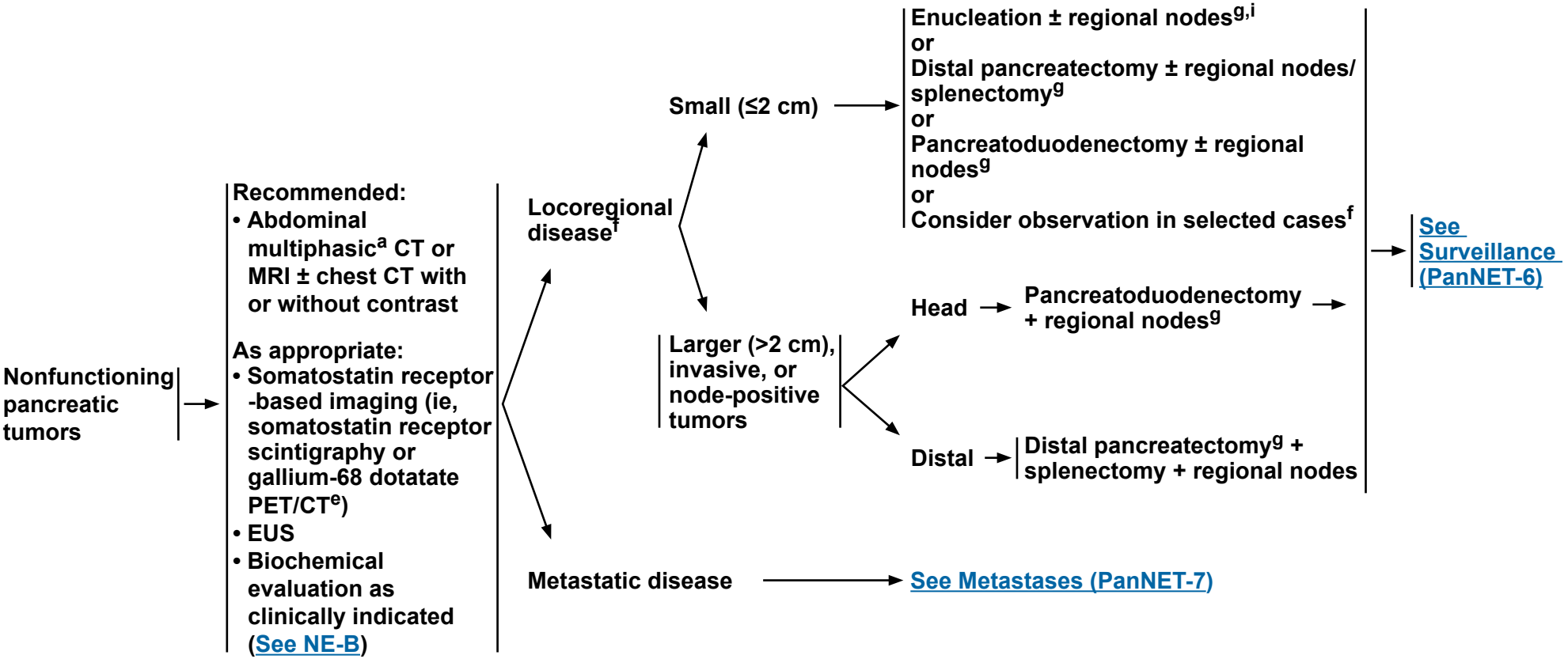
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a]Multiphasic imaging studies are performed with contrast.
[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[c]See Principles of Biochemical Testing (NE-B).
[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[e]PET/CT of skull base to mid-thigh.
[f]Observation can be considered in select cases: small tumors, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities. (Sadot E, et al. Ann Surg Oncol 2016;23:1361-70.) Follow surveillance recommendations on PanNET-6.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[i]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.

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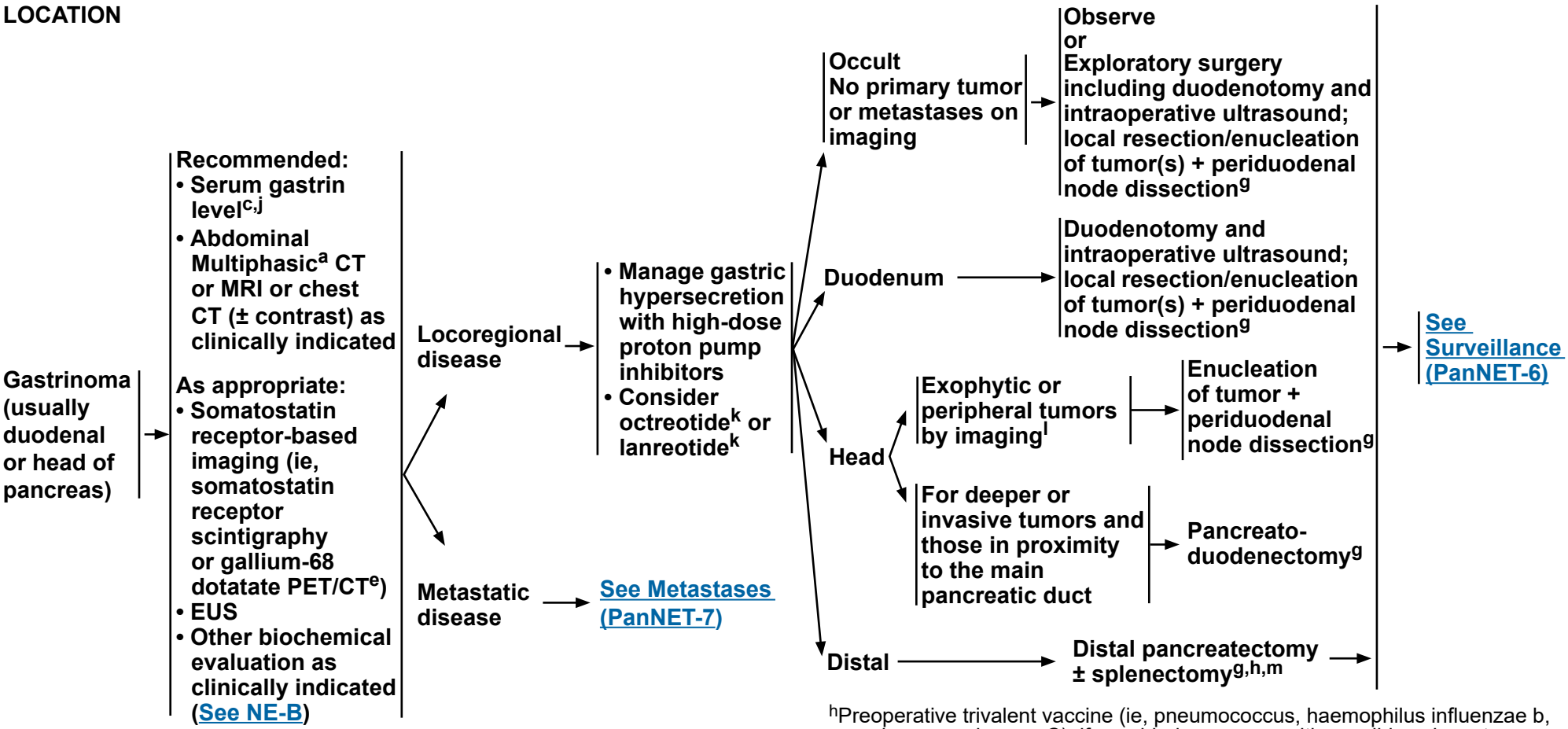
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a]Multiphasic imaging studies are performed with contrast.
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[c]See Principles of Biochemical Testing (NE-B).
[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[e]PET/CT of skull base to mid-thigh.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[j]Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. It should ideally be checked when fasting and off PPI for >1 week. However, PPI should be continued in patients with overt clinical symptoms of gastrinoma and/or risks of complications.
[k]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[l]Not adjacent to the main pancreatic duct.
[m]There is some disagreement among panel members regarding the role of splenectomy in all cases.

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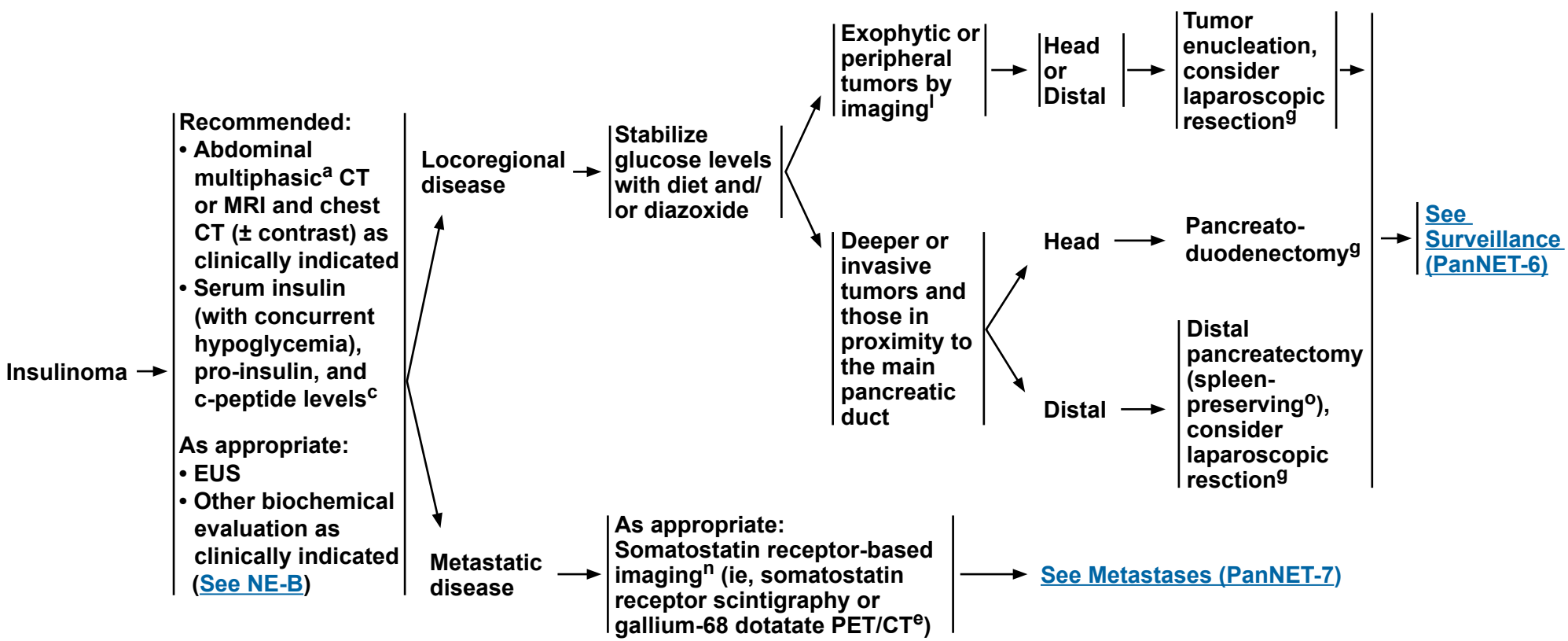

[a]Multiphasic imaging studies are performed with contrast.
[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[c]See Principles of Biochemical Testing (NE-B).
[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[e]PET/CT of skull base to mid-thigh.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[l]Not adjacent to the main pancreatic duct.
[n]Somatostatin receptor-based imaging only if treatment with octreotide or lanreotide is planned. Octreotide or lanreotide should only be given if tumor demonstrates somatostatin receptors. In the absence of somatostatin receptors, octreotide or lanreotide can profoundly worsen hypoglycemia. (See Discussion for details).
[o]Splenectomy should be performed for larger tumors involving splenic vessels.

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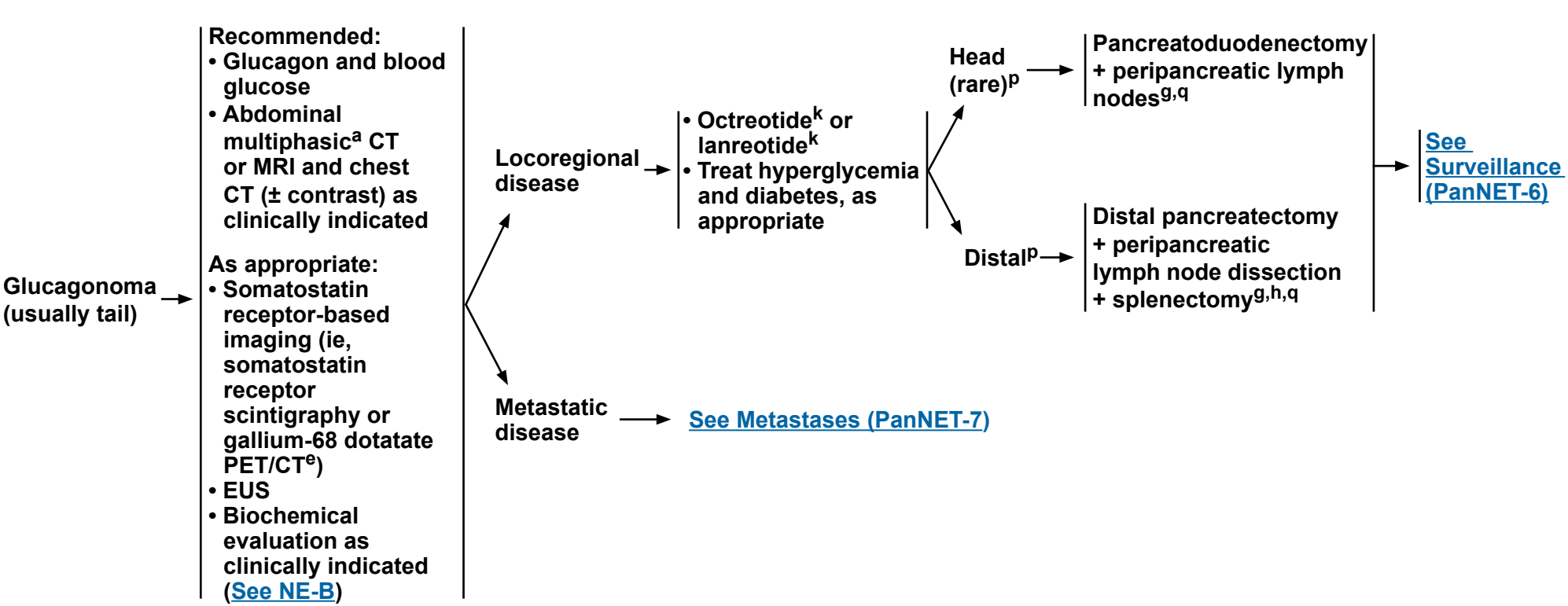
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a]Multiphasic imaging studies are performed with contrast.
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[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]PET/CT of skull base to mid-thigh.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[k]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[p]Small (<2 cm), peripheral glucagonomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.
[q]Hypercoaguable state has been described. Perioperative anticoagulation can be considered.

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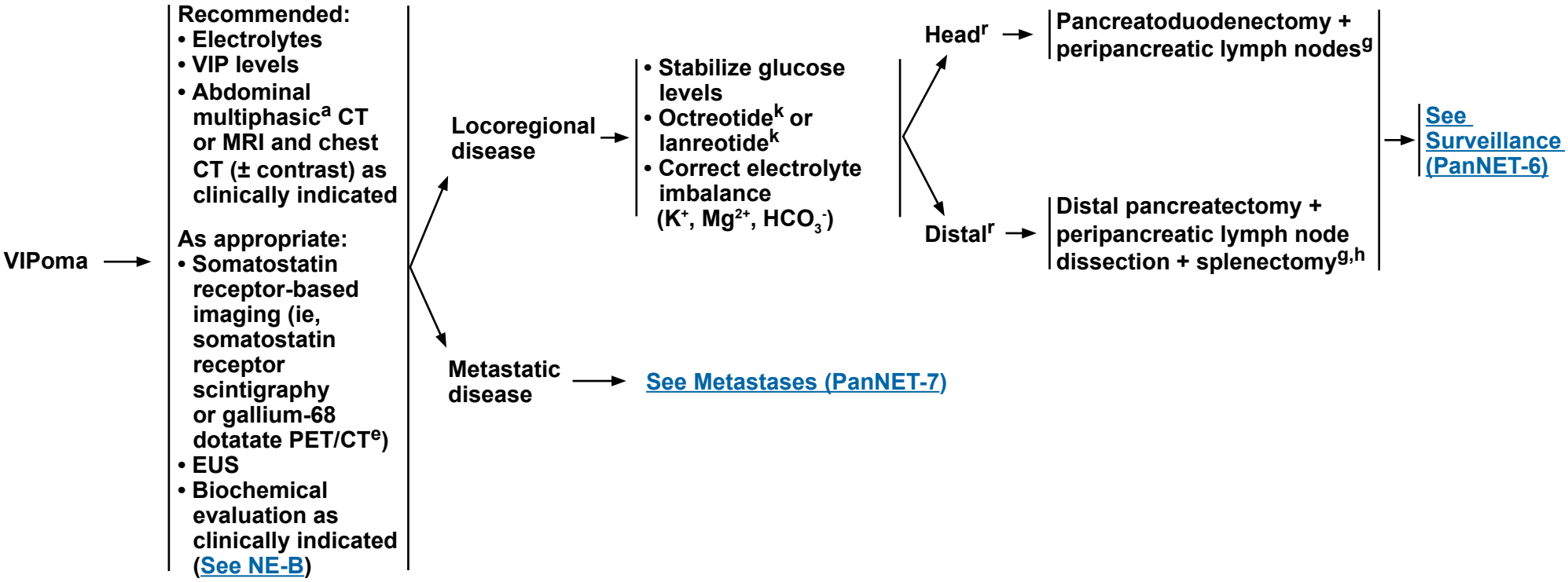

[a]Multiphasic imaging studies are performed with contrast.
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[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[e]PET/CT of skull base to mid-thigh.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[k]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[r]Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.

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SURVEILLANCE[s,t,u] | **RECURRENT DISEASE** | **MANAGEMENT OF RECURRENT DISEASE[g]**

3–12 mo postresection:
- **H&P**
- **Consider biochemical markers as clinically indicated[c]**
- **Abdominal multiphasic[a] CT or MRI and chest CT (± contrast) as clinically indicated**

>1 y postresection to a maximum of 10 y:
- **Every 6–12 mo**
  - **H&P**
  - **Consider biochemical markers as clinically indicated[c]**
  - **Consider abdominal multiphasic[a] CT or MRI and chest CT (± contrast) as clinically indicated**

→ **Disease recurrence[v]** → See Management of Locoregional Unresectable Disease and/or Distant Metastases (PanNET-7)

[a]Multiphasic imaging studies are performed with contrast.
[c]See Principles of Biochemical Testing (NE-B).
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[s]Earlier, if symptoms.
[t]Somatostatin receptor-based imaging and FDG-PET/CT scan are not recommended for routine surveillance.
[u]Surveillance recommendations also apply to cases where observation has been chosen.
[v]In select cases, resection may be considered.

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MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[g]

Locoregional unresectable disease and/or Distant metastases:
- Abdominal/pelvic multiphasic[a] CT or MRI and chest CT (± contrast) as clinically indicated
- Consider somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT[e])
- Biochemical evaluation as clinically indicated (See NE-B)[c]

TREATMENT

If complete resection possible[g,w] → **Resect metastases + primary[x]** → See Surveillance (PanNET-6)

Asymptomatic, low tumor burden, and stable disease →
- Observe with markers and abdominal/pelvic multiphasic[a] CT or MRI every 3–12 mo and chest CT (± contrast) as clinically indicated
- Consider octreotide[k,y] or lanreotide[k,y]

→ 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) → If progressive disease, consider octreotide[k,y] or lanreotide[k,y] (if not already receiving) →

If disease progression[z]:
Everolimus[k] (10 mg/d)
or
Sunitinib[k] (37.5 mg/d)
or
Cytotoxic chemotherapy[k]
or
Consider a hepatic-directed therapy for hepatic-predominant disease:
- Arterial embolization, or
- Hepatic chemoembolization, or
- Hepatic radioembolization (category 2B), or
- Cytoreductive surgery/ablative therapy[aa] (category 2B)

[a]Multiphasic imaging studies are performed with contrast.
[c]See Principles of Biochemical Testing (NE-B).
[e]PET/CT of skull base to mid-thigh.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[k]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[w]Noncurative debulking surgery might be considered in select cases.
[x]Staged or synchronous resection when possible. When performing staged pancreatoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.
[y]For patients with insulinoma, octreotide or lanreotide should be used only if somatostatin scintigraphy is positive. If used, they should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).
[z]If disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.
[aa]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.

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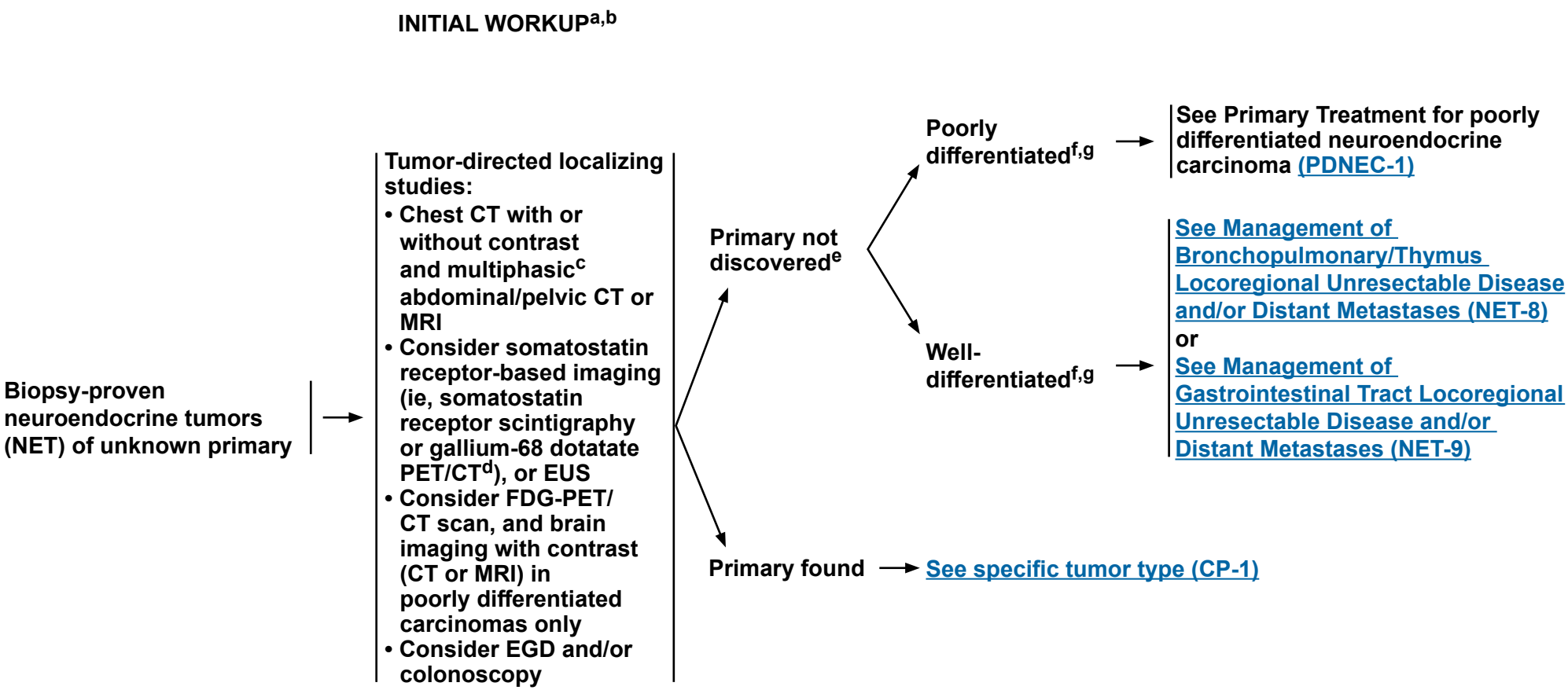

[a]Sequence of initial workup may vary.
[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[c]Multiphasic imaging studies are performed with contrast.
[d]PET/CT of skull base to mid-thigh.
[e]Consider small bowel primary tumor based on symptoms and associated radiologic findings.
[f]Indicate well- or poorly differentiated. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading and staging systems. Pancreas 2010;39:707-712.
[g]See Principles of Biochemical Testing (NE-B).

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NCCN Guidelines Version 3.2017
Adrenal Gland Tumors

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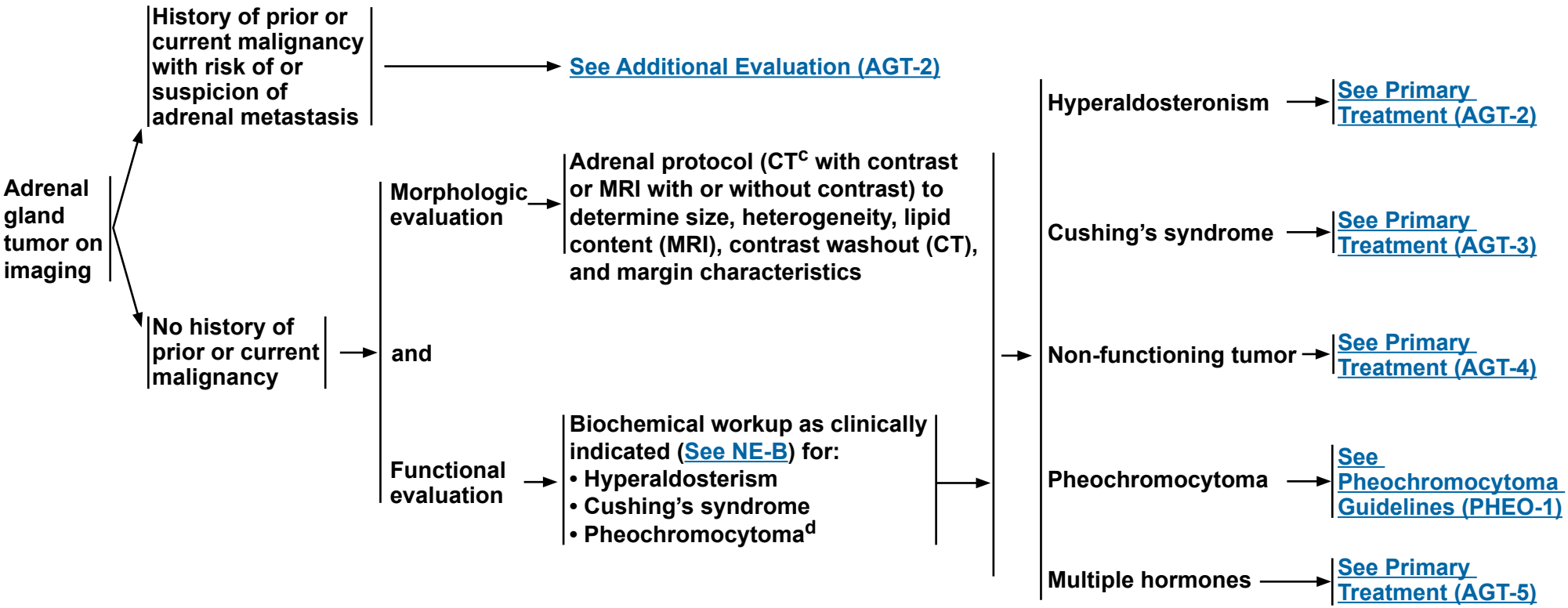
Discussion



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] If unenhanced is <+10 HU, then the tumor is probably benign. If unenhanced is >+10 HU, then use enhanced and washout. If >60% washout in 15 min, the tumor is likely to be benign; if <60%, the tumor is possibly malignant. (Caoili E, Korobkin M, Francis I, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629-633.)
[d] Screening for pheochromocytoma should be considered for asymptomatic patients if radiologic findings are suspicious and surgery is planned.

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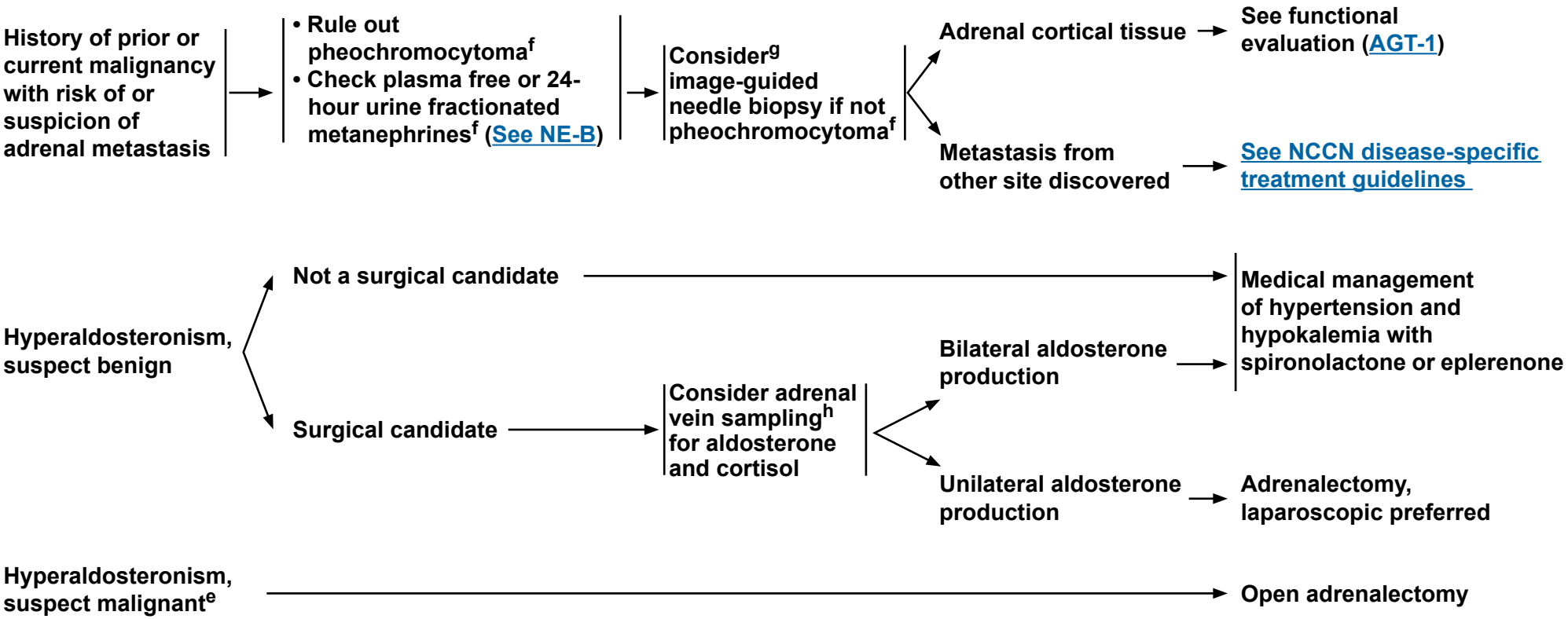

[e]Suspect malignancies with irregular/inhomogeneous morphology, lipid-poor, do not wash-out, tumor >3 cm, or secretion of more than one hormone.
[f]Can proceed with adrenal biopsy if the plasma or urine fractionated metanephrines is less than 2 times the upper limit of normal and clinical suspicion for pheochromocytoma is low.
[g]False negatives are possible; may consider proceeding directly to surgery in selected cases.
[h]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.
[i]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

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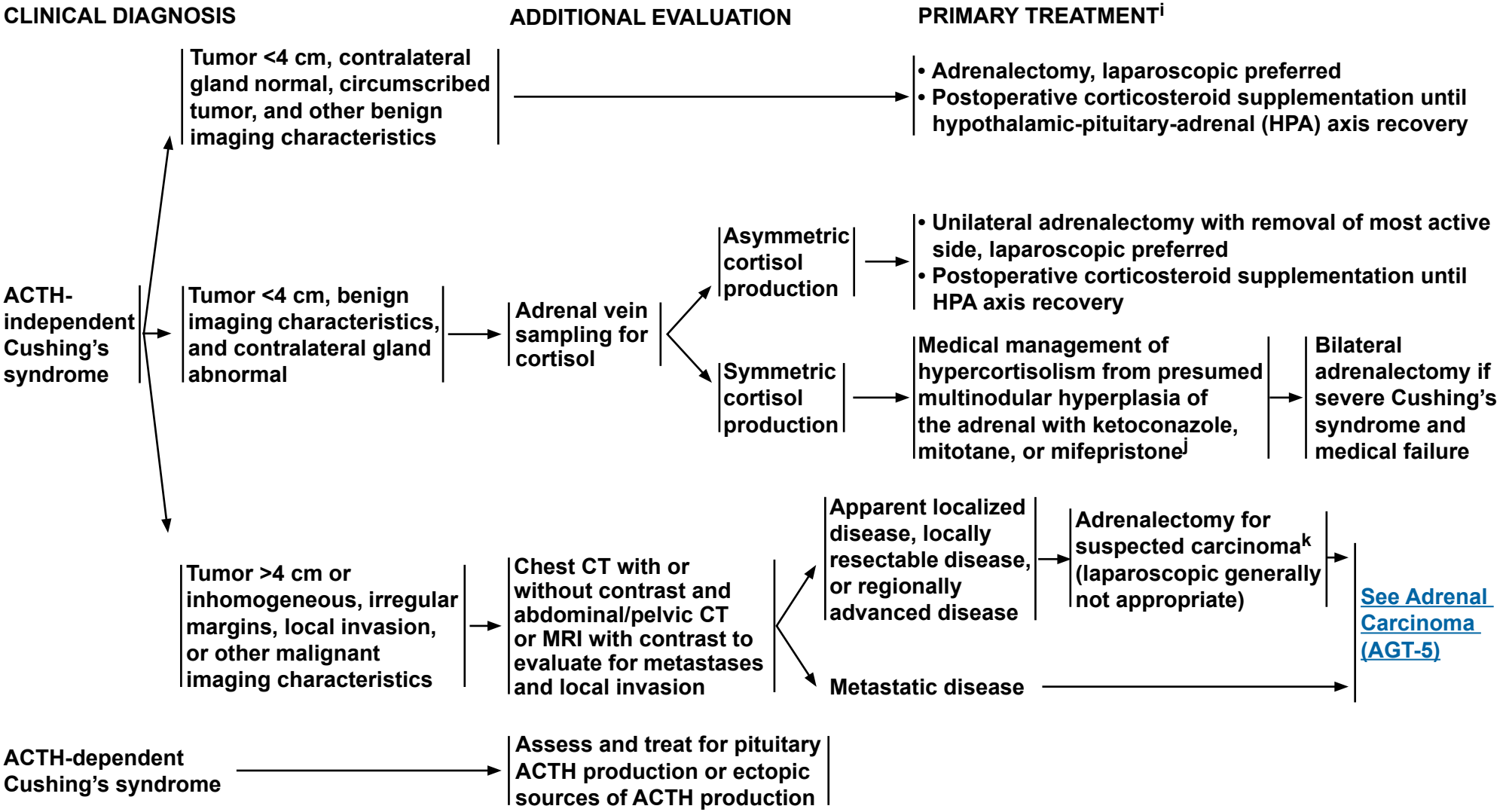

[i] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[j] Consider octreotide or lanreotide for symptom control, if somatostatin receptor scintigraphy is positive.
[k] May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.

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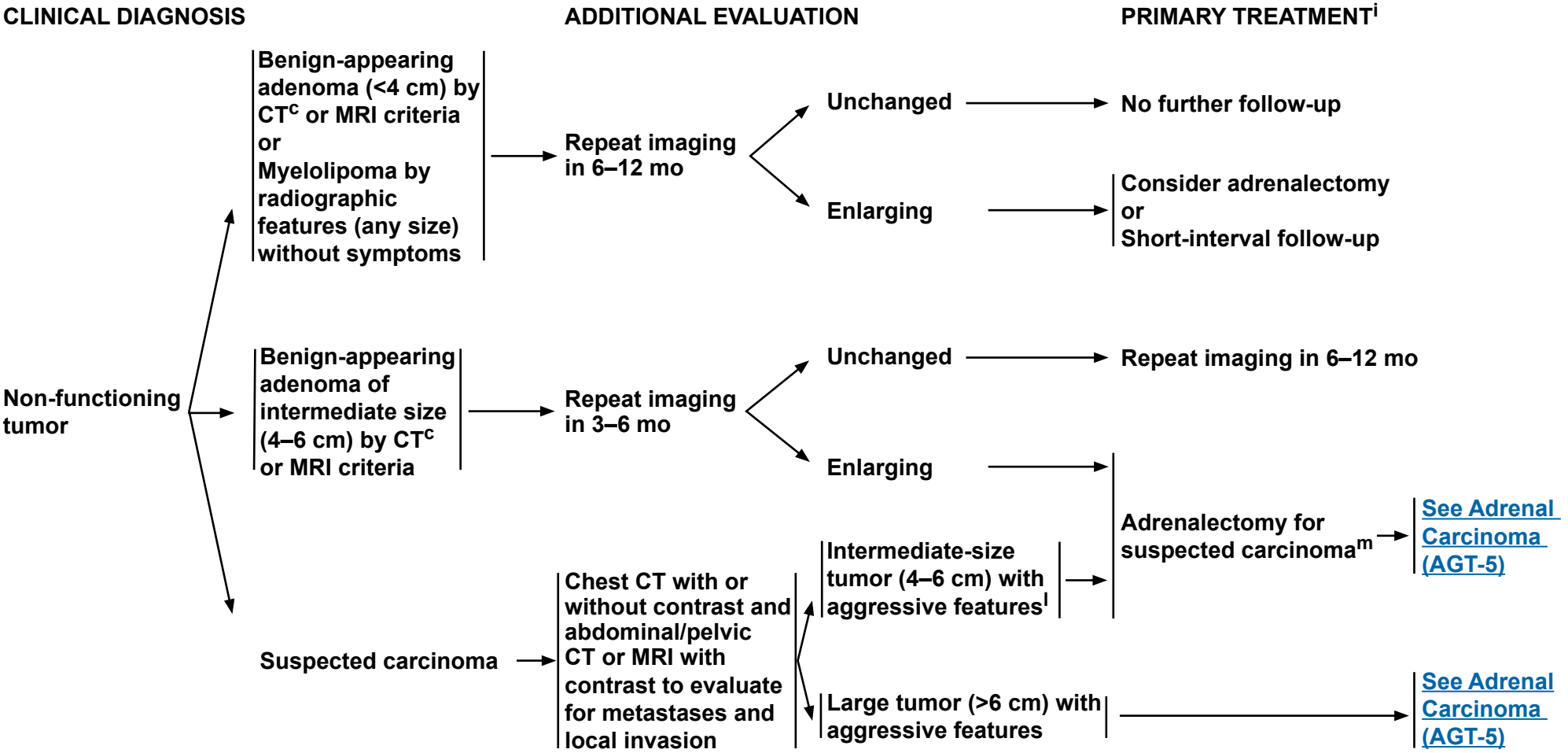

[c]If unenhanced is <+10 HU, then the tumor is probably benign. If unenhanced is >+10 HU, then use enhanced and wash-out. If >60% wash-out in 15 min, the tumor is likely to be benign; if <60%, the tumor is possibly malignant. (Caoili E, Korobkin M, Francis I, et al. Adrenal masses: characterization with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

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

[l]Aggressive features such as inhomogeneous, irregular margins, and local invasion.

[m]If size is resectable by laparoscopy, may explore laparoscopically with planned conversion for evidence of local invasion. The decision for open versus laparoscopic surgery is based on tumor size and degree of concern regarding potential malignancy.

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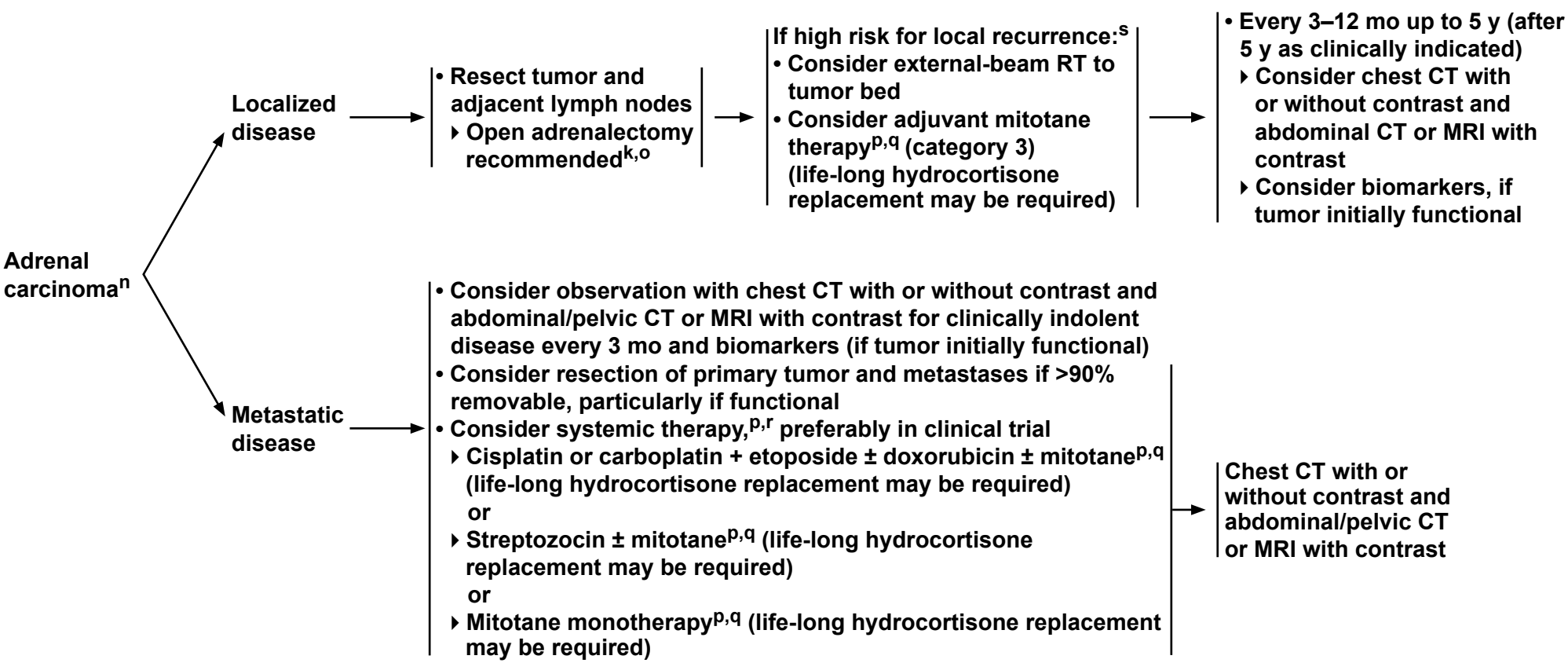

[i] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

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

[n] Chest CT with or without contrast and abdominal/pelvic CT or MRI with contrast to evaluate for metastases and local invasion to stage disease, if not previously done.

[o] Increased risk for local recurrence and peritoneal spread when done laparoscopically.

[p] Monitor mitotane blood levels. Some institutions recommend target levels of 14–20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Mitotane therapy requires steroid replacement therapy.

[q] Mitotane may have more benefit for control of hormone symptoms than control of tumor.

[r] See Discussion for further information regarding the phase III FIRM-ACT trial. (Fassnacht M, Terzolo M, Allolio B, et al; FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. N Eng J Med 2012;366:2189-2197)

[s] High-risk local recurrence features include: positive margins, rupture of capsule, large size, and high grade.

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TUMOR TYPE	EVALUATION[a,b]	PRIMARY TREATMENT
Pheochromocytoma/ paraganglioma →	**Recommended:** • Plasma free or 24-hour urine fractionated metanephrines[b,c,d] • Chest CT with or without contrast and abdominal/ pelvic multiphasic[e] CT or MRI • Genetic counseling recommended[f] **As appropriate, if metastatic disease suspected:** • MIBG scan • Somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT[g]) • FDG-PET/CT (skull base to mid-thigh) • Bone scan, if bone symptoms	→ See Primary Treatment (PHEO-2)

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation. Elevations that are 4 times above the upper limit of normal are diagnostic.
[d] For cervical paraganglioma, consider measuring serum and/or 24-hour urine fractionated catecholamines (for dopamine).
[e] Multiphasic imaging studies are performed with contrast.
[f] A high incidence of inherited disease has been reported in patients with pheochromocytoma/paraganglioma. Certain genetic variants may require more frequent follow-up. (See Discussion)
[g] PET/CT of skull base to mid-thigh.

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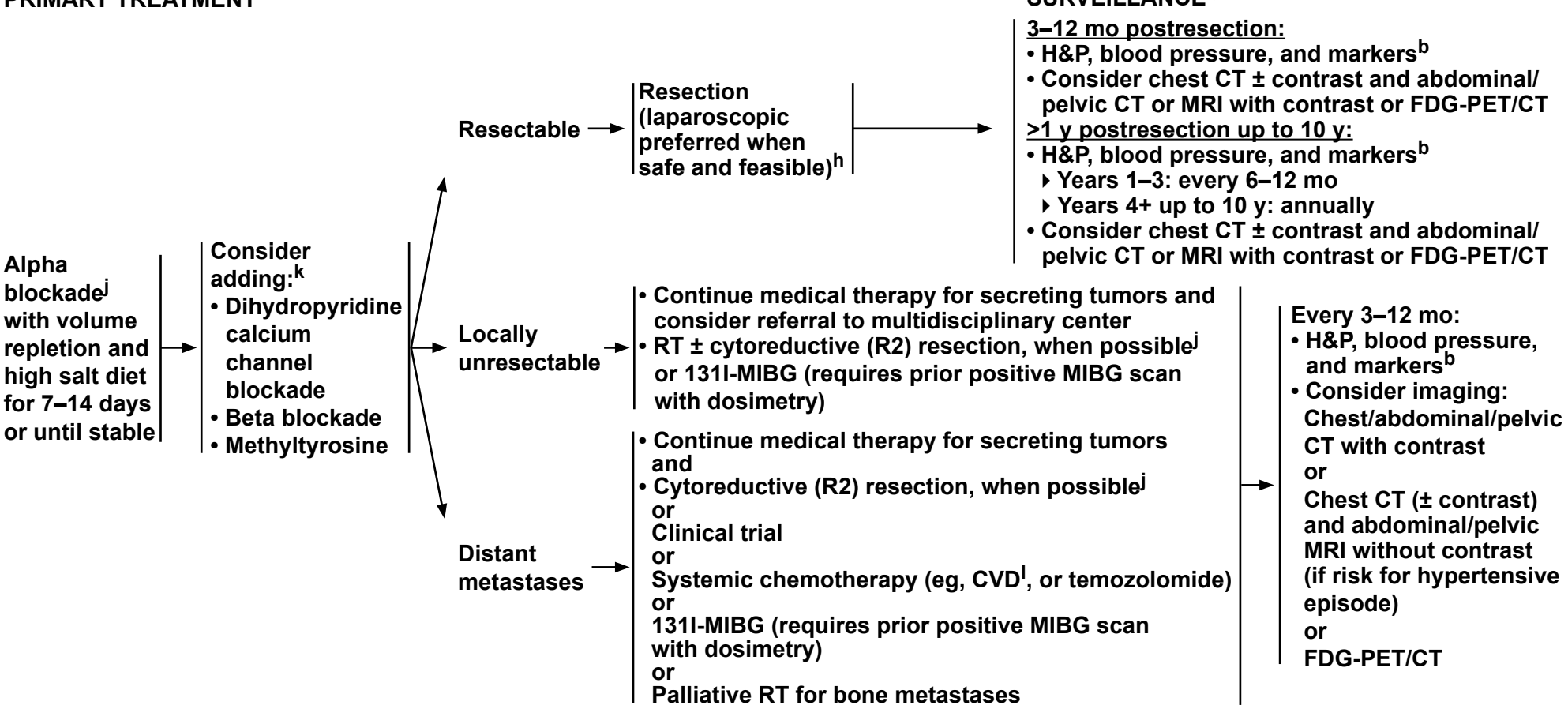

[b] See Principles of Biochemical Testing (NE-B).

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

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

[i] Earlier, if symptoms.

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

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

[l] CVD = cyclophosphamide, vincristine, and dacarbazine

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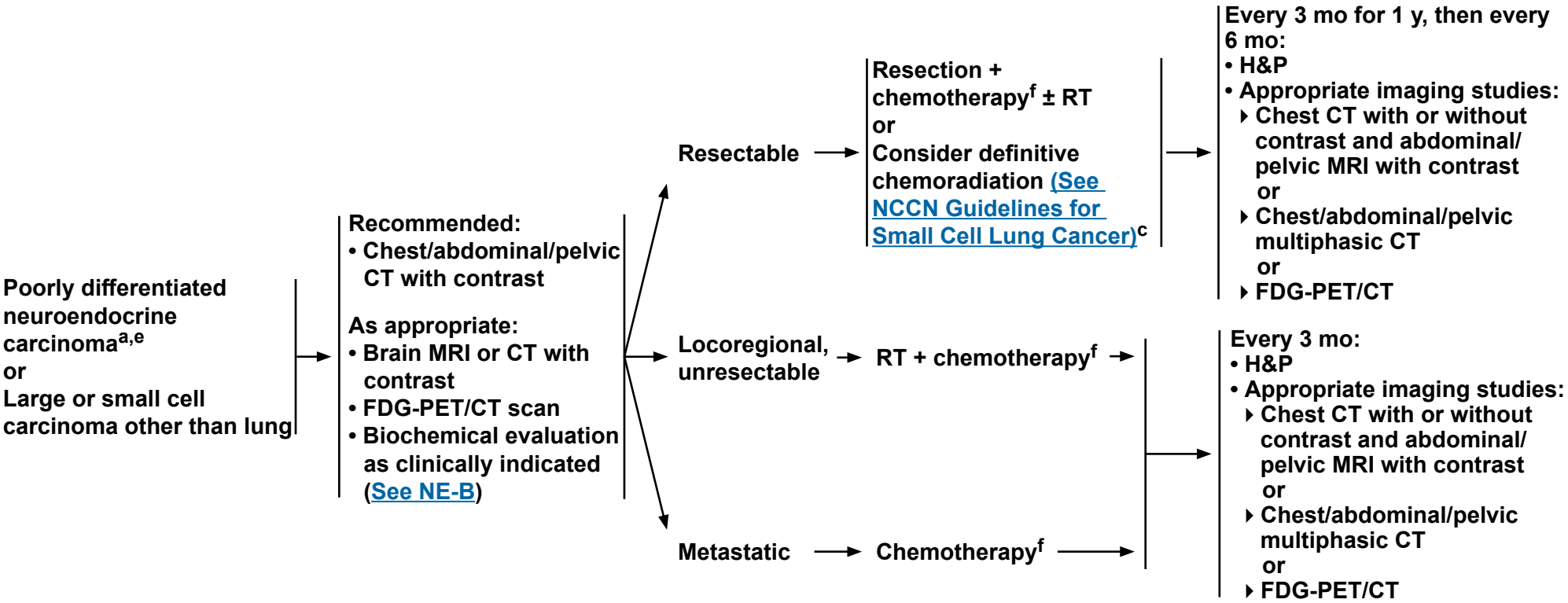

[a]Not all high-grade neuroendocrine cancers are poorly differentiated. NETs with Ki-67 index >20% may be characterized by relatively well-differentiated histology, particularly tumors with Ki-67 index between 20%–50%. Tumors that fall into the "well-differentiate/high-grade" category may respond relatively poorly to cisplatin/etoposide or carboplatin/etoposide, and respond more favorably to treatments described for well-differentiated NETs; see NET-8 or NET-9.

[b]Somatostatin scintigraphy is not part of the routine evaluation of poorly differentiated neuroendocrine tumors, but may be considered for morphologically well-differentiated tumors with higher proliferation index, as appropriate. For options for well-differentiated tumors, see NET-8 or NET-9.

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

[d]Earlier, if symptoms.

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

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

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DIAGNOSIS OF OR CLINICAL SUSPICION OF MEN1

- **A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors: multi-gland parathyroid hyperplasia; pancreatic NET; or pituitary tumors.[a,b]**
  - **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 neuroendocrine carcinoid tumors (10%[b]).**
  - **MEN1 may also be associated with neuroendocrine tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas.[a,b]**
  - **Patients with MEN1 are more likely to have multiple PanNETs than those with sporadic tumors.**
  - **Type 2 gastric neuroendocrine tumors occur frequently in MEN1 patients with gastrinoma.**
  - **A higher incidence of adrenal tumors is also observed in MEN1.**
- **For patients known or suspected to have MEN1, a clinical evaluation includes: See MEN1 Clinical Evaluation and Treatment (MEN1-2)**
  1) **Biochemical tests evaluating hormone levels;**
  2) **Imaging tests needed to localize the site of the tumor or hyperplasia; and**
  3) **Genetic counseling and testing**
- **Genetic counseling and MEN1 genetic testing should be offered to the following:**
  - **An individual with a clinical diagnosis or suspicion of MEN1[a,b,c,d]**
  - **An at-risk relative of an individual with a known germline MEN1 mutation[a]**
- **MEN1 clinical evaluation should be offered to the following:**
  - **Individuals with a clinical diagnosis or suspicion of MEN1 even with a negative MEN1 genetic test**
  - **At-risk relatives even if MEN1 mutation has not been identified in the affected family member or if MEN1 genetic testing has not been performed in the affected or at-risk family member**
- **A consultation with an endocrinologist for all patients with MEN1 should be considered.**

[a]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.
[b]Giusti F, Marini F, Brandi ML. Multiple Endocrine Neoplasia Type 1. 2005 Aug 31 [Updated 2015 Feb 12]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.
[c]A germline MEN1 mutation is seldom found in individuals with a single MEN1-associated tumor and no family history. (Ellard S, Hattersley AT, Brewer CM, Vaidya B. Detection of an MEN1 gene mutation depends on clinical features and supports current referral criteria for diagnostic molecular genetic testing. Clin Endocrinol (Oxf). 2005;62:169-175.)
[d]10% of cases have *de novo MEN1* mutations.

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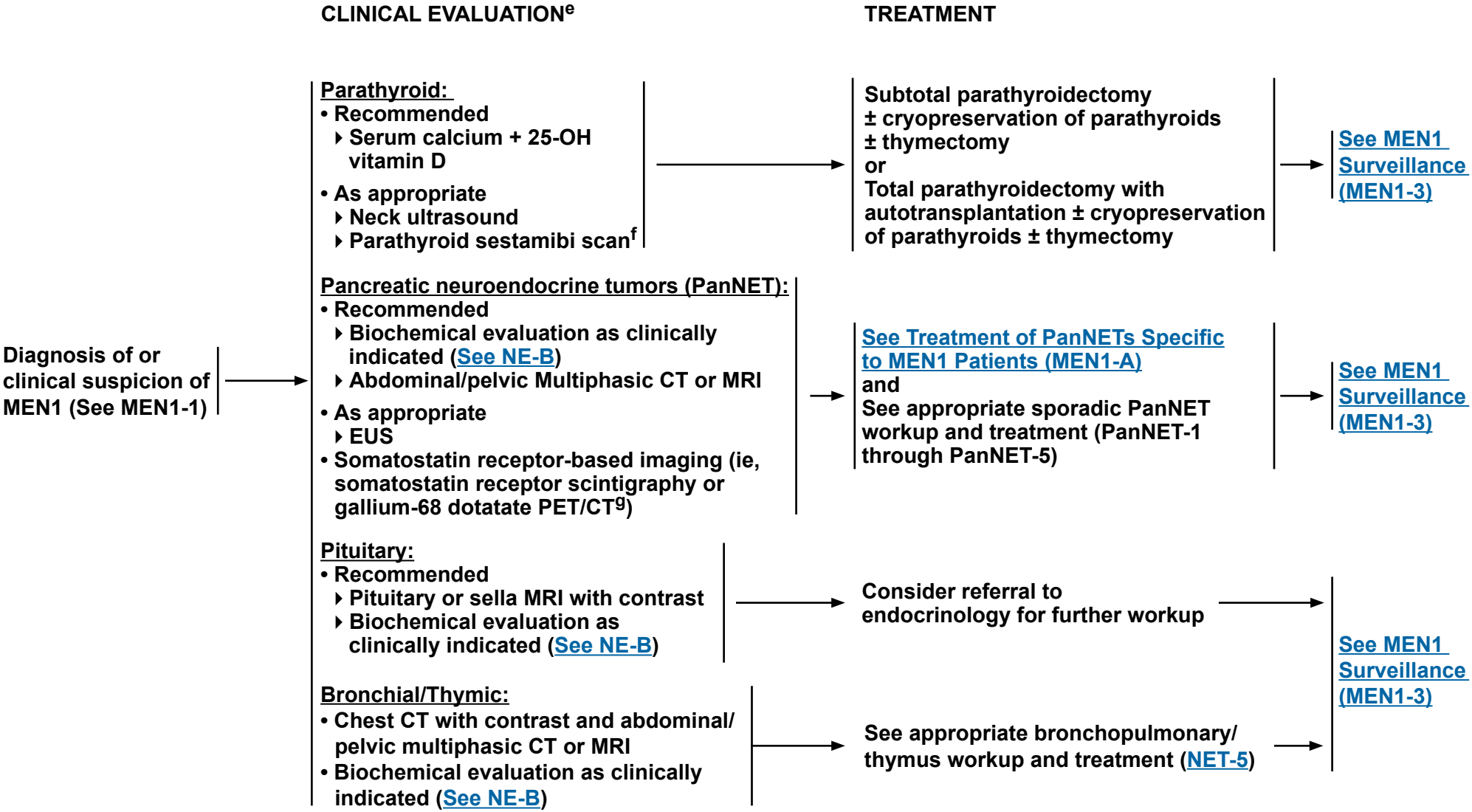

[e]For *MEN1* genetic testing recommendations, see MEN1-1.
[f]A sestamibi scan may not accurately depict the total number of abnormal glands. Patients should recieve 4-gland exploration regardless of sestamibi scan results.
[g]PET/CT of skull base to mid-thigh.

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MEN1 SURVEILLANCE[h]
Patients with MEN1 should be screened for all of the following tumor types:

Parathyroid:
- Calcium annually

→
- If calcium rises:
  - Serum PTH and 25-OH vitamin D
  - Reimage with neck ultrasound and/or parathyroid sestamibi scan
  - Consider neck CT or MRI with contrast

PanNET:
- Follow previously elevated serum hormones or as symptoms indicate
- Consider abdominal/pelvic CT or MRI with contrast every 1–3 y
- Consider serial EUS

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

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

Bronchial/Thymic
- Consider chest CT with contrast every 1–3 y

→ See appropriate workup and treatment for bronchial (NET-6) or thymic (NET-5)

[h]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.

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TREATMENT OF PanNETs SPECIFIC TO MEN1 PATIENTS[1]

- **In general, surgical management of patients with MEN1 is similar to those with sporadic tumors. Refer to the relevant site-specific recommendations earlier in these guidelines. (See PanNET-1 through PanNET-5)**
- **However, one notable exception is the multi-focality of pancreaticoduodenal NETs in patients with MEN1. The role of surgery remains controversial in patients with multifocal tumors.**
- **Decision to resect a pancreatic or duodenal NET in the setting of multifocal disease is complex. If surgery is performed to resect hormonally functional tumor(s), attempts should be made to preoperatively localize the site of the functional tumor. Surgical resection can be considered in the following scenarios:**
  - **Symptomatic functional tumors refractory to medical management**
  - **Tumor larger than 1–2 cm in size**
  - **Tumor with relatively rapid rate of growth over 6–12 months**
- **Endoscopy with EUS is recommended prior to pancreatic surgery in order to preoperatively assess and localize tumors.**
- **MEN1-associated metastatic pancreatic NETs are often slower growing than metastatic sporadic tumors. Observation can be considered for non-functioning indolent tumors.**

[1]Yates CJ, Newey PJ, Thakker RV. Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1. Lancet Diabetes Endocrinol 2015;3:895-905.

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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.**
  - **A clinical diagnosis of MEN2A includes two or more MEN2A-associated tumors in a single individual or in first-degree relatives.[a,b] The most common MEN2A neoplasm is MTC (affecting 98% of patients), followed by adrenal pheochromocytoma (50%), and/or parathyroid hyperplasia (25%).[c]**
    - **Other physical exam findings for patients with MEN2A include lichen planus amyloidosis and Hirschsprung's disease (megacolon; found in 2%–5% of MEN2A neoplasms and familial medullary thryroid cancers only).**
  - **A clinical diagnosis of MEN2B includes the presence of MTC, pheochromocytoma, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, ectopic lenses, distinctive faces with enlarged lips, "marfanoid" body habitus, or inability to cry tears.[a,b] 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%).[c]**
- **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,d]**
  - **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.**

[a]Marquard J, Eng C. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2015 Jun 25]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

[b]Kloos RT, Eng C, Evans D, et al. Medullary thyroid cancer: Management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.

[c]Moore FD, Scoinski MA, Joste NE. Endocrine Tumors and Malignancies. In: Skarin A, ed. Atlas of Diagnostic Oncology (ed 3rd). Philadelphia: Elsevier Science Limited; 2003.

[d]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.

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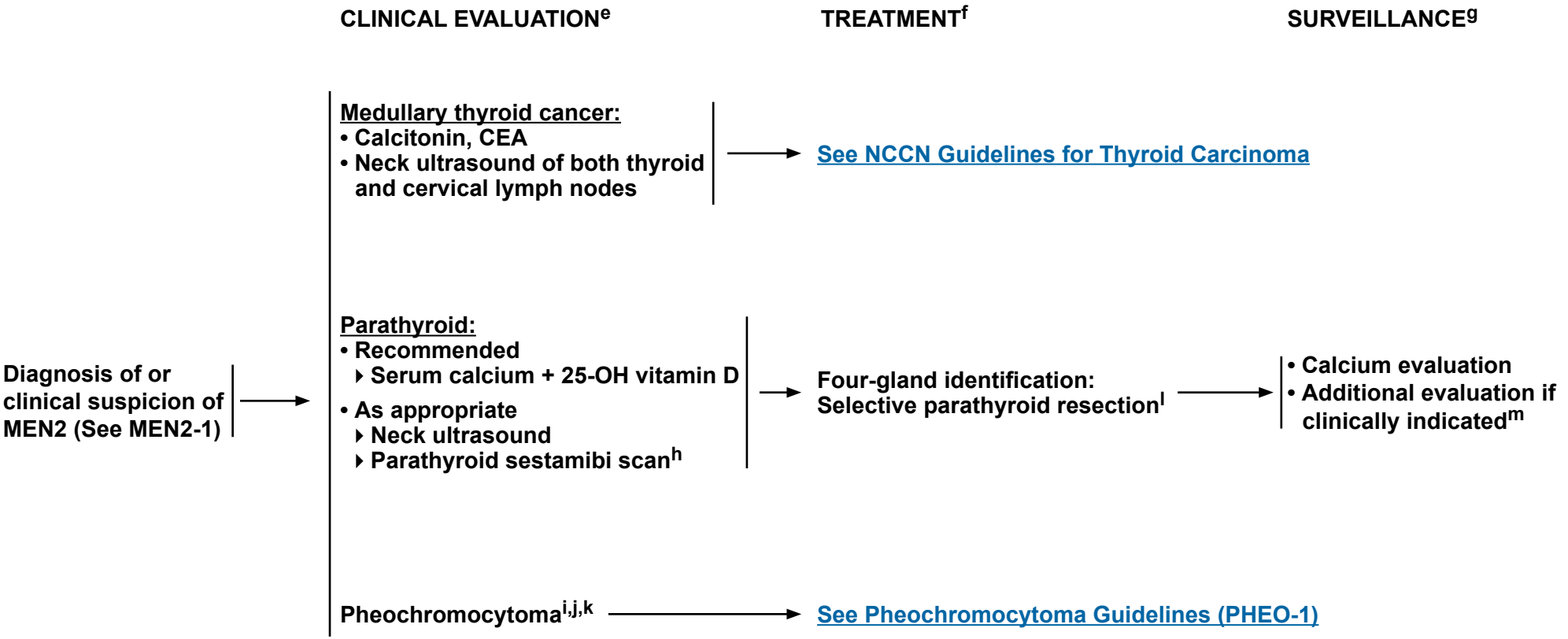

[e]For RET genetic testing recommendations, see MEN2-1.
[f]For the treatment of synchronous tumors, surgical resection of pheochromocytoma should take priority over thyroidectomy for medullary thyroid cancer.
[g]Earlier, if symptoms.
[h]A sestamibi scan may not accurately depict the total number of abnormal glands. Patients should recieve 4-gland exploration regardless of sestamibi scan results.
[i]Evaluation of pheochromocytoma should be done before the administration of any anesthetic or invasive procedure.
[j]More likely to be multifocal.
[k]For synchronous bilateral pheochromocytomas, a bilateral adrenalectomy is recommended
[l]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.
[m]See Principles of Biochemical Testing (NE-B).

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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

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

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, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. IARC, Lyon; 2015.

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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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Functional status

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

Immunohistochemistry and other ancillary techniques

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

Classification and grade

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

Continued on next page

See References on NE-A 4 of 4

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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Mitotic rate

- Mitotic rate should be based on 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 mm^2. Ten HPF is equivalent to 2 mm^2 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 WHO[3] 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]

See References on NE-A 4 of 4

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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

REFERENCES

[1]Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading and staging systems. Pancreas 2010;39:707-712.
[2]Koo J, Mertens RB, Mirocha JM, et al. Value of Islet 1 and PAX8 in identifying metastatic neuroendocrine tumors of pancreatic origin. Modern Pathology 2012; 25:893-901.
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[4]Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449:395-401.
[5]Strosberg JR, Coppola D, Klimstra DS et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas 2010;39,799-800.
[6]Boudreaux JP, Klimstra DS, Hassan MM et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas 2010;39,753-766.
[7]Anthony LB, Strosberg JR, Klimstra DS et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (NETs): well-differentiated NETs of the distal colon and rectum. Pancreas 2010;39,767-774.
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[11]Rindi G, Bordi C, La Rosa S, et al. Gastroenteropancreatic (neuro)endocrine neoplasms: The histology report. Digestive and Liver Disease 2011;43S;S356-S360.
[12]Rekhtman N. Neuroendocrine tumors of the lung. An Update. Arch Pathol Lab Med 2010;134:1628-1638.

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PRINCIPLES OF BIOCHEMICAL TESTING (1 OF 3)[1-10]

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

	Location	Clinical Symptoms	Testing
Neuroendocrine Tumors of Gastrointestinal Tract, Lung, and Thymus (carcinoid tumors)	Primary tumors in GI tract (ileum, appendix, rectum)	• Primary tumors in the GI tract usually are not associated with symptoms of hormone secretion unless extensive metastasis. • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction. • Bronchial/thymic tumors may be associated with classic carcinoid syndrome as well as Cushing's syndrome.	• Chromogranin A (category 3) • 24-hour urine 5-HIAA ▸ Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts. • Test for Cushing's syndrome (NE-B, 2 of 3)
Pancreatic NET (see subtypes below)	Pancreas	Depends on hormone secreted, can be clinically silent	• Serum pancreatic polypeptide (category 3) • Chromogranin A (category 3)
Insulinoma	Pancreas	Hypoglycemia	• Serum insulin • Pro-insulin • C-peptide • See Workup for insulinoma (PanNET-3)
VIPoma	Most common in pancreas, can be extra pancreatic	Diarrhea, hypokalemia	Serum VIP
Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoaguable state	Serum glucagon
Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin*

Continued on next page

*Basal, stimulated as indicated.

See References on NE-B (3 of 3)

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PRINCIPLES OF BIOCHEMICAL TESTING (2 OF 3)[1-10]

	Location	Symptoms	Testing
Pheochromocytoma/ Paraganglioma	Adrenal or extra-adrenal sympathetic or parasympathetic chain	Hypertension, tachycardia, sweating, syncope	• Plasma free or 24-hour urine fractionated metanephrines** • Cervical paragangliomas: consider serum or urine dopamine or methoxytyramine (the metabolite of dopamine)**
Pituitary Tumor	Pituitary (part of MEN1)	May be asymptomatic, depends on the hormone secreted	• Serum IGF-1 (category 2B) • Serum prolactin • LH/FSH • Alpha subunits • TSH (free T4) • Screen for Cushing's syndrome
Cushing's Syndrome	Adrenal, pituitary, or ectopic (often bronchial or thymic)	Central weight gain, striae, hypertension, hyperglycemia, depression, hirsutism	• Screen for hypercortisolemia with 1 of the following tests: ▸ 1 mg overnight dexamethasone suppression test ▸ 2–3 midnight salivary cortisols ▸ 24-hour urinary free cortisol • Confirmatory testing if positive • If hypercortisolemic, then serum ACTH (8 am cortisol) should be done
Hyperaldosteronism	Adrenal	Hypertension, hypokalemia	• Serum aldosterone/plasma renin activity ratio • Confirmatory testing if positive

See References on NE-B (3 of 3)

**Some drugs may interfere with testing results, including: acetaminophen, labetalol, sotalol, α-methyldopa, tricyclic antidepressants, buspirone, phenoxybenzamine, MAO-inhibitors, sympathomimetics, cocaine, sulphasalazine, and levodopa. (Lenders J, Duh QY, Eisenhofer G, et al. Guidelines on pheochromocytoma and paraganglioma. J Clin Endocrinol Metab, June 2014, 99(6): 1915-1942)

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PRINCIPLES OF BIOCHEMICAL TESTING (3 OF 3)

References

[1]Kaltsas G, Androulakis, II, de Herder WW, Grossman AB. Paraneoplastic syndromes secondary to neuroendocrine tumours. Endocr Relat Cancer 2010;17:R173-193.

[2]Oberg K. Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. Clinics (Sao Paulo) 2012;67 Suppl 1:109-112.

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[8]Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008;93:3266-3281.

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[10]Modlin IM, Oberg K, Taylor A, et al. Neuroendocrine tumor biomarkers: current status and perspectives. Neuroendocrinology 2014;100:265-277.

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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.

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 neuroendocrine tumors should include adequate regional lymph node resection (including all palpable disease where feasible) and thorough exploration of synchronous primary tumors (15%–30% incidence).**
- **Resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumor that has regressed should be considered for selected patients with adequate performance status.**
- **Patients with symptomatic recurrence from local effects or hormone hypersecretion can be effectively palliated by subtotal resection of a large proportion of the tumor (typically more than 90%); however, experienced judgment is required for management of patients with an unresectable tumor and/or distant metastases. Planned cytoreductive, incomplete (R2) resection of advanced disease in patients with asymptomatic or non-functional disease is controversial.**
- **Cholecystectomy is recommended when performing surgery for advanced NETs in patients anticipated to receive long-term octreotide therapy, as these patients are at higher risk of developing biliary symptoms and cholecystitis.**
- **Liver-directed therapies (eg, liver resection, thermal ablation, chemoembolization) for hepatic metastases from NETs following pancreatoduodenectomy are associated with increased risk for perihepatic sepsis and liver abscess.**
- **Octreotide therapy should be administered parenterally prior to induction of anesthesia in patients with functional neuroendocrine tumors to prevent carcinoid crisis and be discontinued the next day if there are no issues.**
- **All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C).**
- **In general, laparoscopic resection is preferable for patients suspected to have small (<6 cm), clinically benign, functional adrenal tumors. An open exploration is recommended for tumors that have a high risk of being malignant.**
- **For MEN1-related surgical principles, see MEN1-A.**

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

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

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

- **Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.**
- **Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.**
- **There is no known role for systemic treatment in the adjuvant setting for neuroendocrine tumors.**
- **Doses and schedules are subject to appropriate modifications depending on the circumstances.**
- **For management of hormone-related symptoms for GI tumors, see NET-9.**

Options for Unresectable and/or Metastatic NET of the Gastrointestinal Tract	• Octreotide[a,b] LAR 20–30 mg intramuscular injection, monthly[1] • Lanreotide[a] 120 mg deep subcutaneous injection, monthly[2] • Consider (listed in alphabetical order): ▸ Cytotoxic chemotherapy (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.) ▸ Everolimus[3] ▸ Interferon alfa-2b[4] (category 3)
Options for Unresectable and/or Metastatic NET of the Lung/ Thymus	• See NET-8. Depending on tumor burden and grade, options may include: ▸ Octreotide[b] LAR 20–30 mg intramuscular injection, monthly[1] ▸ Lanreotide 120 mg deep subcutaneous injection, monthly[2] ▸ Everolimus ± octreotide or lanreotide ▸ Temozolomide ± octreotide or lanreotide ▸ Cisplatin + etoposide[c] ± octreotide or lanreotide ▸ Carboplatin + etoposide[c] ± octreotide or lanreotide
Options for Carcinoid Syndrome	• Octreotide[b,1] or lanreotide[2] ± therapy for poorly controlled carcinoid syndrome, including: ▸ Telotristat 250 mg orally, three times daily (for persistent diarrhea)[5], and/or ▸ Additional therapy for disease control (for any persistent symptoms [ie. flushing, diarrhea])

[a]Somatostatin analog dosing also applicable for locoregional disease.
[b]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.
[c]Cisplatin/etoposide or carboplatin/etoposide can be considered for intermediate grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

Continued

See References on NE-D (3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Unresectable and/or Metastatic Pancreatic Neuroendocrine Tumors

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

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

- **Somatostatin analogues (somatostatin analog dosing also applicable for locoregional disease)**
  - **Octreotide[b,d] LAR 20–30 mg intramuscular injection, monthly[1]**
  - **Lanreotide 120 mg deep subcutaneous injection, monthly[2]**
- **Everolimus[6] 10 mg by mouth, daily**
- **Sunitinib[7] 37.5 mg by mouth, daily**
- **Cytotoxic chemotherapies:**
  - **There is no panel consensus on which cytotoxic chemotherapy regimen is best. The following anticancer agents can be considered in patients with bulky, symptomatic, and/or progressive disease: 5-FU, capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide. (See Discussion for details.)**
  - **Commonly used regimens include:**
    - **Temozolomide/capecitabine[8]**
    - **5-FU/doxorubicin/streptozocin (FAS)[9]**
    - **Streptozocin/doxorubicin[10]**
    - **Streptozocin/5-FU[11]**

See References on NE-D (3 of 3)

[b]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]The PROMID trial showed an antitumor effect of octreotide in advanced neuroendocrine tumors of the midgut.[1] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 gastroenteropancreatic NETs.[2]

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

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
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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.

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.

Continued on next page

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)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 2 cm or less
T1a	Tumor size less than 1 cm in greatest dimension
T1b	Tumor size 1–2 cm in greatest dimension
T2	Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor invades peritoneum or 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

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

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)

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

Regional Lymph Nodes (N)

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

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

* This also includes the “PanInIII” classification.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

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

Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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

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

Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4. However, if no tumor is present in the adhesion, microscopically, the classification should be classified pT1-3 depending on the anatomical depth of wall invasion.
*Penetration of the mesoappendix does not seem to be as important a prognostic factor as the size of the primary tumor and is not separately categorized.

Continued on next page

Staging

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

Adrenal

TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

NX	Nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
Stage IV	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
	Any T	Any N	M1

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

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

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

Continued

Staging

American Joint Committee on Cancer (AJCC)
TNM Staging System for Lung (including neuroendocrine tumors) (7th ed., 2010)

Lung

TNM

T ***Primary Tumor***

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*

- **T1a** Tumor 2 cm or less in greatest dimension
- **T1b** Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor with any of the following features of size or extent:

- More than 3 cm but 7 cm or less
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

- **T2a** Tumor more than 3 cm but 5 cm or less in greatest dimension
- **T2b** Tumor more than 5 cm but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

N ***Regional Lymph Nodes***

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M ***Distant Metastasis***

M0 No distant metastasis

M1 Distant metastasis

- **M1a** Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion**
- **M1b** Distant metastasis

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleura (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

Continued

Staging

American Joint Committee on Cancer (AJCC)
TNM Staging System for Lung (including neuroendocrine tumors) (7th ed., 2010)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1-2	N2	M0
	T3	N1-2	M0
	T4	N0-1	M0
Stage IIIB	T1-2	N3	M0
	T3	N3	M0
	T4	N2-3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

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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

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

An analysis of the SEER database estimated that the incidence of neuroendocrine tumors in the United States was 5.25 cases per 100,000 people in the year 2004.[1] This analysis suggested that the incidence of neuroendocrine tumors is increasing, and that the prevalence of individuals with neuroendocrine tumors in the United States may exceed 100,000.[1] Other independent analyses of the SEER database also found that the incidence of gastrointestinal (GI) neuroendocrine tumors increased from 1975 to 2008.[2,3] The reasons for this increase are unclear, although it seems likely that improved diagnosis and classification is one factor.[4]

Most neuroendocrine tumors seem to be sporadic, and risk factors for sporadic neuroendocrine tumors are poorly understood. Neuroendocrine tumors may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia (MEN) types 1 and 2. Multiple endocrine neoplasia type 1 (MEN1), associated with mutations in the *menin* gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands.[5] 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.[6]

Neuroendocrine tumors have also been associated with von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.[7,8]

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,[9] hypertension in patients with pheochromocytoma,[10] and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic neuroendocrine tumors.[11] Patients with hormonal symptoms are considered to have “functional” tumors, and those without symptoms are considered to have “nonfunctional” tumors.

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

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

Literature Search Criteria and Guidelines Update Methodology

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

was performed to obtain key literature in the field published between May 1, 2015 and May 1, 2016, using the following search terms: (neuroendocrine tumor) OR (adrenal cancer) OR (carcinoid) OR (pheochromocytoma) OR (paraganglioma) OR (Multiple Endocrine Neoplasia). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[12]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 138 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

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.[11,13,14] Numerous studies have confirmed that increased mitotic rate and high Ki-67 index are associated with a more aggressive clinical course and worse prognosis.[15-18] 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.[19,20] While technically classified as a high-grade tumor, clinical judgment should be used in making treatment decisions for such cases. A key recommendation is that tumor differentiation, mitotic rate, and Ki-67 index should all be included in the pathology report. Doing so allows the

treating physician to factor these data into the clinical picture to make appropriate treatment decisions.

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

Poorly differentiated neuroendocrine carcinomas are of either small cell or large cell cytology, with greater than 10 mitoses/10 HPF.[21,22]

Considerable debate remains as to the most appropriate Ki-67 proliferative threshold for the determination of tumor grade and consequent treatment decisions.[23,24] A retrospective database review of 252 patients with high-grade GI neuroendocrine carcinoma suggested that platinum-based chemotherapy is most active in those with a Ki-67 index of greater than or equal to 55%.[25] 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.[26] 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.[27] The panel recommends that the current histologic grading system be used more as a general guide, in conjunction with clinical judgment, when treatment decisions are made.

Staging

Neuroendocrine tumors are staged according to the AJCC tumor (T), node (N), metastasis (M) staging system. The AJCC introduced its first TNM staging system for the classification of neuroendocrine tumors in its 7th edition of the AJCC Cancer Staging Manual.[28] Carcinoids of the stomach, duodenum/ampulla/jejunum/ileum, colon/rectum, and appendix have separate staging systems. The association of tumor stage with prognosis has been confirmed in analyses of the SEER database and the National Cancer Data Base.[29-34] A recent analysis of 691 patients with jejunal-ileocecal neuroendocrine tumors treated at the Moffitt Cancer Center between 2000 and 2010 revealed 5-year survival rates of 100%, 100%, 91%, and 72% for stages I through IV, respectively, further validating the TNM staging system.[27] 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.[24] 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.[35] These results have been supported in additional analyses, confirming that the presence of lymph node and distant metastases have the strongest effect on survival.[36,37]

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.[28]

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.[28] The primary tumor (T) is differentiated based on size and involvement of major

vessels or other organs (see *Staging* in the guidelines). A retrospective analysis of 425 patients with pancreatic neuroendocrine tumors treated at the Moffitt Cancer Center between 1999 and 2010 validated this system, with 5-year overall survival rates of 92%, 84%, 81%, and 57% for stages I through IV, respectively ($P < .001$).[38] 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.[39,40] 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%.[40]

Pathologic Reporting

In addition to information on histologic classification and stage, the margin status (positive or negative) and the presence of vascular or perineural invasion should be included in the pathology report; some studies have suggested that these factors may also have prognostic significance.[41,42]

Whether or not tumors are associated with symptoms of hormone hypersecretion (”functioning” or “non-functioning”) is, in general, a part of the clinical rather than histologic diagnosis. Thus, functional status is usually not included in the pathology report. However, if a specific clinical situation suggests that correlation with histologic evidence of peptide hormone may be helpful, then histochemical or immunohistochemical studies may be performed and included in the report.

Other Potential Prognostic Markers

Chromogranin A is a secreted protein that may be elevated in patients with neuroendocrine tumors; elevated levels have been associated with poorer prognosis. The molecular basis of neuroendocrine tumors remains poorly understood, and additional molecular predictors of outcome remain investigational. A recent study found that overexpression of mammalian target of rapamycin (mTOR) or its downstream targets was associated with shorter overall survival in 195 neuroendocrine tissue samples (15% were located in the pancreas; 85% were GI carcinoids).[43] Small bowel carcinoid tumors have been found to have recurrent mutations in the cyclin-dependent kinase inhibitor, CDKN1B (p27),[44] and loss of CDKN1B expression has been reported to be an adverse prognostic factor in gastroenteropancreatic neuroendocrine tumors.[45] Circulating tumor cells (CTCs) have also been studied as possible prognostic markers, based on the idea that tumor cells in the blood would be indicative of more disseminated disease. A recent study found that the presence of greater than or equal to 1 CTC in 7.5 mL of blood was independently associated with worse progression-free survival (PFS) and overall survival in patients with varyingly pre-treated metastatic neuroendocrine tumors from various primary sites.[46]

More research is required, however, before these and other new molecular assays are routinely used in the clinic. A multinational consensus meeting of experts concluded that, to date, no single currently available biomarker is sufficient as a diagnostic, prognostic, or predictive marker in patients with neuroendocrine tumors.[47]

Sporadic Neuroendocrine Tumors

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

Approximately one-third of carcinoid tumors arise in the lungs or thymus, and two-thirds arise in the GI tract. Sites of origin within the GI tract include the stomach, small intestine, appendix, and rectum.[1] The prognosis for patients with carcinoid tumors varies according to the

stage at diagnosis, histologic classification, and primary site of the tumor (see *Histologic Classification and Staging of Neuroendocrine Tumors*, above).

Neuroendocrine tumors of the GI tract, lung, or thymus may secrete various hormones and vasoactive peptides. Bronchial and thymic neuroendocrine tumors have been associated with adrenocorticotropic hormone (ACTH) production and are a cause of Cushing's syndrome.[48,49] Neuroendocrine tumors arising in the small intestine or appendix are more commonly associated with carcinoid syndrome, related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation causing episodic flushing and diarrhea.[50] Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.[51]

The metabolic products released by intestinal neuroendocrine tumors are rapidly destroyed by liver enzymes in the portal circulation. Thus, the classical syndrome, occurring in approximately 8% to 28% of patients with neuroendocrine tumors,[52,53] is not usually observed unless liver metastases or rarely retroperitoneal disease have occurred, in which case hepatic metastases release metabolic products directly into the systemic circulation via the hepatic veins.

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

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

Patients who present with suspected carcinoid tumors should be evaluated with imaging studies to assess disease burden and possible primary location. Commonly used techniques include CT and MRI.

Neuroendocrine tumors of the GI tract, lung, and thymus are highly vascular and can appear isodense with liver on conventional CT scan, depending on contrast phase. Multiphase CT or MRI scans with contrast should therefore be used for evaluation of liver metastasis. Chest CT scans with or without contrast are also recommended as appropriate to assess for lung metastases.

Because most neuroendocrine tumors express high-affinity receptors for somatostatin,[50,54] somatostatin receptor-based imaging may be considered in the initial evaluation of patients with neuroendocrine tumors. Such imaging can provide useful information on overall tumor burden and location; additionally, positive imaging confirms the presence of somatostatin receptors, which can have therapeutic implications. Scintigraphy using ^{111}Indium-diethylenetriaminepentaacetic acid (^{111}In-DPTA)-octreotide is considered to be one standard imaging technique.[55,56] Several studies have also shown diagnostic utility, as well as high sensitivity, of PET/CT imaging using the radiolabeled somatostatin analog gallium-68 (^{68}Ga) dotatate.[57-59] Unless otherwise indicated, somatostatin receptor-based imaging in this discussion includes imaging with either somatostatin receptor scintigraphy or ^{68}Ga-dotatate PET/CT. Additional recommendations vary by disease site and include colonoscopy and small bowel imaging with CT enterography or capsule endoscopy as appropriate for jejunal, ileal, and colonic neuroendocrine tumors; endoscopic ultrasound (EUS) and/or esophagogastroduodenoscopy (EGD) as appropriate for duodenal and gastric neuroendocrine tumors; proctoscopic examination for rectal neuroendocrine tumors; and bronchoscopy as appropriate for bronchopulmonary and thymic neuroendocrine tumors.

Biochemical evaluation can also be helpful in the initial diagnostic evaluation, particularly in patients who have clinical symptoms that are suggestive of hormone hypersecretion. Evaluation of serotonin

secretion, using a 24-hour urine collection for 5-HIAA, is generally recommended in patients with metastatic lung or GI carcinoid tumors, particularly if carcinoid syndrome, manifested by symptoms of flushing and diarrhea, is suspected. Screening for hormones in asymptomatic individuals is not routinely recommended. Chromogranin A is sometimes used as a biochemical marker in non-functioning tumors (category 3). Whereas one meta-analysis calculated the sensitivity and specificity of chromogranin A to be 73% and 95%, respectively, for diagnosis of neuroendocrine tumors,[60] others have questioned its value. Chromogranin A is elevated in patients with renal or hepatic impairment and in patients receiving proton pump inhibitors (PPIs), and in general should not be relied upon in isolation as a diagnostic test. A workup for Cushing's syndrome (discussed in *Evaluation and Treatment of Cushing's Syndrome*, below) may also be indicated in cases of bronchopulmonary or thymic neuroendocrine tumors if signs and symptoms of hypercortisolemia are suspected. Details of the evaluation and diagnosis of a patient with Cushing's syndrome from a bronchial neuroendocrine tumor have recently been published.[61]

Management of Locoregional Disease

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

Gastric Neuroendocrine Tumors

Three types of gastric neuroendocrine tumors are recognized: type 1 (associated with chronic atrophic gastritis or high gastric pH); type 2 (associated with antrum-sparing type A Zollinger-Ellison syndrome); and type 3 (sporadic, unifocal, unassociated with either atrophic gastritis or Zollinger-Ellison syndrome).[62] Types 1 and 2 gastric neuroendocrine tumors are both associated with hypergastrinemia; the major difference between them is that patients with type 1 gastric neuroendocrine tumors generally have antrum-sparing atrophic gastritis with a loss of the usual negative feedback loop on the gastrin-producing cells of the antrum by acid, resulting in hypergastrinemia and excess stimulation of the endocrine cells of the fundus, and patients with type 2 gastric neuroendocrine tumors have evidence of acid hypersecretion secondary to gastrinoma (Zollinger-Ellison syndrome).[62] Type 1 gastric neuroendocrine tumors pursue an indolent course, with a rate of metastases of <5%. Evidence suggestive of type 1 disease includes a histologic diagnosis of atrophic gastritis on gastric biopsy, elevated gastric pH, vitamin B12 deficiency, and positive anti-intrinsic factor antibodies (not all tests need to be done to make a diagnosis). For rare type 1 tumors that are >2 cm, the workup should include multiphasic CT or MRI of the abdomen performed with contrast. Type 2 tumors are rare and occur in the setting of gastrinoma in which elevated gastrin levels produce gastric neuroendocrine hyperplasia and multifocal gastric neuroendocrine tumors.

Annual endoscopic surveillance and endoscopic resection of prominent tumors is recommended for patients with locoregional type 1 gastric neuroendocrine tumors. Antrectomy can be considered if gastric tumors are increasing significantly in size or number. For locoregional type 2 gastric neuroendocrine tumors, the primary gastrinoma should, in general, be resected. If the primary tumor is not resected, endoscopic

surveillance and endoscopic resection of prominent gastric carcinoid tumors should be considered and/or octreotide or lanreotide can be given. Gastric acid hypersecretion should be managed with high-dose PPIs. Patients with nonmetastatic gastric neuroendocrine tumors and normal gastrin levels (type 3) often have more aggressive tumors and are usually treated with radical resection of the tumor and regional lymphadenectomy. For early-stage, smaller tumors, endoscopic or wedge resection can be considered if there is no evidence of lymphadenopathy on EUS.[63] Endoscopic resection should be reserved for small (<1 cm), superficial, low-grade tumors.

Thymic Neuroendocrine Tumors

Localized and locoregional neuroendocrine tumors in the thymus are generally treated with surgical resection without adjuvant therapy if they have been completely resected with negative margins. There is limited data on the utility of radiation with or without chemotherapy in patients with unresectable disease or in the setting of incomplete resection or positive margins. Radiation therapy (RT) is considered by some panel members to be an option for low-grade (typical) tumors (category 3). If tumors are intermediate grade (atypical), treatment with RT with or without cisplatin or carboplatin and etoposide is more generally recommended given evidence that radiation and chemotherapy appear to have greater efficacy in tumors with higher mitotic and proliferative indices.

Bronchopulmonary Neuroendocrine Tumors

Surgery, including lobectomy or other anatomic resection and mediastinal node dissection or sampling, is recommended for patients with stage I, II, and IIIA bronchopulmonary tumors. If surgery is feasible and the disease is in stage I, II, or low grade IIIA, patients may be monitored under surveillance procedures as described (see *Surveillance of Resected Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus*, below). If the stage IIIA disease is intermediate grade, adjuvant therapy using cisplatin or carboplatin with etoposide in the presence or absence of radiotherapy may be considered.

There are limited data on the efficacy of chemoradiation for unresectable IIIA or IIIB lung neuroendocrine tumors. If surgical resection is not medically feasible or if there are positive margins following resection for patients with low-grade, stage IIIA disease, or if patients have low-grade, stage IIIB disease, then RT (category 3) with or without chemotherapy using cisplatin or carboplatin and etoposide (category 3) is considered by some panel members. If the stage IIIA and IIIB disease in this setting are intermediate grade, RT in the presence or absence of concurrent cisplatin or carboplatin and etoposide is generally recommended. Chemoradiation is thought to have the most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices.[64,65]

Neuroendocrine Tumors of the Duodenum, Small Intestine, and Colon

For localized lesions arising in the duodenum, endoscopic resection is recommended if feasible. Transduodenal local excision with or without lymph node sampling and pancreatoduodenectomy are other options for primary treatment of nonmetastatic duodenal neuroendocrine tumors. If endoscopic resection was performed, follow-up upper endoscopy (EGD) should be performed as appropriate.

For patients presenting with tumors in the jejunum, ileum, or colon, surgical resection(s) of the bowel with regional lymphadenectomy is recommended. The surgical procedure should include careful examination of the entire bowel, because multiple synchronous lesions may be present. In addition, the proximity to or involvement of the

superior mesenteric artery and superior mesenteric vein should be assessed during surgery.

Appendiceal Neuroendocrine Tumors

Most appendiceal neuroendocrine tumors are identified incidentally, during appendectomy performed for appendicitis. Most appendiceal neuroendocrine tumors have well-differentiated histology, and for most appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient because metastases are uncommon.[66,67]

However, some controversy exists regarding the management of appendiceal neuroendocrine tumors measuring less than 2 cm with more aggressive histologic features. A population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal neuroendocrine tumors 2 cm or smaller.[68] Some NCCN Member Institutions thus consider more aggressive treatment for 1- to 2-cm tumors with poor prognostic features, such as lymphovascular or mesoappendiceal invasion or atypical histologic features. In a retrospective case series that included 79 patients with appendiceal carcinoid tumors, small-vessel invasion was a risk factor for metastases in patients with tumors <2 cm.[69]

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 with contrast. Chest CT scans with contrast and biochemical evaluations may be performed as appropriate or as clinically indicated. If no distant disease is identified, they should undergo reexploration with a right hemicolectomy. Additionally, a small proportion of appendiceal neuroendocrine tumors may also contain evidence of adenocarcinoma (ie, "adenocarcinoid" or "goblet cell carcinoid"). These tumors should be managed according to the NCCN Guidelines® for Colon Cancer (available at www.NCCN.org).

Neuroendocrine Tumors of the Rectum

The treatment of rectal lesions is based on the size of the primary tumor. For small (<1 cm) and incidental lesions, complete endoscopic resection may be sufficient. All other rectal lesions should be staged using MRI or EUS. If the lesion is ≤2 cm and minimally invasive (T1), endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumors, examination under anesthesia and/or EUS before the procedure should be considered for tumors 1 to 2 cm in size. A recent retrospective review found that metastases were present in 66% of 87 patients with well-differentiated rectal neuroendocrine tumors of 11 to 19 mm.[70]

Tumors larger than 2 cm, those with invasion of the muscularis propria (T2-T4), or those associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection.[71]

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

Surveillance of bronchopulmonary and GI neuroendocrine tumors should include complete patient history and physical examination (H&P) and consideration of a multiphasic CT or an MRI scan with contrast (usually abdominal and/or pelvic). For patients with primary lung and thymic tumors, chest CT scans with or without contrast are recommended. Surveillance imaging of the chest may also be considered if clinically indicated in patients with primary GI tumors. Most patients with neuroendocrine tumors of the jejunum/ileum/colon, duodenum, rectum, and thymus, and type 3 gastric neuroendocrine tumors with normal gastrin levels should be reevaluated 3 to 12 months

after resection (earlier if the patient is symptomatic) and then every 6 to 12 months for up to 10 years.

Relevant biochemical evaluations can also be performed based on pre-resection findings. Chromogranin A may be used as a tumor marker (category 3); although not diagnostic, elevated levels have been associated with recurrence.[72,73] 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; $P < .001$).[74] 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 PPIs. Several panelists therefore caution that rising chromogranin A levels in an asymptomatic patient with a tumor that looks stable on imaging does not necessarily indicate that a patient should be initiated on a new therapy.

5-Hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, in a 24-hour urine sample may also be considered as a biochemical marker in some cases, particularly in patients with metastatic small-intestinal neuroendocrine tumors. During monitoring of patients after treatment of a carcinoid tumor, decreasing levels of 5-HIAA indicate a response to treatment, whereas increasing or excessive concentration indicates that the treatment has not been successful. However, a patient with symptoms may still have a neuroendocrine tumor even if the concentration of 5-HIAA is normal. Diet and a variety of drugs can affect the 5-HIAA test. Therefore, patients should be advised not to eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts for 48 hours before the start of and during urine collection. Medications that can increase 5-HIAA include acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (an ingredient found in some cough medicines), and phenobarbital.

Somatostatin receptor-based imaging or FDG-PET/CT scans (for high-grade tumors) are not routinely recommended for surveillance after definitive resection, but may be indicated to assess disease location and disease burden for comparison in cases of subsequent possible recurrence.

In specific cases, follow-up recommendations for patients with resected GI neuroendocrine tumors differ from the above general recommendations. For rectal tumors smaller than 1 cm, prognosis is excellent and no follow-up is usually required. Follow-up endoscopies with rectal MRI or EUS are recommended for rectal tumors that are between 1 and 2 cm, 6 and 12 months after primary therapy, and then as clinically indicated.

For appendiceal tumors 2 cm or smaller without aggressive features, follow-up examinations are done as clinically indicated. Patients with small, well-differentiated appendiceal neuroendocrine tumors are at very low risk for recurrence,[75-77] and some institutions recommend no follow-up in these patients. Other institutions recommend a follow-up examination 1 year after simple appendectomy and then with decreasing frequency. However, because recurrences have rarely been reported even after resection of small appendiceal tumors, any patients with symptoms of hormone hypersecretion should be more fully evaluated.

Follow-up recommendations also differ to some extent for hypergastrinemic patients with type 1 or 2 gastric neuroendocrine tumors. For these patients, follow-up endoscopies are recommended every 6 to 12 months for the first 3 years and annually thereafter if no

evidence of progression is seen. If clinically indicated, imaging studies should also be performed. Because gastrin levels remain persistently high in patients with atrophic gastritis, gastrin levels are generally uninformative in patients with type 1 gastric neuroendocrine tumors. Antrectomy to remove the source of gastrin production can be considered in patients with type 1 gastric neuroendocrine tumors if new lesions or increasing tumor burden is observed.

Evaluation of Locoregional Unresectable and/or Distant Metastatic Gastrointestinal Tract, Bronchopulmonary and Thymic Neuroendocrine Tumors

Baseline imaging recommendations for patients suspected to have distant metastatic disease include multiphase technique CT or MRI.[78,79] The most common sites of metastases from intestinal neuroendocrine tumors include regional/mesenteric lymph nodes, liver, and bones. When evaluating locoregional unresectable and/or metastatic neuroendocrine tumors of the GI tract, lung, and thymus, abdominal/pelvic multiphasic CT or MRI scans with contrast are recommended. Chest CT scans with contrast are recommended for initial evaluation of locoregional, unresectable, and/or metastatic disease in patients with lung or thymic primary tumors and if carcinoid syndrome is suspected. Chest CT scans may be performed with or without contrast when evaluating for metastases from primary tumors in other sites.

Somatostatin receptor-based imaging is recommended to assess the somatostatin receptor status of locoregional unresectable and/or metastatic neuroendocrine tumors of the GI tract, lung, or thymus, if treatment with octreotide or lanreotide is being considered. Poorly differentiated bronchopulmonary or thymic tumors may have less avidity for ^{68}Ga-dotatate PET/CT;[80] therefore, 18F-fluorodeoxyglucose (FDG)-PET/CT may be considered for neuroendocrine tumors that are poorly differentiated or have atypical histology. If carcinoid syndrome is suspected, somatostatin receptor-based imaging may be considered to assess the somatostatin receptor status of neuroendocrine tumors, and a cardiology consultation and echocardiogram may also be considered to assess whether the patient has carcinoid heart disease.[81]

Baseline levels of chromogranin A (category 3) or 24-hour urine 5-HIAA may also be considered, and then repeated over time to monitor subsequent disease progression. As mentioned previously, if carcinoid syndrome is suspected, evaluation of serotonin secretion, using a 24-hour urine collection for 5-HIAA, is recommended. Bronchial and thymic tumors may also be associated with hypersecretion of ACTH that causes the development of Cushing's syndrome;[82] therefore, if clinically indicated, patients should be screened for hypercortisolemia. If Cushing's syndrome is suspected, see discussion below (see *Evaluation and Treatment of Cushing's Syndrome*, below).

Management of Locoregional Unresectable and/or Distant Metastatic Gastrointestinal Tract Neuroendocrine Tumors

Somatostatin Analogs for Control of Symptoms and Tumor Growth

Patients who have metastatic neuroendocrine tumors and carcinoid syndrome should be treated with octreotide or lanreotide.[83] 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.[84-86]

Lanreotide has a similar mechanism of action as octreotide, but is administered as a deep subcutaneous injection. Several studies have shown it to be effective at controlling symptoms of hormone secretion in patients with carcinoid tumors, gastrinomas, or tumors secreting vasoactive intestinal peptide (VIPomas).[87-91] The multinational phase III ELECT trial randomized 115 patients with carcinoid syndrome who were either naïve to or responsive to octreotide to receive 120 mg of lanreotide or placebo and evaluated the number of days patients required use of rescue octreotide.[92] Patients in the lanreotide arm required less frequent rescue octreotide than those in the placebo arm (33.7% vs. 48.5%; *P* = .017), supporting the use of lanreotide for symptom control.

If carcinoid syndrome is poorly controlled, telotristat, in combination with octreotide or lanreotide, should be considered for persistent diarrhea. Telotristat or telotristat ethyl is a novel, small-molecule tryptophan hydroxylase (TPH) inhibitor, which decreases urinary 5-HIAA levels and the frequency of bowel movements (BMs) in patients with carcinoid syndrome.[93,94] It was approved by the FDA in February 2017 and the recommendation to use telotristat for persistent diarrhea in this context, is based on the results of the TELESTAR study, a multicenter, randomized, double-blind, placebo-controlled phase III trial of 135 patients with metastatic neuroendocrine tumors and a documented history of carcinoid syndrome, who were experiencing an average of ≥4 BMs a day while receiving stable-dose somatostatin analog therapy for at least 3 months prior to enrollment in the study.[95] Patients were randomized to receive placebo, telotristat ethyl (250 mg) or telotristat ethyl (500 mg), in a 1:1:1 ratio three times per day orally for 12 weeks during a double-blind treatment period. From baseline to week 12, mean BM frequency reductions per day for placebo, telotristat ethyl (250 mg), and telotristat ethyl (500 mg) were -0.9, -1.7, and -2.1, respectively. In addition, both telotristat dosages significantly decreased mean urinary 5-HIAA compared to placebo at week 12 (*P* < .001).[95] Compared to placebo, treatment with telotristat at either dosage, did not result in a statistically significant change in the number of observed flushing episodes,[95] therefore, additional options may be considered to manage other symptoms associated with carcinoid syndrome.

During treatment for carcinoid syndrome, a cardiology consultation and echocardiogram to assess whether the patient has carcinoid heart disease should also be performed every 2 to 3 years.[83] Cardiac heart disease is frequent in patients with carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation.[96,97] A study of 250 patients with carcinoid syndrome showed that patients with 5-HIAA levels of 300 µmol or greater (57 mg) over 24 hours and with 3 or more flushing episodes per day were more likely to have carcinoid heart disease.[98] To monitor disease control and/or progression, surveillance imaging of the abdomen and pelvis using multiphasic CT or MRI every 3–12 months and chest CT scans with or without contrast should be considered.

In patients with GI tract primary tumors who have clinically significant tumor burden or progressive disease, initiation of either octreotide or lanreotide is recommended to potentially control tumor growth if they are not already receiving it. The recommendation to consider octreotide in these patients is based on the results of the PROMID study, a placebo-controlled phase III trial of 85 patients with metastatic midgut neuroendocrine tumors, which showed median times to tumor progression of 14.3 and 6 months in the octreotide LAR and placebo groups, respectively (*P* = .000072).[99] After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and in 37.2% of patients in the placebo group. Results of long-term survival of patients in the PROMID study were recently reported.[100] After

long-term follow-up, median OS was not significantly different between the arms (83.7 months in the placebo arm and 84.7 months in the octreotide arm; HR, 0.83; 95% CI, 0.44–1.46; *P* = .51).[101] However, post-study treatment included octreotide in 38 of 43 patients in the placebo arm, possibly confounding interpretation of long-term survival results.

The recommendation that lanreotide be considered for control of tumor growth in patients with clinically significant tumor burden or progressive disease is based on results of the CLARINET study. The CLARINET study randomized 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors to receive either lanreotide or placebo and followed patients for PFS. Results from this trial showed that treatment with lanreotide for 2 years resulted in an improvement in PFS over placebo (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; *P* < .001).[102]

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

Resection of Metastatic Disease

In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection of the primary tumor and metastases with curative intent. One study of 172 patients who underwent hepatic resection of metastatic neuroendocrine tumors showed that long-term survival can be achieved in selected cases: the reported 10-year overall survival rate was 50.4%.[103] A recent meta-analysis reported 5-year overall survival rates ranging from 41% to 100% in patients undergoing hepatic resection.[104] Most patients with resected metastatic disease, however, will eventually experience recurrence.[105,106] 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.[104] However, it is not uncommon for patients with small bowel primary tumors to experience symptoms of intermittent abdominal pain from episodic bowel obstruction or bowel ischemia related to the primary tumor and surrounding fibrosis. Palliative small bowel resection is recommended in these patients.

If resection is performed and future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy can be considered given the association between long-term treatment with somatostatin analogs and the development of biliary symptoms and gallstones.[83]

Hepatic-Directed Therapies for Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract

For patients with unresectable, hepatic-predominant, progressive disease, hepatic-directed therapies may be considered, mainly with the palliative goals of extending life and relieving hormonal symptoms.[107-110]

Cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B).[111-115] For unresectable liver metastases, hepatic regional therapy (arterial embolization,[116] chemoembolization,[117-119] or radioembolization [category 2B])[119-126] is recommended.

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

For patients with progressive metastatic GI tract carcinoid tumors, everolimus can be considered. Everolimus is an inhibitor of mTOR and was well tolerated and showed evidence of antitumor effect in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial.[127] In the randomized phase III RADIANT-2 trial, 429 patients with advanced neuroendocrine tumors and carcinoid syndrome were randomized to receive octreotide LAR with everolimus or placebo.[128] 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.[128] Other side effects have also been described.[129-131]

A subsequent trial, RADIANT-4, was an international, double-blind, placebo-controlled, phase 3 trial that randomized 302 patients with progressive, non-functional, lung or GI neuroendocrine tumors 2:1 to receive everolimus or placebo.[132] In contrast to RADIANT 2, patients in RADIANT 4 were not receiving a somatostatin analog at the time of study enrollment and concurrent somatostatin analog was not a study requirement. Median PFS was 11.0 months (95% CI, 9.2–13.3) in the everolimus arm and 3.9 months (95% CI, 3.6–7.4) in the placebo arm. The hazard ratio for progression or death was 0.48 (95% CI, 0.35–0.67; P < .001). Drug-related grade 3/4 adverse events included stomatitis (9% vs. 0%), infections (7% vs. 0%), diarrhea (7% vs. 2%), anemia (4% vs. 1%), fatigue (3% vs. 1%), and hyperglycemia (3% vs. 0%). A recent report highlights the outcomes of 169 pre-treated patients with advanced neuroendocrine tumors of the pancreas (n = 85) or other sites (n = 84) who received everolimus through a compassionate use program.[133] An increased risk of adverse events in patients who had received previous radiolabeled peptide therapy or chemotherapy was noted.

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

Cytotoxic chemotherapy: The benefits associated with cytotoxic chemotherapy in patients with advanced carcinoid tumors appear, at best, to be modest. Tumor response rates are generally low, and no PFS benefit has been clearly demonstrated.[134]

Capecitabine was tested in patients with metastatic carcinoid tumors in a phase II trial; no objective responses were reported although 13 of 19 patients were reported to have experienced stable disease.[135] 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.[136] 5-FU was assessed in the phase III E1281 trial in combination with streptozocin or doxorubicin.[137] Response rates in both arms were around 16%. Dacarbazine was given following progression, with a response rate of 8%. Responses to temozolomide in advanced carcinoid are rare.[138]

A phase II trial assessed bevacizumab plus capecitabine and included 49 patients with GI neuroendocrine tumors.[139] A PFS of 23.4 months was reported, with 18% of patients achieving a partial response and 70% achieving stable disease.

The panel lists cytotoxic chemotherapy for neuroendocrine tumors of the GI tract 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. For patients with clinically significant bronchopulmonary or thymic tumor burden that is low or intermediate grade, temozolomide either administered alone or in combination with octreotide or lanreotide is an option to manage tumor burden and any associated symptoms.[64,140]

Alpha Interferon: Use of interferon in the setting of advanced GI tract carcinoid tumors is a category 3 recommendation. Interferon alpha has been shown in several large, non-randomized series to be associated with an antitumor effect in patients with advanced carcinoid tumors.[85,141-144] In a recent, large randomized study led by the Southwest Oncology Group, treatment with alpha interferon (5 million units 3 d/wk) was compared to treatment with bevacizumab (15 mg/kg administered every 21 days) in more than 400 patients with progressive neuroendocrine tumors.[145] Treatment with octreotide was included in both arms of this study. In a preliminary report of the results, no significant difference in PFS was observed; however, the long PFS durations in both arms of the study (15.4 and 16.6 months for interferon and bevacizumab, respectively) suggest both drugs may be active in this setting.[145] Because of its potential side effects, interferon is usually not initiated until failure of somatostatin analog treatment.[134]

Radiolabeled Somatostatin Analogs for Advanced Neuroendocrine Tumors of the Gastrointestinal Tract

Several early studies initially reported that treatment with radiolabeled somatostatin analogs was associated with tumor responses in patients with advanced carcinoid tumors.[146-150] A prospective phase II study of radiopeptide therapy in 90 patients with metastatic carcinoid tumors refractory to octreotide showed that treatment was associated with improvement in symptoms; radiographic regression, however, was relatively uncommon.[151] Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.[152-154]

A recent prospective study randomized more than 200 patients with advanced midgut neuroendocrine tumors to receive treatment with either ^{177}Lu-DOTATATE or high-dose octreotide. Results of this study showed that treatment with ^{177}Lu-DOTATATE was associated with a significant improvement in PFS (not reached vs. 8.4 months; $P <$ .0001).[155] Objective tumor responses were observed in 18% of patients who received ^{177}Lu-DOTATATE versus 3% in the control group ($P <$ .001).[155]

Liver Transplantation for Liver Metastases of Neuroendocrine Tumors of the Gastrointestinal Tract

Several series have now reported the results of liver transplantation patients with carcinoid tumors whose metastases are confined to the liver.[156-161] Results from a multicenter database of 85 patients at 28 centers who underwent liver transplantation for neuroendocrine tumors were also reported.[162] A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.[163] The panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

Management of Locoregional Unresectable and/or Distant Metastatic Bronchopulmonary or Thymic Neuroendocrine Tumors

Asymptomatic patients with low tumor burden may be observed with markers and abdominal or pelvic multiphasic CT or MRI scans every 3 to 12 months. A chest CT scan with or without contrast may be performed if clinically indicated. Alternatively, such patients may be initiated on treatment with octreotide or lanreotide. No clear consensus

exists on the timing of octreotide or lanreotide initiation in asymptomatic patients with metastatic neuroendocrine tumors and low tumor burden. Although initiation of octreotide or lanreotide can be considered in these patients, deferring initiation until evidence of tumor progression is seen may also be appropriate in selected patients.

Lung neuroendocrine tumors include a spectrum from low-grade typical carcinoids to intermediate-grade atypical carcinoids.[164] If patients present with asymptomatic, low tumor burden that is low grade, they can be observed with chest CT scans with contrast and abdominal/pelvic multiphasic CT or MRI scans every 3 to 6 months. Alternatively, these patients can be treated with octreotide and lanreotide. As with GI primary tumors above, there is no clear consensus on the timing of initiation of octreotide or lanreotide in such patients and either approach may be appropriate in selected patients.

If patients with advanced low-grade lung or thymic neuroendocrine tumors present with clinically significant tumor burden, initiation of octreotide and lanreotide may be considered. Additional options for the management of advanced low-grade tumors include initiation of everolimus or temozolomide. Both treatments may be given with or without octreotide or lanreotide.

Patients with advanced intermediate-grade lung or thymic neuroendocrine tumors should generally be initiated on systemic treatment. Options include initiation of octreotide or lanreotide. Additional options include initiation of everolimus (based on the results of the RADIANT 4 study, described above). Temozolomide represents another option; temozolomide monotherapy was associated with partial responses in 14% of patients with progressive metastatic bronchial neuroendocrine tumors in a retrospective study of 31 patients[140], or initiation of treatment with carboplatin or cisplatin and etoposide. Carboplatin or cisplatin and etoposide is generally considered for tumors on the higher end of the atypical category with respect to Ki-67 and grade.[64] These treatments may be given with or without octreotide or lanreotide.

Although rare, some patients may present with multiple lung nodules and widespread peripheral airway neuroendocrine cell hyperplasia. In this case, a diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) can be made.[164] This condition is generally indolent, and patients can be observed with chest CT scans without contrast every 12 months or for new symptoms. If patients are symptomatic, treatment with octreotide or lanreotide is recommended.

Neuroendocrine Tumors of the Pancreas

According to a population-based study, malignant pancreatic neuroendocrine tumors account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence.[165] 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.[165,166] 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.[40] An estimated 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms.[11,40] Consistent with these numbers, analysis of the NCCN Neuroendocrine Tumors Outcomes Database found that 22% of patients with pancreatic neuroendocrine tumors had a hormonal syndrome.[52] Of these functioning tumors, up to 70% are insulinomas, and only 10% are associated with metastases. Approximately 15% are glucagonomas. Gastrinomas and somatostatinomas account for another 10%; gastrinomas and

somatostatinomas (80%–90%) are associated with a relatively high risk for metastases.[166] The remaining rare pancreatic neuroendocrine tumors include VIPoma, and the recently described cholecystokininoma (CCKoma).[167]

Pancreatic neuroendocrine tumors occurring in patients with MEN1 are typically multiple and require different treatment strategies from those used for patients with sporadic pancreatic neuroendocrine tumors, which are usually solitary (see *MEN1*, below). Gastrinoma and insulinoma are the most common pancreatic neuroendocrine tumors in patients with MEN1.[168]

Evaluation of Neuroendocrine Tumors of the Pancreas

Personal and family history should be evaluated for the possibility of MEN1 (see *Multiple Endocrine Neoplasia*, below). The recommended evaluation also includes an abdominal multiphasic CT or MRI scan with contrast and/or a chest CT scan with or without contrast, if clinically indicated. For evaluation of nonfunctioning pancreatic tumors, the chest CT scan may be omitted. Hormone-secreting tumors may result in significant clinical symptoms even when very small, and lesion identification can be difficult.[169] Somatostatin receptor-based imaging and EUS can also be considered as appropriate.[170]

Biochemical evaluation is also often considered in patients with pancreatic neuroendocrine tumors because many pancreatic neuroendocrine tumors secrete specific hormones.[166] Biochemical evaluation is generally guided by the presence of symptoms that might indicate the presence of excess hormone. Screening for hormones in asymptomatic individuals is not routinely recommended. The range of symptoms associated with hormonal secretion is diverse. Classic syndromes include those associated with insulinomas, which secrete insulin, resulting in fasting or nocturnal hypoglycemia. Gastrinomas secrete gastrin, and patients often present with recurrent peptide ulcers. Glucagonomas are associated with the development of diabetes mellitus and/or migratory necrolytic erythema. Patients with somatostatinomas may also present with diabetes mellitus and/or diarrhea/steatorrhea from secretion of somatostatin. VIPomas are characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) from secretion of vasoactive intestinal polypeptide (VIP). The guidelines describe appropriate tests for each of these situations. For nonfunctioning tumors, pancreatic polypeptide (PP; category 3) and chromogranin A (category 3) may also be tested as appropriate.

Chromogranin A levels are elevated in 60% or more of patients with either functioning or nonfunctioning pancreatic endocrine tumors.[171-173] 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; $P < .001$).[74] Chromogranin A was also found to be a prognostic factor in a prospective study of patients treated with everolimus.[174] 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 PPIs, those with renal or liver failure, those with hypertension, and those with chronic gastritis.

Evaluation of Gastrinomas

Gastrinoma should be suspected in patients with severe and refractory gastroduodenal ulcers or symptoms such as dyspepsia, usually accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of basal and stimulated serum gastrin levels.[175] Diagnosis of gastrinoma can be confounded by the concurrent use of PPIs, 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 PPIs or antacids. To be useful for diagnosis, gastrin levels (basal or stimulated) must be measured after the patient is off PPI therapy for at least 1 week. After excluding retained gastric antrum by history, a combination of fasting serum gastrin level greater than 10 times the elevated and a gastric pH less than 2 is diagnostic of a gastrinoma. Patients who have clinical manifestations suspicious for a gastrinoma and a gastric pH less than 2 but with less than 10 times the elevation of serum gastrin levels require further testing.[176]

In addition, imaging studies (abdominal multiphasic CT/MRI scan with contrast or chest CT scan with or without contrast) often aid not only in localizing the tumor but also in confirming the diagnosis. Other tests, such as somatostatin receptor-based imaging, 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.[177]

Evaluation of Insulinomas

Insulinomas are generally small tumors that are best localized with EUS, which has been shown to localize approximately 82% of pancreatic endocrine tumors.[178] 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).[179] Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative.

Serum insulin (with concurrent hypoglycemia), pro-insulin, and C-peptide should be tested.[180] An insulin level greater than 3 mcIU/mL (usually >6 mcIU/mL), C-peptide concentrations of at least 0.6 ng/mL, and proinsulin levels of greater than or equal to 5 pmol/L when fasting blood glucose is less than 55 mg/dL indicated the presence of these tumors.[180]

To rule out metastatic disease, abdominal multiphasic CT or MRI scans with contrast should be performed accompanied by chest CT scans with or without contrast if clinically indicated. 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 receptor-based imaging may consequently be less useful as an imaging technique in insulinomas than in other tumor subtypes. Somatostatin receptor-based imaging should be performed if octreotide or lanreotide is being considered as a treatment for metastatic disease. Octreotide or lanreotide should only be administered to patients whose tumors are somatostatin-receptor positive, and patients with insulinoma should be carefully monitored when receiving octreotide or lanreotide because in some cases these drugs can profoundly worsen hypoglycemia (see *Preoperative Management*, below).[181]

The *New England Journal of Medicine* published a case report describing the diagnosis of insulinoma in a lactating patient presenting with periodic numbness and prolonged episodes of confusion and lethargy.[182]

Evaluation of Glucagonomas and VIPomas

For patients with recent-onset diabetes, cachexia, and/or a necrolytic erythematous skin rash, the panel recommends a blood test for glucagon and blood glucose. For both glucagonomas and VIPomas,

abdominal multiphase contrast-enhanced CT or MRI scans with contrast may be useful for identifying large tumors or metastatic disease. Chest CT scans with or without contrast can be performed as clinically indicated. Somatostatin receptor-based imaging and EUS can be performed as appropriate.

For suspected VIPomas with characteristic watery diarrhea, testing for VIP and electrolytes is recommended. A recent case report describes the diagnosis and treatment of a patient with VIPoma.[183]

Primary Treatment of Locoregional Resectable Neuroendocrine Tumors of the Pancreas

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

Preoperative Management

Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. Octreotide or lanreotide can be considered for symptom control in most pancreatic neuroendocrine tumor subtypes.[83] Octreotide or lanreotide should be used with caution in patients with insulinoma, because they can also suppress counterregulatory hormones such as growth hormone (GH), glucagon, and catecholamines. In this situation, octreotide and lanreotide can precipitously worsen hypoglycemia, and can result in fatal complications.[181] Octreotide and lanreotide should not be used in patients with insulinoma in patients who have a negative result by somatostatin receptor-based imaging.

In addition, specific measures are often recommended based on symptoms. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Everolimus can also be considered in this scenario.[184] For gastrinomas, gastrin hypersecretion may be treated with high-dose PPIs. For patients with glucagonoma, appropriate measures should be taken to treat hyperglycemia and diabetes, including the use of IV fluids. All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcus group c).

Surgical Management of Nonfunctioning Pancreatic Neuroendocrine Tumors

Most patients with localized pancreatic neuroendocrine tumors should undergo surgical resection, absent any contraindications. Exceptions include patients with other life-limiting comorbidities, high surgical risk, or widely metastatic disease. Additionally, several studies have suggested that patients with incidentally discovered tumors <1 cm in size may be safely followed in some cases, depending on the site of the tumor.[185,186] Other studies, including an analysis of the SEER database, suggest that some small tumors (measuring <2 cm in size in these studies) can pursue a more aggressive course.[187-189] Other retrospective studies suggest nonoperative management can be safe for nonfunctioning pancreatic neuroendocrine tumors that are <1.7 cm or <3 cm.[190,191] Based on these limited data, the panel includes observation alone as an option for selected cases of incidentally discovered small pancreatic neuroendocrine tumors, but recommends surgical resection for larger tumors absent contraindications.

Resection for larger (>2 cm), node-positive, or malignant-appearing nonfunctional tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

Lymph node resection should also be considered for tumors of 1 to 2 cm, because of the small but real risk of lymph node metastases.[192,193]

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,[194] 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,[195] can achieve lymph node retrieval comparable to distal pancreatectomy with en-bloc splenectomy.

Surgical Management of Insulinomas

The primary treatment for exophytic or peripheral insulinomas, because they are primarily benign, is enucleation. This procedure can be performed laparoscopically for localized solitary tumors within the body and tail of the pancreas. Sporadic tumors are usually solitary, whereas familial tumors are multiple. If enucleation is not possible because of invasion or the location of the tumor within the pancreas, then pancreatoduodenectomy for tumors in the head of the pancreas or distal pancreatectomy with preservation of the spleen for smaller tumors not involving splenic vessels may be considered. Distal pancreatectomy can be performed laparoscopically, and a recent meta-analysis reported that laparoscopic procedures are safe for patients with insulinomas and may be associated with shorter hospital stays.[196]

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.[197,198] Therefore, perioperative anticoagulation can be considered because of the increased risk of pulmonary emboli.

Surgical Management of VIPomas

Distal VIPomas are treated with distal pancreatectomy with resection of peripancreatic lymph nodes and spleen. Pancreatoduodenectomy with dissection of peripancreatic nodes is recommended for tumors in the

head of the pancreas. Small (<2 cm) peripheral VIPomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas.

Surgical Management of Other Pancreatic Neuroendocrine Tumors

The treatment recommendations for tumors secreting hormones such as somatostatinoma, ACTH, PTHrP, and PP are similar to those for nonfunctioning tumors. Tumors that are small (<2 cm) and peripheral can be enucleated with or without removal of regional nodes, or distal pancreatectomy can be performed with or without removal of regional nodes and with or without splenectomy. Deeper, larger (>2 cm), or invasive tumors are treated with pancreatoduodenectomy if they are located in the head of the pancreas, and with distal pancreatectomy and splenectomy if they are distally localized. Resection for larger (>2 cm) or malignant-appearing tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

Surveillance of Resected Pancreatic Neuroendocrine Tumors

Disease recurrence has been observed in 21% to 42% of patients with pancreatic neuroendocrine tumors and can occur after many years.[199-201] Higher lymph node ratio and Ki-67 status may indicate a higher chance of recurrence.[199] Patients should undergo follow-up 3 to 12 months after resection, or earlier if the patient presents with symptoms, and then every 6 to 12 months for a maximum of 10 years with an H&P and appropriate biochemical markers. Abdominal multiphasic CT or MRI with contrast and chest CT scans as clinically indicated can also be considered. These surveillance recommendations may also apply to cases where observation of patients with metastatic disease has been chosen. Less frequent surveillance may be appropriate for low-risk tumors such as well-differentiated stage I pancreatic neuroendocrine tumors. Somatostatin receptor-based imaging or FDG-PET/CT scans are not recommended for routine surveillance.

The optimal duration of surveillance is unknown. In one study of 123 patients with resected sporadic pancreatic neuroendocrine tumors, most recurrences occurred within 5 years of resection, and all recurrences occurred within 10 years.[202] In select cases, including resectable locoregional or oligometastatic recurrence, surgical resection may be considered.

Management of Locoregional Unresectable and/or Metastatic Neuroendocrine Tumors of the Pancreas

To evaluate the extent of locoregional unresectable disease and/or distant metastases, multiphasic CT or MRI scans with contrast of the abdomen and pelvis should be performed. Somatostatin receptor-based imaging may also be considered. A chest CT scan with or without contrast and appropriate biochemical evaluation may be carried out if clinically indicated. Metastases in patients with neuroendocrine tumors of the pancreas, when they develop, often occur first in the liver. In patients with limited hepatic disease, surgical excision of both the primary tumor and liver metastases should be considered with curative intent when possible and can be performed in a staged or synchronous fashion. A recent meta-analysis reported that 5-year OS ranges from 41% to 100% in this population of patients.[104] 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.[203] Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence.[105,106] Additional resection or ablation may be possible. A study of 172 patients who had liver resection of metastatic neuroendocrine tumors (55 with the primary tumor in the

pancreas) showed that significant long-term survival can be achieved after recurrence in many patients, with a 10-year overall survival rate of 50.4%.[103]

If resection is performed and future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy can be considered given the association between long-term treatment with somatostatin analogs and the development of biliary symptoms and gallstones.[83]

Unfortunately, most patients who present with advanced pancreatic neuroendocrine tumors have unresectable disease. For selected patients with unresectable disease who are asymptomatic and have low tumor burden and stable disease, observation can be considered, with marker assessment and abdominal and pelvic multiphasic CT or MRI scans every 3 to 12 months until clinically significant disease progression occurs. Chest CT scans with or without contrast may also be performed if clinically indicated. In addition, however, treatment with lanreotide or octreotide can be considered (see discussion below). The optimal time to begin therapy in this patient population is not known.

For symptomatic patients with unresectable disease, those who initially present with clinically significant tumor burden, or those with clinically significant disease progression, octreotide or lanreotide should be considered if patients are not already receiving treatment with these options. Several different options can be considered if the disease continues to progress. Systemic options include treatment with biologically targeted agents (everolimus or sunitinib, category 2A) or treatment with cytotoxic chemotherapy (category 2A). These options, as well as hepatic-directed therapies, are discussed in more detail in the following sections.

Somatostatin Analogs

Patients with pancreatic neuroendocrine tumors and symptoms of hormone secretion should, in most cases, receive treatment with either lanreotide or octreotide and/or other medication to manage their symptoms as previously described. Patients without hormone-related symptoms who have uptake with somatostatin scintigraphy can also be considered for treatment with octreotide or lanreotide. Results from the CLARINET study, in which 204 patients with gastroenteropancreatic neuroendocrine tumors (including both carcinoid and pancreatic neuroendocrine tumors) were randomized to receive treatment with either lanreotide or placebo, showed that treatment with lanreotide was associated with in an improvement in PFS (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; $P < .001$).[102] Although no randomized studies to date have directly shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial showed an improvement in its primary endpoint of time to tumor progression (14.3 vs. 6 months; $P = .000072$) in carcinoid tumors of the midgut.[99] Lanreotide and octreotide share the same mechanism of action, and the panel believes that either lanreotide or octreotide are appropriate options for tumor control in this setting.

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

Molecularly Targeted Therapies

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

Everolimus, administered orally at a dose of 10 mg once daily, was evaluated in a multicenter study (RADIANT-3) enrolling 410 patients with advanced, progressive, pancreatic neuroendocrine tumors.[204] In

this study, the median PFS duration for patients randomized to everolimus was 11.0 months, compared with 4.6 months for patients receiving placebo ($P < .001$). Subset analyses of RADIANT-3 suggested that the PFS benefit associated with everolimus is independent of prior or concurrent somatostatin analog therapy or prior chemotherapy.[205-207] Adverse events associated with everolimus include stomatitis, hyperglycemia, and, in rare cases, pneumonitis.[204] Other side effects have also been described.[129-131] A recent report highlights the outcomes of 169 pre-treated patients with advanced neuroendocrine tumors of the pancreas (n = 85) or other sites (n = 84) who received everolimus through a compassionate use program.[133] A higher risk of adverse events was noted in patients with previous radiolabeled peptide therapy and chemotherapy.

Sunitinib, administered orally at a dose of 37.5 mg once daily, was compared with placebo in a multicenter randomized study of patients with advanced, progressive, metastatic pancreatic neuroendocrine tumors.[208] 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%.[208] 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.[209] Adverse events associated with sunitinib include fatigue and, in rare cases, congestive heart failure.[210] Other side effects have also been described.[211,212]

Cytotoxic Chemotherapy for Advanced Pancreatic Neuroendocrine Tumors

Cytotoxic chemotherapy is another option for patients with unresectable or metastatic pancreatic neuroendocrine tumors (category 2A). While a number of regimens have been associated with antitumor activity in this setting, there is no panel consensus on which cytotoxic chemotherapy regimen is best. The alkylating agents streptozocin and temozolomide appear to have the most antitumor activity in pancreatic neuroendocrine tumors.

Streptozocin is FDA-approved for use in patients with advanced pancreatic neuroendocrine tumors. The combination of doxorubicin and streptozocin was initially reported to be associated with an overall response rate of 69% and a survival benefit in a relatively small randomized study of patients with advanced pancreatic neuroendocrine tumors.[213] A retrospective review from MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin.[214] A phase II trial assessed bevacizumab combined with 5-FU and streptozocin.[215] A PFS of 23.7 months was reported, with 56% of patients achieving a partial response and 44% achieving stable disease.

More recently, oral temozolomide-based therapy has been used in patients with advanced pancreatic neuroendocrine tumors. Temozolomide has been administered using different schedules, either alone or in combination with other agents.[138,216-219] 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.[219] Another retrospective review of the temozolomide and capecitabine combination reported a 61% response rate in 18 patients, with 1 surgically proven complete pathologic

response.[220] A small recent retrospective study (7 patients) reported a response rate of 43%.[221]

Temozolomide-based combination regimens have also been formally evaluated in prospective, phase II studies. One such study assessed the safety and efficacy of temozolomide administered with bevacizumab, a monoclonal antibody targeted against vascular endothelial growth factor (VEGF).[216] Five of the 15 patients (33%) with pancreatic neuroendocrine tumors had a radiographic response (with no responses in the 19 patients with carcinoid tumors), and the toxicity was acceptable. The combination of temozolomide with everolimus has also been studied and found to be safe, with partial responses observed in 40% of patients with pancreatic neuroendocrine tumors.[222]

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

Other cytotoxic agents appear to be less active than streptozocin or temozolomide in pancreatic neuroendocrine tumors. 5-FU was assessed in the phase II/III E1281 trial in combination with streptozocin or doxorubicin in patients with neuroendocrine tumors of various locations, including the pancreas.[137] Response rates in both arms were around 16%. Dacarbazine was given following progression, with a response rate of 8%. Other studies have also shown the combination of 5-FU and streptozocin to be effective in this setting.[223,224] 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.[136]

Radiolabeled Somatostatin Analogs for Advanced Pancreatic Neuroendocrine Tumors

Treatment with radiolabeled somatostatin analogs has been reported to result in tumor responses in patients with advanced pancreatic neuroendocrine tumors.[146-150] Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.[153,154] In general, these studies have enrolled only patients with evidence of high tumoral somatostatin receptor expression. A randomized study of high-dose octreotide vs. ^{177}Lu-DOTATATE has been reported in patients with advanced midgut neuroendocrine tumors, and results from this study suggest this approach is both safe and associated with improved PFS in this setting.[225] Prospective, randomized studies of radiolabeled somatostatin analogs have not yet been completed in patients with advanced pancreatic NET. At this time, treatment with radiolabeled somatostatin analogs remains investigational in patients with pancreatic neuroendocrine tumors.[226]

Hepatic-Directed Therapies

Hepatic-directed therapies may be considered in patients with progressive hepatic-predominant metastatic disease, to reduce tumor bulk and relieve symptoms of hormone hypersecretion.[109] The panel lists cytoreductive surgery or ablative therapy (ie, RFA[115], cryotherapy, microwave[112,114]) as category 2B recommendations for these patients. Although some groups report that the risks of cytoreductive surgery outweigh its benefits,[227] others have reported good outcomes.[228,229]

Additional options include hepatic regional therapies including bland hepatic arterial embolization,[116] radioembolization (category 2B),[120-126] and chemoembolization.[230] Whereas embolization in general is

considered an effective approach in patients with hepatic-predominant disease,[107,108,110] only limited data compare the various embolization techniques, and the optimal embolization approach remains uncertain.

Liver Transplantation

Several series have now reported the results of liver transplantation in patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver.[156-161,231] A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.[163] The panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

Neuroendocrine Tumors of Unknown Primary

In a SEER database analysis, a primary tumor site could not be found in as many as 4,752 (13%) of 35,618 neuroendocrine tumors.[1] When a neuroendocrine tumor of unknown primary is diagnosed, attempts are usually first made to identify the origin of the neoplasm to help guide treatment decisions. If the primary tumor cannot be identified, treatment decisions are generally guided by tumor histology (see *Histologic Classification and Staging of Neuroendocrine Tumors*, above). Many of these tumors are poorly differentiated and aggressive.[232]

Evaluation of Neuroendocrine Tumors of Unknown Primary

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

Given the differences in systemic treatment approaches for carcinoid and pancreatic neuroendocrine tumors, establishing whether or not a patient has a primary pancreatic neuroendocrine tumor can have important treatment implications. Potential primary sites may be investigated with imaging studies, such as chest CT scans with or without contrast, and multiphasic abdominal and pelvic CT or MRI scans. Many neuroendocrine tumors express specific receptors for amines or peptides (eg, somatostatin receptors), and somatostatin receptor-based imaging may be helpful in localizing primary neuroendocrine tumors.[58,233] Ultrasound or EUS of the pancreas is useful for patients with possible insulinomas or other neuroendocrine tumors of the pancreas. In addition, radionucleotide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. An FDG-PET/CT scan and brain imaging with contrast (CT or MRI) can occasionally be useful in finding a primary tumor, but are less sensitive in well-differentiated neuroendocrine tumors and should only be considered in cases of poorly differentiated tumors.

Colonoscopy can also be considered, especially in cases of well-differentiated liver metastases, to identify possible primary tumors in the small intestine or colon.[234] It is not uncommon for small bowel carcinoid tumors to be small and difficult to visualize, although in some cases imaging may demonstrate an associated mesenteric mass. Exploratory surgery is generally not recommended for purely diagnostic purposes. However, if a small bowel primary tumor is suggested by symptoms and radiologic findings and if metastases are completely resectable, surgery can be considered.[234]

Primary Treatment of Neuroendocrine Tumors of Unknown Primary

If the primary tumor is not identified, poorly differentiated neuroendocrine tumors should be treated as described for *Poorly*

Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas, below. In the absence of a primary tumor identified in the pancreas, well-differentiated tumors should be treated similarly to typical carcinoid tumors, as described above.

Adrenal Gland Tumors

Adrenocortical carcinomas (ACCs) are rare (incidence, 1–2 per million).[235-237] ACC has a bimodal age distribution, with peak incidences in early childhood and the fourth to fifth decades of life. The female-to-male ratio is approximately 1.5 to 1.[238,239] Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and MEN1.[5,240-243] 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[244,245]) and alterations at the 11p15 locus (site of the *IGF-2* gene[246,247]) seem to occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.[235,248-250] Signs and symptoms associated with hypersecretion of cortisol, called *Cushing's syndrome*, include weight gain, weakness (primarily in proximal muscles), hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae, buffalo hump, supraclavicular fat pad enlargement, hyperglycemia, and hypokalemia. Aldosterone-secreting tumors may present with hypertension, weakness, and hypokalemia. Androgen-secreting tumors in women may induce hirsutism, deepening of the voice, and oligo/amenorrhea.[248] 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.[248,251]

Evaluation and Treatment of Adrenal Gland Tumors

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

The morphologic evaluation should include an adrenal protocol CT with contrast or MRI with or without contrast to determine the size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics. Functional evaluation should include evaluation for hyperaldosteronism, Cushing's syndrome, and pheochromocytoma, as described here and below. Most adrenal cortical carcinomas express multiple hormones. Therefore, when the evaluation shows that several hormones are expressed, adrenal cortical carcinomas are likely.

Evaluation and Treatment of Hyperaldosteronism

When hyperaldosteronism (also called *primary aldosteronism*) is suspected, plasma aldosterone and renin activity should be assessed. Patients with primary aldosteronism have elevated plasma levels of aldosterone and low levels of renin activity. The plasma aldosterone-to-renin ratio in patients with primary hyperaldosteronism is usually greater than 30.[252] Confirmatory testing is indicated for positive results, because false positives can occur. Electrolytes should also be measured, because excessive aldosterone production causes both retention of sodium and excretion of potassium. The Endocrine Society has developed detailed guidelines for the detection, diagnosis, and treatment of primary aldosteronism.[253]

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.[254,255]

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

Evaluation and Treatment of Cushing's Syndrome

Patients who present with symptoms of Cushing's syndrome should be screened for evidence of hypercortisolemia with 1 of the following tests: 1) overnight 1-mg dexamethasone suppression test with 8 AM plasma cortisol; 2) 2 to 3 midnight salivary cortisols; or 3) free cortisol in a 24-hour urine sample.[256,257] Confirmatory testing should be performed if positive. Elevated levels of cortisol are indicative of Cushing's syndrome. In addition to treatment of the underlying hypercortisolemia, patients who experience symptoms secondary to increased adrenocortical steroid levels often require aggressive treatment of associated conditions such as hypertension, hyperglycemia, and hypokalemia.

Patients who are hypercortisolemic should have levels of serum ACTH assessed by an 8 AM cortisol measurement. Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, or neuroendocrine tumors in the lung, thyroid, pancreas, or bowel are possible sources. These patients should be assessed and treated for pituitary or ectopic sources of ACTH production. A case report from the Massachusetts General Hospital provides an example of the evaluation, diagnosis, and treatment of a patient with Cushing's syndrome resulting from a bronchial carcinoid.[61]

Cushing's syndrome can also be associated with either benign adrenal tumors (adrenal adenoma) or malignant adrenal tumors. Malignancy should be suspected if the tumor is larger than 4 cm or is inhomogeneous with irregular margins and/or local invasion and other malignant imaging characteristics. Chest CT scans with or without

contrast and CT or MRI scans with contrast of the abdomen and pelvis is required to evaluate for metastases and local invasion. Benign adrenal tumors (ie, <4 cm, contralateral gland normal, circumscribed tumor, other benign imaging characteristics) are generally resected with a laparoscopic adrenalectomy, when feasible. Postoperative corticosteroid supplementation is required until recovery of the hypothalamic-pituitary-adrenal (HPA) axis.

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

Medical management of hypercortisolism is achieved with adrenostatic agents, including ketoconazole, mitotane, and/or mifepristone. Ketoconazole is most commonly used (at doses of 400–1200 mg/d) because of its easy availability and relatively tolerable toxicity profile. The data supporting use of other individual drugs for the management of Cushing's disease are limited.[258] Octreotide or lanreotide can also be considered for ectopic Cushing's syndrome if the tumor is somatostatin scintography-positive, although it may be less effective in controlling ectopic ACTH secretion than it is in other contexts. Bilateral adrenalectomy is generally recommended when medical management of ectopic Cushing's syndrome fails.

Treatment of Nonfunctioning, Benign Adrenal Tumors

Adrenal tumors that do not secrete hormones are often discovered incidentally during scans for unrelated reasons (*incidentalomas)*. Most nonfunctioning tumors are benign and can be left untreated. Masses showing radiographic features of myelolipoma are considered benign. In addition, tumors smaller than 4 cm that are homogenous, with smooth margins, and that appear lipid-rich according to CT or MRI criteria are also usually benign. If no change in size is noted on repeat imaging in 6 to 12 months, no further follow-up is required. Adrenalectomy can be considered if the mass is enlarging. 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.[259] 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.[260] 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.[259] MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.[261,262] 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.

Chest CT scans with or without contrast and CT or MRI scans with contrast of the 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.[263]

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.[254,255]

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.[264-266] The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany.[267] In the Italian cohort, nearly half of the patients received adjuvant mitotane (47/102 patients) at doses ranging from 1 to 5 g/d, whereas none of the 75 German patients received adjuvant mitotane. The median duration of treatment was 29 months. In follow-up, disease-free and overall survivals were significantly longer in those treated with mitotane versus the controls, suggesting that adjuvant mitotane may be an effective postoperative strategy. The randomized phase III ADIUVO trial is currently underway to assess the efficacy of adjuvant mitotane in patients with ACCs considered to be at low to intermediate risk for progression (ClinicalTrials.gov identifier: NCT00777244). Disease-free survival is the primary endpoint.

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

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

Management of Metastatic Adrenal Carcinoma
Resection may be considered if greater than 90% of the tumor and metastases can be removed. Otherwise, systemic therapy should be initiated. Observation with chest CT scans with or without contrast, abdominal/pelvic CT or MRI scans, 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.[268-270] Partial response rates are thought to be 10% to 30% at most.[271]

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.[272] Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%.[273] 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; $P = .07$).[274] However, response rates and PFS were improved with the 4-drug regimen and an overall survival benefit was seen in those who did not cross over to the other combination (17.1 vs. 4.7 months). Rates of serious adverse events were similar in the arms.

However, the toxicity of concurrent chemotherapy plus mitotane should be considered when making treatment decisions, and mitotane monotherapy may still be appropriate in selected cases. The optimal doses and duration of mitotane treatment for metastatic disease have not yet been standardized, but some institutions recommend target levels of 14 to 20 mcg/mL, if tolerated. Higher doses may be difficult for patients to tolerate, whereas lower doses may be less effective.[271] Steady-state levels may be reached several months after initiation of mitotane. As noted above, because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed to prevent adrenal insufficiency. This replacement therapy may be needed for the remainder of the patient's lifetime. Follow-up CT or MRI scans should be performed.

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.[275] 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.[276] In fact, a study showed that 87.5% of patients presenting with these tumors prior to age 20 harbored a germline mutation in one of several genes tested if they also had metastatic disease.[277] 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.[278] Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see *Surveillance of Pheochromocytomas/Paragangliomas*, below).

Evaluation for Pheochromocytomas/Paragangliomas

A patient with possible pheochromocytoma should be evaluated with fractionated metanephrines in 24-hour urine or free metanephrines in plasma; elevated levels of metanephrines are suggestive of pheochromocytoma.[279] Concurrent medications should be reviewed before metanephrine testing for those that interfere with plasma metanephrines evaluation, including acetaminophen, certain beta- and alpha-adrenoreceptor blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors.[280] Elevations in metanephrine levels that are 4 times above the upper limit of normal are diagnostic. Urine or plasma catecholamines are no longer routinely recommended for the evaluation of pheochromocytoma: 15% to 20% of patients with pheochromocytoma have normal levels of urine catecholamines due to intermittent secretion in some tumors and insignificant secretion by others.[281] Measurement of serum and/or 24-hour urine fractionated catecholamines for dopamine levels can be considered for cervical paragangliomas.

Chest CT scans with or without contrast and abdominal/pelvic multiphasic CT or MRI scans are also recommended. Other imaging studies, including somatostatin receptor-based imaging, FDG-PET/CT, metaiodobenzylguanidine (MIBG) scan, and bone scan, should be performed as appropriate if metastatic disease is suspected.

Genetic Counseling/Testing in Pheochromocytomas/Paragangliomas

While many pheochromocytomas are thought to be sporadic, increasing evidence shows that a number of pheochromocytomas are in fact associated with inherited genetic syndromes.[275,282] Pheochromocytomas occur in patients with MEN2A, MEN2B, and other familial diseases such as neurofibromatosis, von Hippel-Lindau syndrome, and Osler-Weber-Rendu syndrome. In addition to germline mutations associated with these syndromes (ie, *RET, NF1*, *VHL*, *SMAD4, ENG, ALK1*), germline mutations in *SDHB*, *SDHA*, *SDHAF2*, *SDHD*, *SDHC*, *TMEM127*, *MAX*, *HIF2A*, and *MDH2* have also been associated with an increased incidence of pheochromocytomas and paragangliomas.[282-288] Patients younger than 45 years of age 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.[285] Because a significant proportion of patients with a pheochromocytoma or paraganglioma have a heritable mutation,[282] genetic counseling is recommended in patients with such a diagnosis and in those with a family history of these tumors, with genetic testing when appropriate. The Endocrine Society has published guidelines that include a genetic testing decision algorithm.[279]

Individuals with known germline mutations associated with pheochromocytomas and paragangliomas should undergo lifelong

biochemical and clinical surveillance, beginning at age 10 years or ≥10 years before the earliest age of diagnosis in the family.[285] The type and timing of the surveillance should be based on which gene is affected and take into account known genotype-phenotype relationships. MRI may be the preferable imaging modality for tumor detection in these individuals in order to limit radiation exposure.

Primary Treatment of Pheochromocytomas/Paragangliomas

Surgical resection is the mainstay of treatment for both benign and malignant pheochromocytomas and paragangliomas. Surgery or stress can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Therefore, patients with pheochromocytomas or paragangliomas should receive preoperative alpha-adrenergic blockade with aggressive volume repletion and high-salt diet for 7 to 14 days or until stable. Alpha 1-selective receptor blockers include terazosin, doxazosin, and prazosin, and non-selective receptors include phenoxybenzamine. If additional blood pressure control is needed after alpha blockade, the addition of dihydropyridine calcium channel blockers can be considered. Calcium channel blockers are not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Methyltyrosine can be used in addition to alpha blockade to control blood pressure. Beta blockade (B1-selective blockers or non-selective beta blockers) can also be added to alpha blockade to control tachycardia. Generally, alpha and beta blockers should be administered independently, and use of combination beta/alpha blockers is not recommended. Non-selective alpha blockade phentolamine (IV) can be used intraoperatively for additional blood pressure control.

Resection is the recommended treatment for patients with resectable tumors. A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas.[289-291] For locally unresectable tumors, RT can be considered, with cytoreductive resection, when possible. Alternatively, if tumors are positive on MIBG scan with dosimetry,[292,293] treatment with iodine-131-MIBG therapy is recommended. In addition, medical therapy should be continued for unresectable secreting tumors and referral to multidisciplinary centers should be considered.

When distant metastases are present, cytoreductive resection is also recommended when possible, and medical therapy should be continued for secreting tumors. Other options for treating unresectable, metastatic disease include: 1) clinical trial; 2) systemic chemotherapy (eg, cyclophosphamide/vincristine/dacarbazine [CVD] or temozolomide)[217,294-297]; 3) iodine-131-MIBG therapy after confirming dosimetrically that tumors take up MIBG;[292,293] or 4) palliative RT for bone metastases.

A retrospective review of 52 evaluable patients treated with various systemic chemotherapy regimens for metastatic pheochromocytomas or paragangliomas showed that patients with a response to chemotherapy (reduction in symptoms, antihypertensive medications, or tumor size) had a median survival of 6.4 years and non-responders had a median survival of 3.7 years.[295] Approximately 33% of patients exhibited a tumor response.

A review of 48 patients with pheochromocytoma or paraganglioma treated with iodine-131-MIBG therapy at 4 centers showed that, while partial responses were rare, stable disease was achieved after 83.1% of treatments.[298] A meta-analysis of 17 studies that included a total of 243 patients with malignant paraganglioma or pheochromocytoma found a stable disease rate of 52% (95% CI, 0.41–0.62) after iodine-131-MIBG therapy.[299] Partial and complete responses were seen in 27% and 3% of patients, respectively.

Surveillance of Pheochromocytomas/Paragangliomas

Surveillance intervals for patients with pheochromocytomas or paragangliomas are similar to those for other neuroendocrine tumors. Following complete resection, H&P should be performed and blood pressure and tumor markers should be measured after 3 to 12 months, then every 6 months for the first 3 years, and annually for up to 10 years. In addition, chest CT scans with or without contrast, abdominal/pelvic CT or MRI scans with contrast, or FDG-PET/CT scans can be considered. Timing for these surveillance events and procedures can be earlier if symptoms dictate. In addition, individuals with hereditary paraganglioma/pheochromocytoma may require more frequent follow-up.

High Grade or Poorly Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas

Although rare, extrapulmonary, poorly differentiated neuroendocrine carcinomas occur in a wide variety of organs. They are characterized by a high mitotic index and high proliferative index (Ki-67). However, not all high-grade neuroendocrine cancers are poorly differentiated. A subgroup of neuroendocrine tumors with Ki-67 index >20% may be characterized by relatively well-differentiated histology, particularly tumors with Ki-67 index between 20% and 50%. The Ki-67 index has implications in tumor response to platinum-based chemotherapy (discussed below). The most aggressive of these tumors histologically resemble classic small cell carcinoma of the lung. The most frequent organs involved, listed in order of decreasing frequency, are the cervix, esophagus, pharynx and larynx, colon and rectum, and prostate. Most extrapulmonary poorly differentiated neuroendocrine carcinomas are aggressive and require combined multimodality treatment, usually following a treatment paradigm that parallels the treatment of small cell lung cancer. These tumors are rarely associated with a hormonal syndrome.

Evaluation of High Grade or Poorly Differentiated/Large or Small Cell Carcinomas

CT scans with contrast of the chest, abdomen, and pelvis are recommended as baseline staging studies. Brain MRI or CT scans with contrast should be performed as clinically indicated, and should be considered routinely in poorly differentiated neuroendocrine carcinomas of the thorax and neck. FDG-PET/CT and/or plasma ACTH or other biochemical markers are recommended as clinically indicated. Somatostatin scintigraphy is not part of the routine evaluation of poorly differentiated neuroendocrine tumors, but may be considered, particularly for the subgroup of high grade but morphologically well-differentiated tumors.

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

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

Small cell lung regimens, such as cisplatin or carboplatin with etoposide, are generally used as primary treatment. Evolving data, however, suggest that well-differentiated tumors with intermediate Ki-67 levels (in the 20%–55% range) may not respond as well to platinum/etoposide as patients with higher Ki-67 (>55%).[25] Clinical judgment should be used in selecting systemic therapy regimens for

patients with Ki-67 levels in this intermediate range. Some panel members believe that treatments used for lower grade tumors may be reasonable in this population. Particularly for high-grade tumors that are well-differentiated, systemic options as described for the management of locoregional unresectable or metastatic bronchopulmonary, thymic, and GI tract disease may be considered as appropriate. Octreotide or lanreotide therapy can be considered for symptom control in the rare cases of hormone-secreting, poorly differentiated tumors that are unresectable or metastatic if found to be somatostatin-receptor positive.

Surveillance of Poorly Differentiated/Large or Small Cell Carcinomas

After surgery, surveillance consists of a routine H&P along with appropriate imaging studies (chest CT with or without contrast and abdominal/pelvic MRI with contrast or chest/abdominal/pelvic multiphasic CT, or FDG-PET/CT) every 3 months for the first year and every 6 months thereafter. Patients with locoregional, unresectable disease and with metastatic disease should be monitored at least every 3 months with a H&P and appropriate imaging studies as described.

Multiple Endocrine Neoplasia

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

MEN1 is associated with the germline mutation or inactivation of the tumor suppressor gene *MEN1* (chromosomal locus 11q13 encoding the menin protein),[300] whereas MEN2 and familial MTC are associated with germline mutations of the proto-oncogene, *RET* (chromosomal locus 10q11.2), that lead to activation of the tyrosine kinase receptor, RET.[301] Somatic mutation of the *MEN1* gene is also the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids.[5] Somatic *RET* mutations are found in sporadic MTC.[302]

MEN1

MEN1 (or Wermer syndrome) is typically characterized by tumors of the parathyroid and pituitary glands and neuroendocrine tumors of the pancreas, but may also be associated with carcinoid tumors (eg, thymus, bronchial, gastric), adrenal tumors, and multiple lipomas and skin angiomas. Over 98% of patients with MEN1 either have or will develop primary hyperparathyroidism, and about 50% will develop symptoms from functioning benign or malignant neoplasms of the pancreas.[5] 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.[303,304] Approximately 2% and 5% of patients with MEN1 develop thymic and bronchial neuroendocrine tumors, respectively.[305] 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.[306]

Examples of functional syndromes include hypercalcemia related to multiple abnormal parathyroid glands; galactorrhea or amenorrhea associated with a prolactinoma; Zollinger-Ellison syndrome associated with gastrinoma and hypersecretion of gastrin; and Cushing's syndrome or acromegaly related to a pituitary tumor or solitary or bilateral adrenal tumors. Ectopic Cushing's syndrome may be caused by a pancreatic neuroendocrine tumor, a thymic carcinoid, a bronchial carcinoid, or MTC. In addition, although rare, patients may develop symptoms as a result of an excess of several hormones from more than one gland, such as hyperparathyroidism and a simultaneous gastrinoma, insulinoma, or a functioning pituitary tumor. However, in most patients, a single hormonal syndrome dominates the clinical picture.

About 80% of patients with MEN1 and hypoglycemia related to insulinoma have multiple islet cell neoplasms. Patients with MEN1 and Zollinger-Ellison syndrome also frequently have more than one tumor. Of these tumors, 70% are gastrin-secreting carcinoids in the duodenum and/or periduodenal lymph nodes. Nonfunctioning pancreatic neuroendocrine tumors are usually larger when clinically detected, and are more likely to be associated with metastases at the time of presentation. The development of metastatic pancreatic neuroendocrine tumors or metastatic carcinoid tumors of the thymus are the most common causes of death associated with MEN1. The clinical characteristics of pancreatic endocrine tumors are summarized under *Neuroendocrine Tumors of the Pancreas*, above.

Evaluation of MEN1 Syndromes

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

Evaluation for Parathyroid Tumors in MEN1

Primary hyperparathyroidism associated with parathyroid adenomas is the most common manifestation of MEN1. Measurement of serum calcium levels and 25-OH vitamin D are recommended if hyperparathyroidism is suspected.

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.[307,308]

Evaluation for Pancreatic Tumors in MEN1

Approximately 75% of patients with MEN1 and pancreatic neuroendocrine tumors have associated symptoms of hormone hypersecretion. The various characteristics of endocrine tumors of the pancreas (eg, gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma) are summarized under *Neuroendocrine Tumors of the Pancreas*, above. The workup for pancreatic neuroendocrine tumors in the context of MEN1 is similar to that for sporadic pancreatic

neuroendocrine tumors. Abdominal/pelvic multiphasic CT or MRI is recommended. Imaging with EUS and somatostatin receptor-based imaging 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 or sella MRI with contrast is recommended when evaluating for pituitary tumors. Various laboratory tests are also used to evaluate for suspected pituitary tumors. The panel lists serum prolactin and IGF-1 levels among recommended tests (category 2B). Elevated prolactin levels are indicative of prolactinoma, and increased IGF-1 occurs in acromegaly.

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

Evaluation for Bronchial/Thymic Tumors in MEN1

Chest CT with contrast or abdominal/pelvic multiphasic CT or MRI is recommended to evaluate for bronchopulmonary or thymic tumors in patients with MEN1. Other biochemical evaluation should be done as clinically indicated.

Genetic Counseling/Testing in MEN1

Genetic counseling and *MEN1* genetic testing should be offered to individuals with suspicion of or a clinical diagnosis of MEN1 (see *Evaluation of MEN1 Syndromes*, above) and to at-risk relatives of individuals with known germline *MEN1* mutations.[303,309] It should be noted that a germline *MEN1* mutation is uncommon in individuals with a single MEN1-associated tumor and no family history. Only 10% of patients with MEN1 have a *de novo* germline mutation in *MEN1*, and thus no family history of MEN1-associated tumors.

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

Primary Treatment of MEN1 Syndromes

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

Primary Treatment of Parathyroid Tumors in MEN1

Treatment options for parathyroid hyperplasia in patients with MEN1 include subtotal parathyroidectomy with or without thymectomy (the bilateral upper thymus is a common site of ectopic parathyroid glands and thymic carcinoid tumors) with or without cryopreservation of parathyroid tissue. Total parathyroidectomy with autotransplantation of parathyroid tissue with or without thymectomy, and with or without cryopreservation of parathyroids, is another recommended option.[310,311] A randomized, prospective trial compared these surgical approaches in 32 patients with MEN1 and hyperparathyroidism.[312] No significant differences were observed in outcomes including recurrent hyperparathyroidism. Adverse outcomes include persistent hyperparathyroidism (2%–5%) and hypocalcemia (1%) because of

inadequate or excessive resection, respectively, even by expert surgeons. Additionally, postoperative bleeding or hoarseness due to injury to the recurrent laryngeal nerve may occur in about 1% of patients.

Primary Treatment of Pancreatic Tumors in MEN1

Treatment of pancreatic neuroendocrine tumors associated with MEN1 is similar to sporadic pancreatic neuroendocrine tumors and focuses on surgical excision preceded by medical management if necessary (see relevant site-specific recommendations in *Neuroendocrine Tumors of the Pancreas*, above). However, in contrast to patients with sporadic disease where a tumor is usually solitary, pancreatic neuroendocrine tumors associated with MEN1 are frequently multiple.[313] Removal of a single functioning tumor, although a reasonable approach for sporadic tumors, may miss additional tumors in the setting of MEN1. MEN1-associated metastatic pancreatic neuroendocrine tumors are often slower growing than metastatic sporadic tumors. Observation can be considered for non-functioning, indolent tumors. Surgical resection should be considered in cases of: 1) symptomatic functional tumors refractory to medical management; 2) a tumor larger than 1 to 2 cm in size; or 3) a tumor with a relatively rapid rate of growth over 6 to 12 months. The panel recommends endoscopy with EUS prior to pancreatic surgery to preoperatively assess and localize tumors.

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

All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C) preoperatively. Furthermore, in patients undergoing abdominal surgery in whom octreotide or lanreotide treatment is planned, prophylactic cholecystectomy can be considered, due to a higher risk of cholelithiasis in patients receiving somatostatin analogs.[83] Metastatic disease in patients with MEN1 is treated as in patients with neuroendocrine tumors arising sporadically, according to the appropriate tumor type.

Primary Treatment of Pituitary Tumors in MEN1

The panel recommends consultation with endocrinology for the treatment of patients with pituitary tumors associated with MEN1, including those with prolactinoma, Cushing's disease, acromegaly, and nonfunctioning tumors.

Primary Treatment of Bronchial/Thymic Tumors in MEN1

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

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.[314] The patients are also more likely to have or develop new parathyroid carcinomas, pancreatic neuroendocrine tumors, pituitary tumors, and/or bronchial/thymic tumors. Carcinoid tumors occur in approximately 3% of patients with MEN1.[309] 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.[309]

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

Surveillance for MEN-1–associated pancreatic neuroendocrine tumors is accomplished by following serum hormones as symptoms indicate or if they were previously elevated. Cross-sectional imaging with abdominal/pelvic CT or MRI with contrast every 1 to 3 years or serial EUS can also be considered in patients with MEN1.

Surveillance for pituitary tumors includes a brain MRI with contrast of the pituitary every 3 to 5 years. Prolactin, IGF-1, and other previously abnormal pituitary hormones should be followed every 3 to 5 years or as symptoms indicate.

For surveillance for bronchial or thymic carcinoid tumors, the panel suggests that cross-sectional chest CT with contrast be considered every 1 to 3 years.

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

MEN2 and Familial MTC

MEN2 can be further subdivided into MEN2A (Sipple syndrome) and MEN2B based on the spectrum of accompanying endocrine tumors and disorders. MTC is seen in nearly all patients with MEN2A and MEN2B and is often the first manifestation of the syndrome.[166] Patients with MEN2A may also have or develop pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%).[166] Some patients with MEN2A have lichen planus amyloidosis or Hirschsprung's disease. Most patients with MEN2B have mucosal neuromas or intestinal ganglioneuromas in addition to MTC; 50% of these patients have pheochromocytoma, but almost none have hyperparathyroidism (<1%).[166] Nearly all patients with MEN2B have Marfanoid habitus and/or poor dentition. Some patients also have ectopic lenses in the eye or very flexible joints.

MTC is a calcitonin-secreting tumor of the parafollicular or C cells of the thyroid, accounting for about 4% to 7% of thyroid cancers but about 15% of all thyroid cancer deaths. About 75% of MTC cases are sporadic, whereas approximately 25% are considered familial or hereditary. Familial MTC associated with MEN2 normally arises in the first to third decades of life, but sporadic MTC is typically diagnosed in the fourth to fifth decades of life. All types of familial MTC are typically multifocal and preceded by C-cell hyperplasia; however, sporadic MTC is usually unifocal. Familial MTC arising in the absence of other endocrine malignancies or disorders is the least aggressive, whereas MTC associated with MEN2B is the most aggressive. MEN2A, MEN2B, and familial MTC are all autosomal-dominant inherited diseases and are associated with germline mutations of the proto-oncogene, *RET*.[6,315]

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

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

Evaluation of MEN2A, MEN2B, and Familial MTC

A clinical diagnosis of MEN2A includes findings of 2 or more MEN2A-associated tumors (MTC, pheochromocytoma, or hyperparathyroidism) in a single individual or in first-degree relatives.[316,317] 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.[316,317] For patients known or suspected to have MEN2A or MEN2B, a clinical evaluation includes: 1) biochemical tests evaluating hormone levels; 2) imaging tests to localize MEN2-associated tumors; and 3) genetic counseling and testing.

Before surgical resection of MTC in these patients, basal calcitonin and carcinoembryonic antigen (CEA) levels should be measured, because these test results help guide the extent of nodal dissection required, particularly in patients with occult disease detected by screening. Patients with low calcitonin and high CEA levels usually have more aggressive tumors. Neck ultrasound of thyroid and cervical lymph nodes should also be performed to document intrathyroidal tumors and to possibly identify cervical lymph node metastases.

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

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

Genetic Counseling/Testing in MEN2

Genetic counseling and *RET* genetic testing should be offered to individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2 (see *Evaluation of MEN2 Syndromes*, above).[316,317] Genetic counseling and testing should also be offered to at-risk relatives of an individual with a known germline *RET* mutation at a very young age.[316,317] All patients with MTC should be tested for germline mutation of the *RET* oncogene even if the family history is not suggestive of a hereditary syndrome, because about 50% of patients with presumed sporadic MTC have a *de novo* germline mutation.[317]

Even with negative *RET* genetic test results, individuals with clinical diagnosis or suspicion of MEN2 should undergo regular surveillance for MEN2-associated tumors. Similarly, at-risk relatives should have MEN2 surveillance even if the affected relative had a negative test result or no genetic testing.[316] See *MEN2 Surveillance*, below.

Primary Treatment of MEN2A, MEN2B, and Familial MTC

In patients with a positive *RET* oncogene test who are otherwise asymptomatic, prophylactic thyroidectomy is performed during the first 5 years of life depending on the aggressiveness of the inherited *RET* mutation or at diagnosis,[316,318-320] 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. In addition, patients may have synchronous pheochromocytoma and MTC. In these cases, resection of pheochromocytoma should take priority over thyroidectomy.

Patients with MEN2 and familial MTC may be prone to hypoparathyroidism because the thyroid gland is often already removed prophylactically or for treatment of C-cell hyperplasia or MTC. The consensus of the panel is for 4-gland exploration (regardless of sestamibi scan results, which are frequently misleading or uninformative with regard to the number of abnormal glands) and selective resection of abnormal parathyroid glands, and for leaving normal parathyroid glands in place (marked with a clip or stitch during thyroid surgery) when possible. Subtotal parathyroidectomy is recommended when all glands appear abnormal. Some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC, while others believe the risk of hypoparathyroidism with this approach (about 6%) is too high to warrant the procedure. If a normal parathyroid gland is not preserved in situ in patients with MEN2A, it can be autotransplanted to the forearm, since recurrent primary hyperparathyroidism occurs in almost 20% of these patients. If hyperparathyroidism recurs with a documented elevated PTH level in the ipsilateral basilic vein, the tumor can be removed or subtotally resected.

Management of patients with pheochromocytoma and MEN2 is similar to that of pheochromocytoma in other settings, although the possibility of multiple (ie, bilateral) pheochromocytomas should be considered if surgical resection is being planned. A bilateral adrenalectomy may be necessary. An interesting retrospective, population-based, observational study of 563 patients with MEN2 and pheochromocytoma from 30 centers across 3 continents found that adrenal-sparing resections led to similar rates of recurrence with lower rates of adrenal insufficiency or steroid dependency (43% vs. 86%).[321] More studies are needed, however, before this approach can be routinely recommended.

MEN2 Surveillance

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

After subtotal or total parathyroidectomy, the panel recommends calcium levels be evaluated to screen for parathyroid tumors. Additional evaluation should be performed if clinically indicated.

Future Trial Design

Recent successes have shown that large randomized controlled trials studying treatments for neuroendocrine tumors can provide practice-changing results. Current recommendations for clinical trials in neuroendocrine tumors include the following[322]:

- Pancreatic neuroendocrine tumors should be studied separately from tumors in other locations.
- Well-differentiated and poorly differentiated neuroendocrine carcinomas should be studied in separate trials.
- PFS is an appropriate primary endpoint for phase III trials and many phase II trials.

- Trials studying treatment for hormonal symptoms are as critical as those assessing effects on tumor progression and should include quality-of-life endpoints.

Rigorous studies will allow continued progress in the development of improved treatments for patients with neuroendocrine tumors.

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