National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroendocrine and Adrenal Tumors

Version 4.2018 — January 07, 2019

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*Manisha H. Shah, MD/Chair †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Matthew H. Kulke, MD/Chair †
Dana-Farber/Brigham and Women's Cancer Center

*Whitney S. Goldner, MD/Vice Chair ð
Fred & Pamela Buffett Cancer Center

Al B. Benson, III, MD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Emily Bergsland, MD †
UCSF Helen Diller Family Comprehensive Cancer Center

Jordan D. Berlin, MD †
Vanderbilt-Ingram Cancer Center

Lawrence S. Blaszkowsky, MD †
Massachusetts General Hospital Cancer Center

Jennifer Chan, MD †
Dana-Farber/Brigham and Women's Cancer Center

Jennifer Eads, MD † Þ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Paul F. Engstrom, MD †
Fox Chase Cancer Center

Paul Fanta, MD †
UC San Diego Moores Cancer Center

Thomas Giordano, MD, PhD ≠
University of Michigan Comprehensive Cancer Center

Thorvardur R. Halfdanarson, MD Þ †
Mayo Clinic Cancer Center

Daniel Halperin, MD †
The University of Texas MD Anderson Cancer Center

Jin He, MD, PhD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Martin J. Heslin, MD ¶
University of Alabama at Birmingham Comprehensive Cancer Center

Gregory P. Kalemkerian, MD/Liaison †
University of Michigan Comprehensive Cancer Center

Fouad Kandeel, MD, PhD ð
City of Hope National Medical Center

Sajid A. Khan, MD ¶
Yale Cancer Center/Smilow Cancer Hospital

Wajih Zaheer Kidwai, MD †
Yale Cancer Center/Smilow Cancer Hospital

Pamela L. Kunz, MD †
Stanford Cancer Institute

Boris W. Kuvshinoff, II, MD, MBA ¶
Roswell Park Comprehensive Cancer Center

Christopher Lieu, MD †
University of Colorado Cancer Center

Robert Merritt, MD/Liaison ¶
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Gareth Morris-Stiff, MD, PhD ¶
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Venu G. Pillarisetty, MD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Leonard Saltz, MD † Þ
Memorial Sloan Kettering Cancer Center

Julie Ann Sosa, MD ¶ ð
Duke Cancer Institute

Jonathan R. Strosberg, MD †
Moffitt Cancer Center

Craig A. Sussman, MD Þ
Vanderbilt-Ingram Cancer Center

Nikolaos A. Trikalinos, MD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Nataliya A. Uboha, MD, PhD †
University of Wisconsin Carbone Cancer Center

Jonathan Whisenant, MD †
Huntsman Cancer Institute at the University of Utah

Terence Wong, MD ϕ
Duke Cancer Institute

James C. Yao, MD †
The University of Texas MD Anderson Cancer Center

NCCN
Jennifer Burns
Ndiya Ogba, PhD
Griselda Zuccarino-Catania, PhD

[NCCN Guidelines Panel Disclosures]

¶ Surgery/Surgical oncology
† Medical oncology
ð Endocrinology
≠ Pathology
Þ Internal medicine
ϕ Nuclear medicine
* Discussion Section Writing Committee

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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/clinicians.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines for Patients® are available at www.nccn.org/patients.

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Updates in Version 4.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2018 include:

MS-1

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

Updates in Version 3.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 2.2018 include:

PHEO-2

- **The following treatment option has been revised for locally unresectable, and metastatic pheochromocytoma/paraganglioma: "*HSA iobenguane I 131 or other* I131-MIBG (requires prior positive MIBG scan ~~with dosimetry~~)."**
- **Footnote "k" added: "HSA iobenguane I 131 is an FDA approved option."**

Updates in Version 2.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 1.2018 include:

Global

- **Removed "if equivocal CT findings" where somatostatin receptor-based imaging is recommended.**
- **Footnote revised: "*Gallium-68 dotatate (^{68}Ga-dotatate) PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status.* PET/CT of skull base to mid-thigh; CT with IV contrast when possible..."**
- **Footnote revised: "If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. *For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E."***
- **Footnote added where ^{177}Lu-dotatate is recommended: "See Principles of Peptide Receptor Radionuclide Therapy (PRRT) with lutetium 177 Lu-dotatate (^{177}Lu-Dotatate) (NE-E)."**

NET-8

- **Added to primary therapy with octreotide or lanreotide: "*(if somatostatin receptor positive and/or hormonal symptoms)."* (Also on NET-9)**
- **Added the following option for patients with clinically significant tumor burden and low grade (typical) bronchopulmonary/thymus tumors, or those with evidence of progression: "Consider PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive and progression on octreotide/lanreotide)." (Also on NET-9 for intermediate grade [atypical] bronchopulmonary/thymus tumors)**
- **Moved treatment recommendations for those with intermediate grade (atypical) disease, and those with multiple lung nodules or tumorletes and evidence of DIPNECH to NET-9.**

NET-10

- **Added the following option for patients with unresectable locoregional advanced disease of the GI tract and/or distant metastases, if disease progression following therapy with octreotide or lanreotide: "PRRT with ^{177}Lu-dotatate, if somatostatin receptor positive (category 1 for mid-gut tumors)."**
- **Removed "consider" from the following options for those with disease progression following therapy with octreotide or lanreotide: "Hepatic directed therapy for hepatic-predominant disease; Interferon alfa-2b (category 3); Cytotoxic chemotherapy (category 3), if no other options feasible."**
- **Added footnote "hh": "Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive." (Also on NET-11)**

NET-11

- **For those with poorly controlled carcinoid syndrome, revised last option: "Consider other systemic therapy *based on disease site."***

PanNET-1

- **Footnote "f" revised: "Observation can be considered for small (<1 cm) *low-grade*, incidently discovered tumors. ~~and low-grade tumors~~. Decision based..."**

PanNET-7

- **Added the following option for patients with unresectable locoregional advanced pancreatic NET and/or distant metastases, if disease progression following therapy with octreotide or lanreotide: "PRRT with ^{177}Lu-dotatate, if somatostatin receptor positive."**

PHEO-2

- **Added the following options for locally unresectable pheochromocytoma/paraganglioma or those with distant metastases: "PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive)."**
- **Moved surveillance recommendations onto PHEO-3.**

NE-D (1 of 3)

- **Updated table to include PRRT with ^{177}Lu-dotatate. (Also on NE-D, 2 of 3)**

NE-E

- **New section added, titled "Principles of Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-dotatate."**

Continued

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Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

Global

- Changed the name of the guidelines to "NCCN Guidelines for Neuroendocrine *and Adrenal* Tumors."
- Added "if equivocal CT findings" where somatostatin receptor-based imaging is recommended.
- Gallium-68 dotatate PET/CT has been made the preferred somatostatin receptor-based imaging modality.
- Footnote revised: "PET/CT of skull base to mid-thigh; ***CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs."***

NET-2

- Under evaluation for tumors >2 cm or incomplete resection, the following option has been added: "Consider somatostatin receptor-based imaging if equivocal CT findings (ie, gallium-68 dotatate PET/CT [preferred] or somatostatin receptor scintigraphy)"

NET-3

- Small, completely resected incidental tumors:
  - New pathways have been added for negative margins versus indeterminate margins. For indeterminate margins:
    - ◊ Endoscopy has been added to assess for residual disease for those with indeterminate margins and low-grade disease.
    - ◊ Refer to treatment pathway for all other rectal tumors if positive margins or intermediate-grade disease.
- All other rectal tumors:
  - Evaluation options revised: ~~Endo~~Rectal MRI or ~~EUS~~ endorectal ultrasound
  - Surveillance: "EUS" changed to "Endorectal ultrasound"

NET-4

- Footnote "k" revised: *"*Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. *To confirm diagnosis,* it should ideally be checked..."

NET-5

- Added corresponding stage of disease to each pathway.
- For locoregional disease, following incomplete resection and/or positive margins:
  - Options for low-grade disease were revised: "***Consider observation or*** consider RT (category 3) ± ***systemic therapy"***
  - Options for intermediate-grade disease revised: "Consider ***observation or consider RT ± systemic therapy*** ~~***cisplatin/etoposide or carboplatin/ etoposide***~~
- For locoregional, unresectable disease, new pathways added for low-grade and intermediate-grade tumors:
  - Options for low grade include: "Consider observation or consider systemic therapy or consider RT (category 3) ± systemic therapy"
  - Options for intermediate grade include: "Consider RT ± systemic therapy or consider systemic therapy"
- Footnote "r" added: "There is a gap issue and therapeutic challenge in managing patients who fall into this category due to a lack of data. However, the panel suggests use of these options in select cases or as needed."

NET-6

- Under evaluation:
  - Added: "Other biochemical evaluation as clinically indicated."
  - Removed "chromogranin A (category 3)"
- Clarified which pathways to follow for localized, locoregional/resectable, locoregional/unresectable, and metastatic disease.
- Adjuvant therapy options revised for:
  - Locoregional/resectable disease, intermediate grade
  - Locoregional/unresectable disease, low grade
  - Locoregional/unresectable disease, intermediate grade
- Footnote "u" added: "Bronchopulmonary neuroendocrine tumors are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1)."
- Footnote "v" added: "Systemic therapy options include those recommended for locoregionally advanced/metastatic disease. See Principles of Systemic Anti-Tumor Therapy (NE-D)."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

NET-7

- If >1 y postresection, timing of surveillance changed to every 12–24 mo.
- Footnote "w" revised: "Earlier, if symptoms. *If initial scans are negative, the frequency of follow-up scans may decrease. For high-grade tumors, more frequent surveillance may be appropriate."*

NET-8

- Evaluation, last sub-bullet revised: "Biochemical workup for Cushing's syndrome if ~~clinically indicated~~ *not previously done."*
- Treatment options revised for those with clinically significant tumor burden and low grade (typical) *or evidence of disease progression: "*Consider: *Observation if asymptomatic or* octreotide or lanreotide or everolimus ~~± octreotide or lanreotide or Temozolomide ± octreotide or lanreotide~~"
- Treatment options revised for intermediate grade (atypical): "Consider: *Observation for select patients or* octreotide or lanreotide or everolimus ~~± octreotide or lanreotide or Temozolomide ± octreotide or lanreotide~~ *or chemotherapy (for select patients)."*
- Added temozolomide as a chemotherapy option in footnote "bb".
- Added to fourth diagnosis: "Multiple lung nodules *or tumorlets* and..."
- Added after primary treatment, "Consider changing therapy if progression on first-line therapy."
- Timing of surveillance changed to every 12–*24* mo for those with multiple lung nodules or tumorlets.
- Footnote "z" added: "Neuroendocrine tumors are highly heterogeneous and all elements need to be considered (eg, burden of disease, symptoms, histopathology, rate of growth) when determining the best course of treatment."
- Footnote "aa" added: "Observation can be considered for tumors on the lower end of the spectrum."
- Footnote "cc" revised: "If disease progression, treatment with octreotide or lanreotide *should be continued in patients with functional tumors and* may be ~~continued~~ *used* in combination with any of the subsequent options."
- Changed heading: "Locoregional *advanced* ~~unresectable~~..." (Also on NET-9 and PanNET-7)

NET-9

- First option revised for those with disease progression: ~~Consider~~ Everolimus (10 mg/d)
- Footnote "ee" revised: "Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated. *However, taking a careful history is recommended as surgery may be an option for asymptomatic patients with previous, intermittent obstructions. "*
- Footnote removed: "Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive."

NET-10

- Evaluation
  - First bullet revised: "Biochemical evaluation with 24-hour urine *or plasma* 5-HIAA."
  - Second bullet added: "Echocardiogram"
  - Third bullet replaced prior imaging recommendations: "Imaging to assess disease progression (see NET-8 or NET-9)"
- Options revised for those with poorly controlled carcinoid syndrome: "For any persistent symptoms (ie, flushing, diarrhea) consider additional therapy for disease control: *Consider hepatic arterial embolization ± cytoreductive surgery for hepatic predominant disease or consider telotristat (250 mg, by mouth 3 times a day) or consider other systemic therapy* ~~and/or for persistent diarrhea, consider telotristatgg in combination with octreotide or lanreotide~~"
- Surviellance, first bullet revised: "Echocardiogram every 2–3 y *or as clinically indicated*"
- Footnote "hh" added: "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." (Also removed from NE-D, 1 of 3)

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

NET-10 (continued)
- Footnote "jj" added: "Safety and effectiveness of everolimus in the treatment of patients with carcinoid syndrome have not been established.
- Footnote removed: "Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive."

Neuroendocrine Tumors of the Pancreas

PanNET-1
- Recommended evaluation, added: "Consider testing for inherited genetic syndromes." (Also on PanNET-2 thru PanNET-5 under "as appropriate")
- For small tumors, "observation *for select cases"* has been moved to the top of the management options, and footnote "f" has been revised to clarify when observation is recommended: "Observation can be considered ~~in select cases:~~ *for* small *(<1 cm)* incidently discovered tumors*, and low-grade tumors.* Decision based on estimated surgical risk, site of tumor, and patient comorbidities."
- Footnote "d" revised: "For all patients with PanNET, evaluate personal and family history for possibility of MEN1 ~~and~~ *or other hereditary syndromes as appropriate."*

PanNET-2
- Management of locoregional, distal disease revised: "Distal pancreatectomy ± + splenectomy + *regional nodes*"
- Footnote removed: "There is some disagreement among panel members regarding the role of splenectomy in all cases."
- Footnote "j" revised: "*If a diagnosis has not been confirmed by biopsy, serum gastrin may be a helpful diagnostic tool.* Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. *To confirm diagnosis,* it should ideally..."

PanNET-3
- Evaluation, second bullet revised: "Serum insulin ~~(with concurrent hypoglycemia)~~, pro-insulin, and c-peptide levels *during concurrent hypoglycemia*"
- Moved somatostatin receptor-based imaging under evaluation, "As appropriate."

PanNET-5
- For locoregional disease:
  - Removed "stabilize glucose levels"
  - After "correct electrolyte imbalance" added "and dehydration".

Neuroendocrine Tumors of Unknown Primary

NUP-1
- Removed footnote: "Sequence of initial workup may vary."

Adrenal Gland Tumors

AGT-1
- Removed footnote: "Screening for pheochromocytoma should be considered for asymptomatic patients if radiologic findings are suspicious and surgery is planned."

AGT-2
- Prior or current malignancy with risk/suspicion of adrenal metastasis:
  - First evaluation bullet removed: "rule out pheochromocytoma."
  - Additional evaluation revised: "Consider image-guided needle biopsy if *clinical suspicion of* ~~not~~ pheochromocytoma *is low and metanephrines are normal*"
- Footnote removed: "Can proceed with adrenal biopsy if the plasma or urine fractionated metanephrines is normal is less than 2 times the upper limit of normal and clinical suspicion for pheochromocytoma is low."

AGT-3
- This page has been significantly revised. Recommendations for benign-appearing lesions have been removed and footnote "h" has been added: "For benign-appearing lesions, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome: Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

AGT-4
- This page has been significantly revised. Recommendations for benign-appearing lesions have been removed and footnote "j" has been added: "For benign-appearing lesions, refer to the AACE/ACE guidelines for the management of adrenal incidentalomas: Zeiger MA, Thompson GB, Duh QY, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2009;15 Suppl 1:1-20."

AGT-5
- Clinical diagnosis revised: "~~Adrenal~~ *Adrenocortical* carcinoma"
- Workup added: "Genetic testing"; and "consider MSI or MMR testing."
- Under treatment for metastatic disease, third bullet added: "Consider local therapy (ie, RFA, RT)"
- Footnote "n" added: "Testing for gene mutations associated with Lynch syndrome."
- Footnote "o" added: "Pembrolizumab should be considered for mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options."

Pheochromocytoma

PHEO-2
- For locally unresectable disease, first treatment revised: "Continue medical therapy for secreting tumors ~~and consider referral to multidisciplinary center~~; *and..."*
- For patients with distant metastases, first option added: "Observe if asymptomatic."

Poorly Differentiated Carcinomas/Large or Small Cell

PDNEC-1
- Revised tumor type to clarify it refers to "extrapulmonary" disease; and added "unknown primary (poorly differentiated)" to the list of options.
- Revised the primary treatment options for resectable disease: "*Therapy options depend on sites of disease. Options may include:* Resection + *adjuvant* chemotherapy ± *RT; Neoadjuvant chemotherapy ± RT + resection; Chemotherapy alone; RT alone;* ~~Consider~~ Definitive chemoradiation (See NCCN Guidelines for Small Cell Lung Cancer)
- Revised primary treatment options for locoregional unresectable disease: "*Concurrent or sequential* RT + chemotherapy *or chemotherapy."*
- "FDG-PET" removed from surveillance options.
- Footnote "f" revised: *"Chemotherapy options include* small cell lung cancer regimens, *FOLFOX, FOLFIRI, and temozolomide ± capecitabine*. ~~such as cisplatin/etoposide or carboplatin/etoposide are generally recommended as primary treatment.~~ However..."

Multiple Endocrine Neoplasia, Type 1

MEN1-1
- First bullet revised: "A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors *in a single patient*..."

MEN1-2
- Recommended evaluation options revised for parathyroid disease (Also on MEN2-2)
  - "25-OH vitamin D" removed
  - "PTH" added
- "As appropriate" evaluation options revised (Also on MEN2-2):
  - Second bullet: "Parathyroid sestamibi *with SPECT* scan"
  - Added "4-D CT"
  - Footnote "f" added: "Preference of scan will depend on institutional practice/protocol."
  - Footnote removed: "A sestamibi scan may not accurately depict the total number of abnormal glands. Patients should receive 4-gland exploration regardless of sestamibi scan results."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

MEN1-3

- Added annual PTH to parathyroid surveillance and removed from second column.
- Pituitary, first bullet: Changed "brain MRI" to "pituitary or sella MRI."
- Bronchial/thymic, added MRI as an option with footnote "j": "For prolonged surveillance, studies without radiation are preferred."
- Footnote "i" added for surveillance: "Consider referral to an endocrinologist."

Multiple Endocrine Neoplasia, Type 2

MEN2-2

- Treatment revised for parathyroid tumors: "*Parathyroidectomy* ~~Four-gland identification: Selective parathyroid resection~~"
- Surveillance for parathyroid tumors. first bullet revised: "*Evaluate* calcium ~~evaluation~~, PTH, *calcitonin, and metanephrines."*

Principles of Pathology for Diagnosing and Reporting of NET

NE-A (1 of 3)

- Under optional information, second bullet removed: "Immunohistochemical staining for specific peptide markers."
- Table 1 revised:
  - Row added for well-differentiated, high-grade NET
  - Column added for Pancreatic NET
  - Reference added: "Lloyd RV, Osamaru RY, Klöppel G, et al. WHO Classification of Tumours of Endocrine Organs. IARC, Lyon, 2017."
  - Information below the table has been removed.
- Footnote "b" added: "Similar classification for GI NET is expected."

NE-A (2 of 3)

- Under functional status, last line removed: "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. "
- Under immunohistochemistry and other ancillary techniques, last bullet revised: "...thyroid transcription factor 1 (TTF-1); intestinal ~~or pancreatic~~ origin by CDX2..."
- Mitotitc rate, first bullet revised: " Mitotic rate should be based on counting mitoses in ~~at least 40 fields at 40x magnification in~~ the areas of highest mitotic density..."
- Ki-67 Index, the following bullets have been removed:
  - "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. "
  - "Although the 2004 WHO does not utilize Ki-67 as part of its grading system for thymus and lung NETs, it may be quite useful in the setting of small biopsies and cytology specimens when there is insufficient tissue for an accurate mitotic count. The Ki-67 index cut-points are not currently well-defined but tend to parallel those proposed in GEP-NETs, and generally the data suggest that Ki-67 proliferation rates of <20% exclude small cell lung carcinoma."
  - Reference removed: "Rekhtman N. Neuroendocrine tumors of the lung. An Update. Arch Pathol Lab Med 2010;134:1628-1638."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for Neuroendocrine Tumors from Version 3.2017 include:

Principles of Biochemical Testing

NE-B (1 of 3)

- NET of GI tract, lung, and thymus (carcinoid tumors), second bullet revised under testing: "24-hour urine *or plasma* 5-HIAA"

NE-B (2 of 3)

- Added footnote: "For additional information on biochemical testing for Cushing's syndrome, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome: Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831."

Surgical Principles for Management of NET

NE-C

- First bullet, revised: "...Non-functional PanNETs 1–2 cm in size have a small (7%–26%), but measurable risk of lymph node metastases; therefore, *serial imaging is recommended and* lymph node resection should be considered. *For prolonged surveillance, imaging studies without radiation are preferred."*

Principles of Systemic Anti-Tumor Therapy

NE-D (1 of 3)

- Last bullet, link added to new page, "management of carcinoid syndrome."
- Recommendations for carcinoid syndrome have been removed. See NET-10.
- Octreotide LAR dose changed from 20–30 mg to 30 mg intramuscular injection, monthly.
- Revised types of lung/thymus NET for which the systemic therapy options apply: "Options for *Incompletely Resected,* Locoregionally Advanced and/or Metastatic NET of the Lung/Thymus."
- Replaced "± octreotide or lanreotide" with footnote "b": "If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the systemic therapy options."
- Footnote "a" added: "Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67). There are 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."

NE-D (3 of 3)

- References added:
  - Pavel ME, Baudin E, Oberg KE, et al. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Ann Oncol 2017;28(7):1569-1575.
  - Pavel ME, Singh S, Strosberg JR, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18(10): 1411-1422.

Staging

ST-1

- Staging tables have been updated based on the AJCC 8th edition.

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 advanced disease and/or distant metastases
  - Bronchopulmonary/thymus (See NET-8)
  - GI Tract (See NET-10)
- Carcinoid Syndrome (See NET-11)

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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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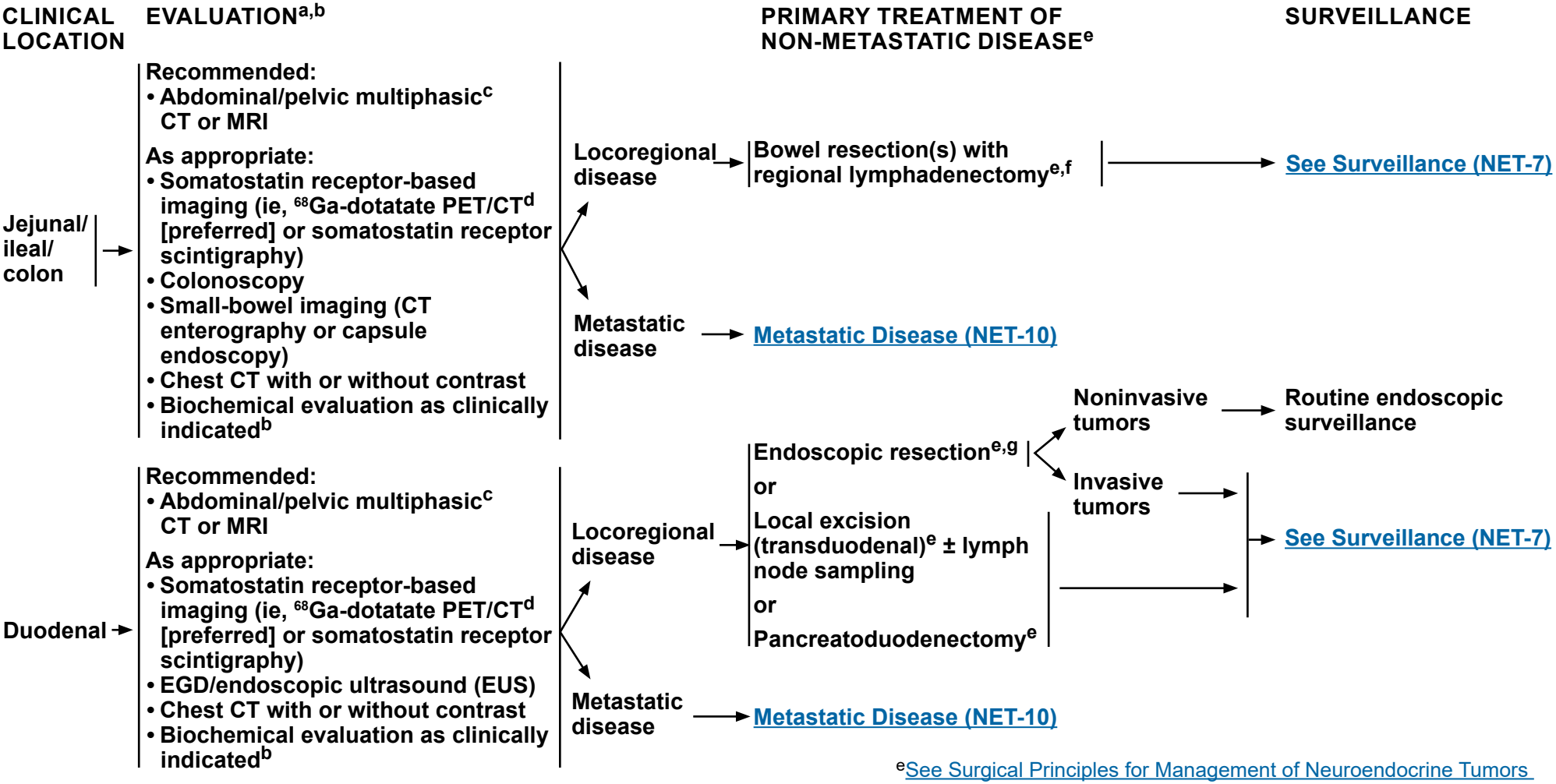

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with IV contrast.
[d] Gallium-68 dotatate (^{68}Ga-dotatate) PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.
[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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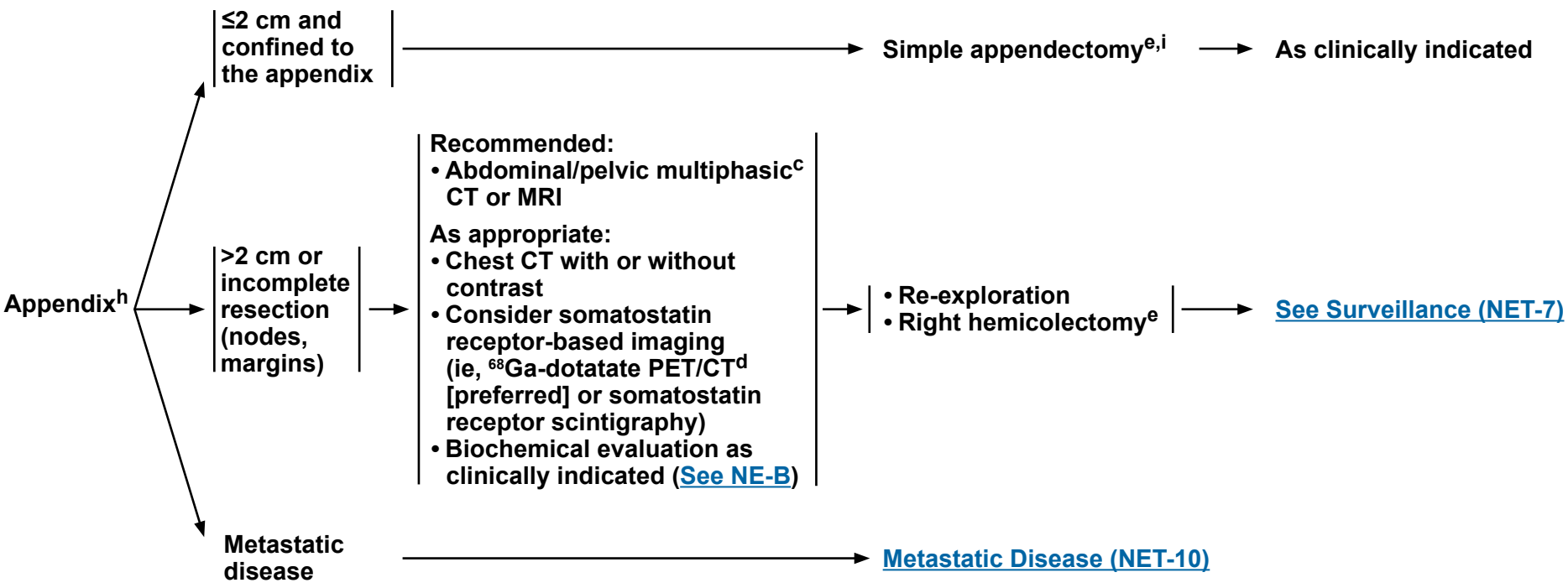

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[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h] Some appendiceal neuroendocrine tumors will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. 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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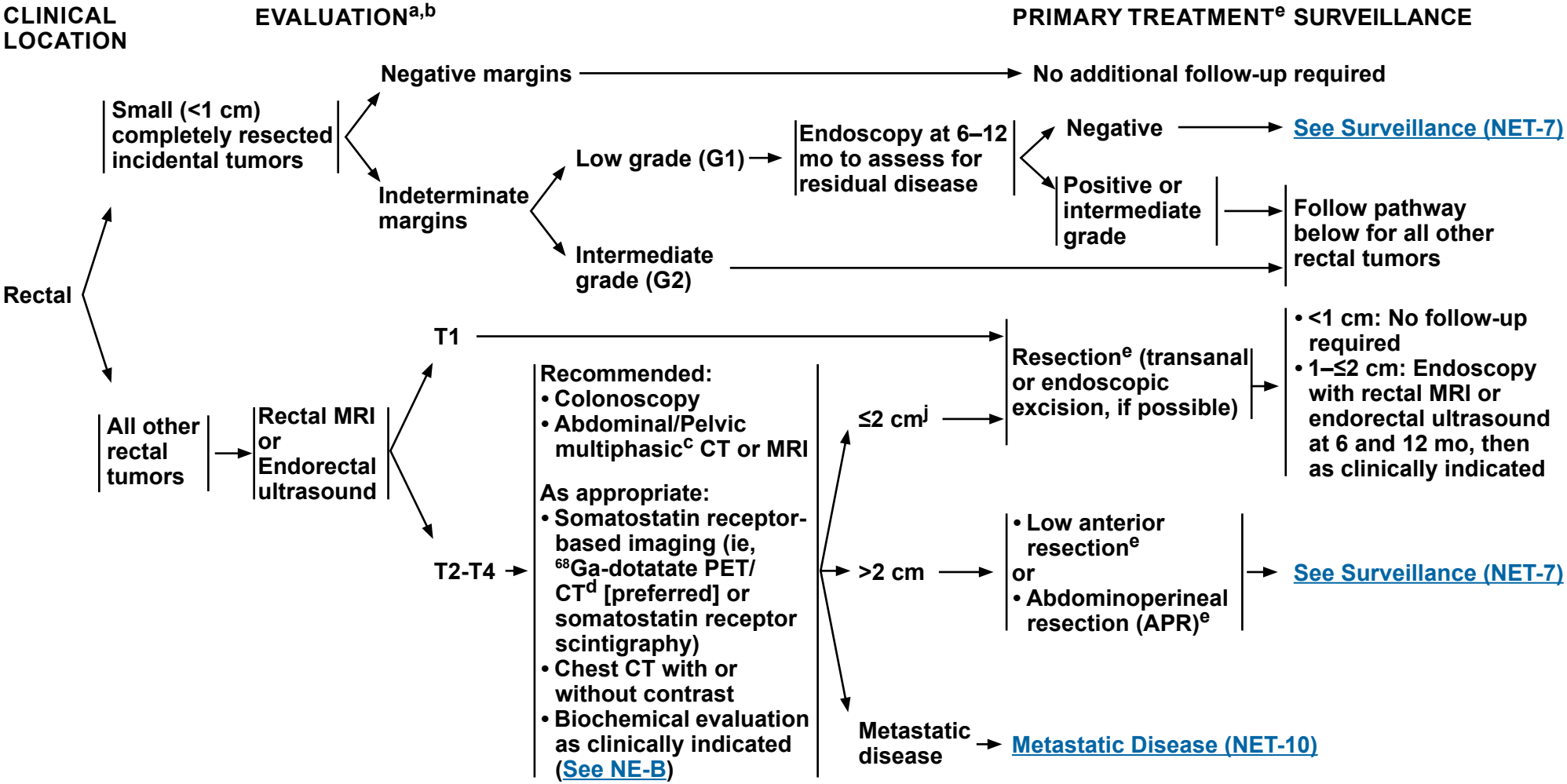

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[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[j] For 1- to 2-cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.

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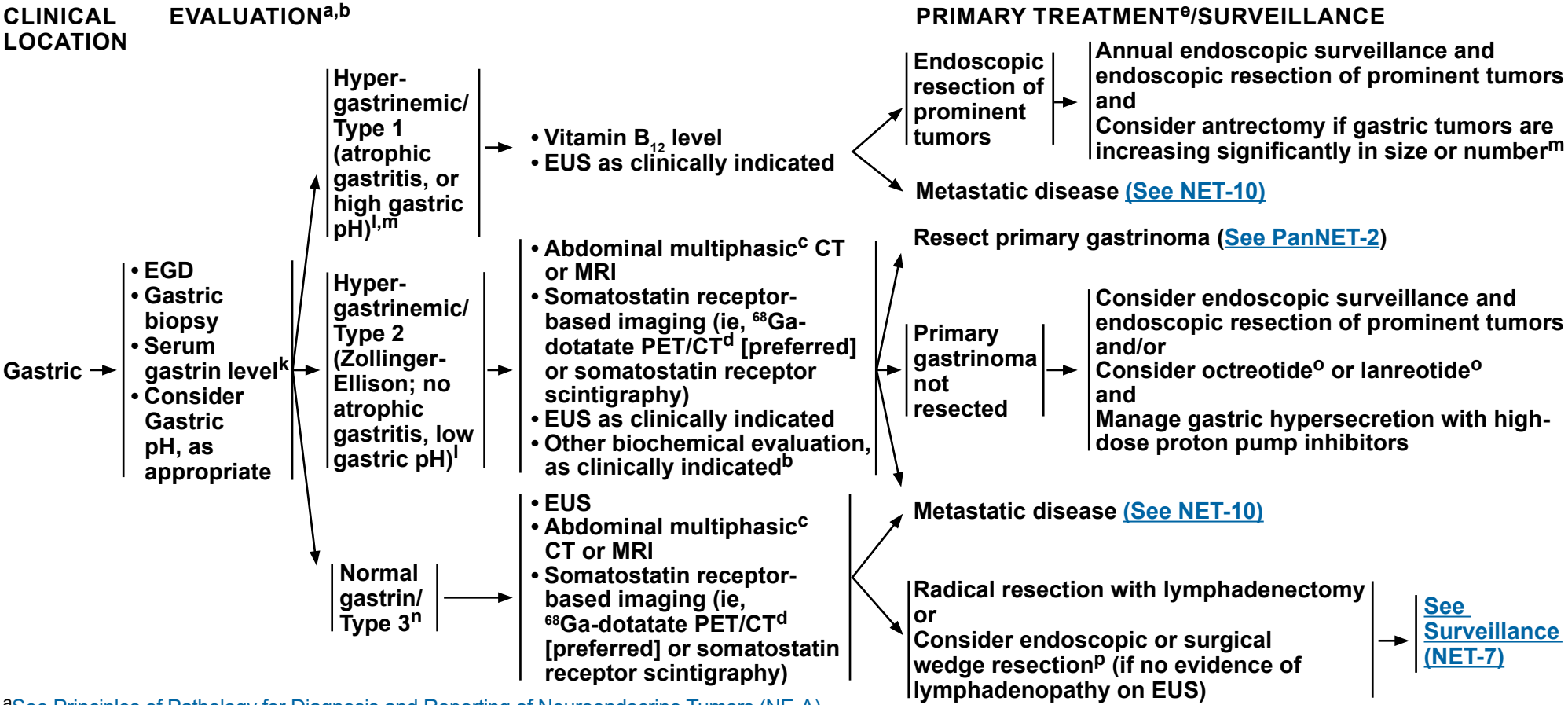

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[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with IV contrast.
[d] 68Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[k] Serum gastrin can be falsely elevated with proton pump inhibitor (PPI) use. To confirm diagnosis, 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, NET-10.
[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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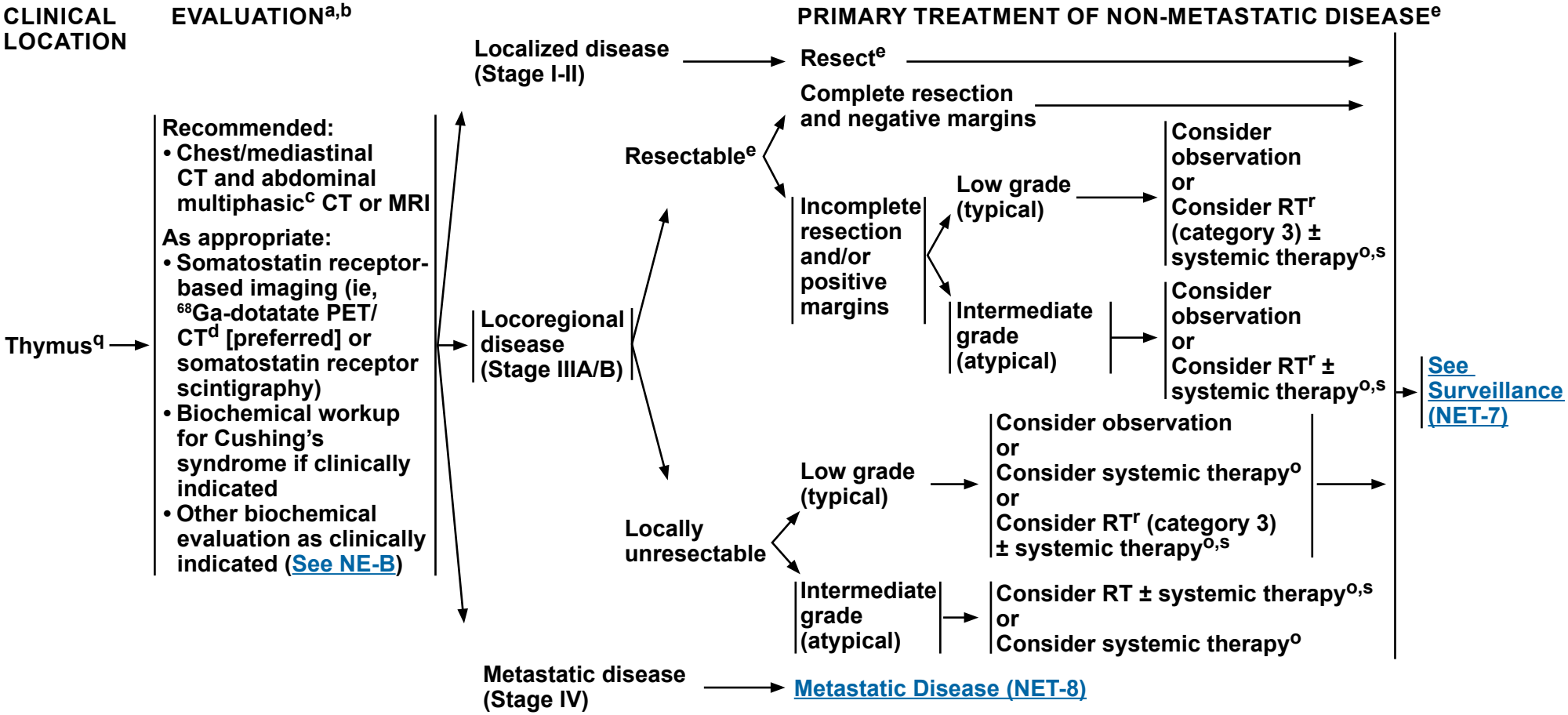

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[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[q] Thymic neuroendocrine tumors are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1)
[r] There is a gap issue and therapeutic challenge in managing patients who fall into this category due to a lack of data. However, the panel suggests use of these options in select cases or as needed.
[s] Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67). There are 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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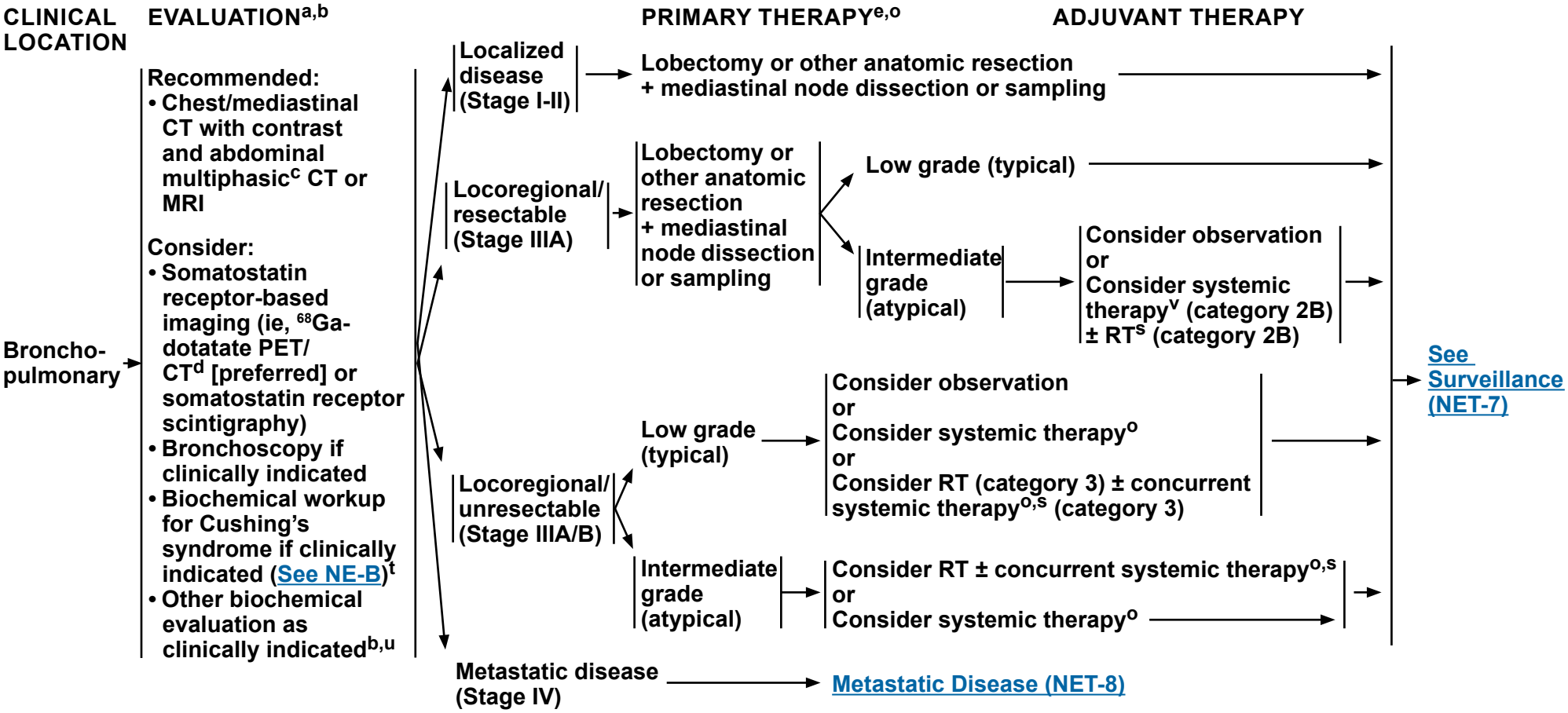

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[t] If Cushing's syndrome suspected, assess for and treat ectopic sources of ACTH production.
[u] Bronchopulmonary neuroendocrine tumors are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[v] Systemic therapy options include those recommended for locoregionally advanced/ metastatic disease. See Principles of Systemic Anti-Tumor Therapy (NE-D).

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SURVEILLANCE[c,w,x]
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 12–24 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[y]** →

RECURRENT DISEASE

MANAGEMENT OF RECURRENT DISEASE[e]

See Management of Bronchopulmonary/Thymus Locoregional Advanced Disease and/or Distant Metastases (NET-8)
or
See Management of Gastrointestinal Tract Locoregional Advanced Disease and/or Distant Metastases (NET-10)
or
See Management of Carcinoid Syndrome (NET-11)

[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with IV contrast.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[w] Earlier, if symptoms. If initial scans are negative, the frequency of follow-up scans may decrease. For high-grade tumors, more frequent surveillance may be appropriate.
[x] Somatostatin receptor-based imaging and FDG-PET/CT scan are not recommended for routine surveillance.
[y] In select cases, resection may be considered.

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

BRONCHOPULMONARY OR THYMUS

EVALUATION[b,c]

Locoregional advanced 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, ^{68}Ga-dotatate PET/CT[d] [preferred] or somatostatin receptor scintigraphy)**
  - **FDG-PET/CT for atypical histology**
  - **Biochemical workup for Cushing's syndrome if not previously done (See NE-B)[t]**

TREATMENT[o,z]

Asymptomatic, low tumor burden and low grade (typical) → **Observe or Octreotide or lanreotide (if somatostatin receptor positive imaging and/or hormonal symptoms)** → **Chest CT with contrast and abdominal/pelvic multiphasic[c] CT or MRI every 3–6 mo**

Clinically significant tumor burden and low grade (typical) or Evidence of progression → **Consider observation if asymptomatic or Consider octreotide or lanreotide (if somatostatin receptor positive imaging and/or hormonal symptoms) or Consider everolimus or Consider peptide receptor radionuclide therapy (PRRT) with lutetium 177 Lu dotatate (^{177}Lu-dotatate) (if somatostatin receptor positive imaging and progression on octreotide/lanreotide)[aa]** → **Consider changing therapy if progression on first-line therapy[o,bb]**

Intermediate grade (atypical) → See Treatment (NET-9)

Multiple lung nodules or tumorlets and evidence of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) → See Treatment (NET-9)

[b] See Principles of Biochemical Testing (NE-B).
[c] Multiphasic imaging studies are performed with IV contrast.
[d] ^{68}Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible.PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.
[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 suspected, assess for and treat ectopic sources of ACTH production.
[z] Neuroendocrine tumors are highly heterogeneous and all elements need to be considered (eg, burden of disease, symptoms, histopathology, rate of growth) when determining the best course of treatment.
[aa] See Principles of Peptide Receptor Radionuclide Therapy (PRRT) with lutetium 177 Lu-dotatate (^{177}Lu-Dotatate) (NE-E).
[bb] If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E.

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MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES[e,o]
BRONCHOPULMONARY OR THYMUS

TREATMENT[o,z]

Intermediate grade (atypical) →
- **Consider observation for select patients[cc]**
- **or**
- **Consider octreotide or lanreotide (if somatostatin receptor positive imaging and/or hormonal symptoms)**
- **or**
- **Consider everolimus**
- **or**
- **Consider PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive imaging and progression on octreotide/lanreotide)[aa]**
- **or**
- **Consider chemotherapy[dd] (for select patients)**

→ **Consider changing therapy if progression on first-line therapy[o,bb]**

Multiple lung nodules or tumorlets and evidence of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) →
- **Observe**
- **±**
- **Octreotide or lanreotide (if somatostatin receptor positive imaging and/or hormonal symptoms)**

→ **Chest CT (without contrast) every 12–24 mo or for new symptoms**

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

[z] Neuroendocrine tumors are highly heterogeneous and all elements need to be considered (eg, burden of disease, symptoms, histopathology, rate of growth) when determining the best course of treatment.

[aa] See Principles of PRRT with ^{177}Lu-Dotatate (NE-E).

[bb] If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E.

[cc] Observation can be considered for tumors on the lower end of the spectrum.

[dd] For primary therapy, cisplatin/etoposide, carboplatin/etoposide, or temozolomide can be considered for intermediate-grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

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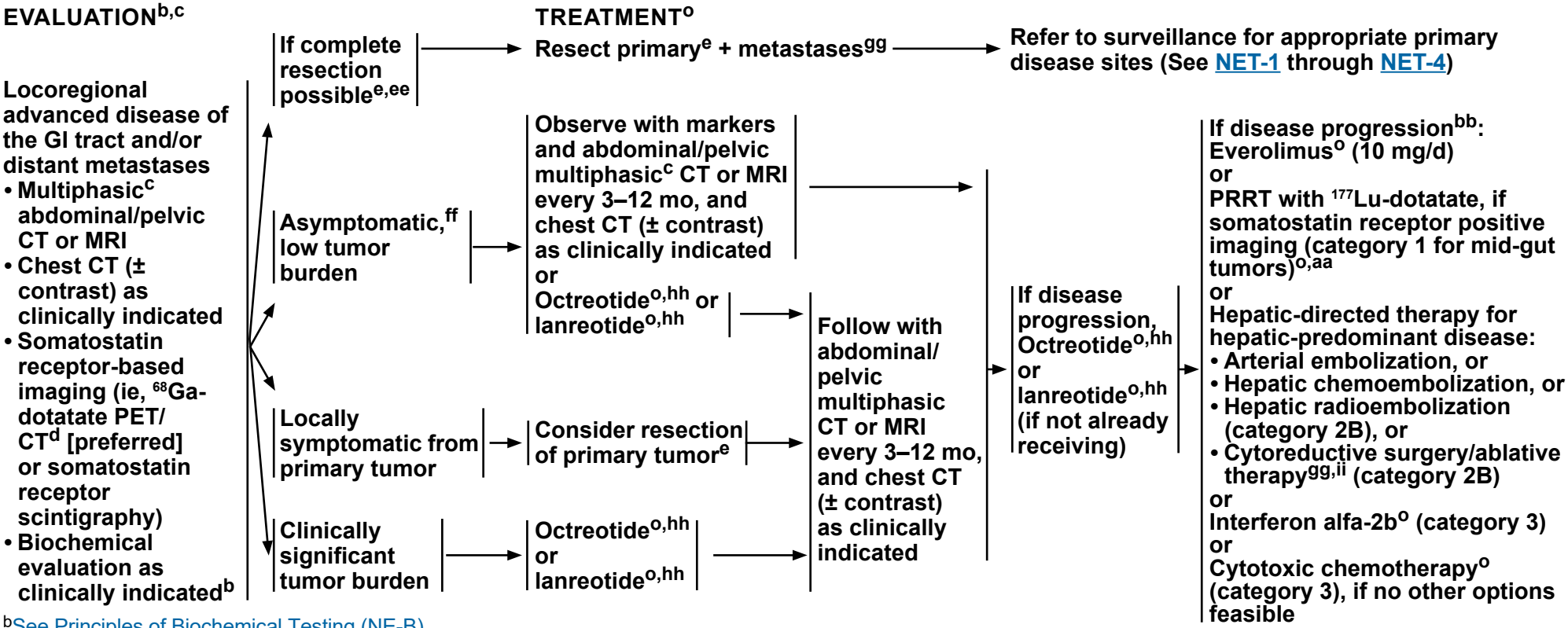
MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES[c]



[b] See Principles of Biochemical Testing (NE-B).
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[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[aa] See Principles of PRRT with 177Lu-Dotatate (NE-E).
[bb] If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with 177Lu-dotatate, see NE-E.
[ee] Noncurative debulking surgery might be considered in select cases.
[ff] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated. However, taking a careful history is recommended as surgery may be an option for asymptomatic patients with previous, intermittent obstructions.
[gg] 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.
[hh] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[ii] Only if near complete resection can be achieved.

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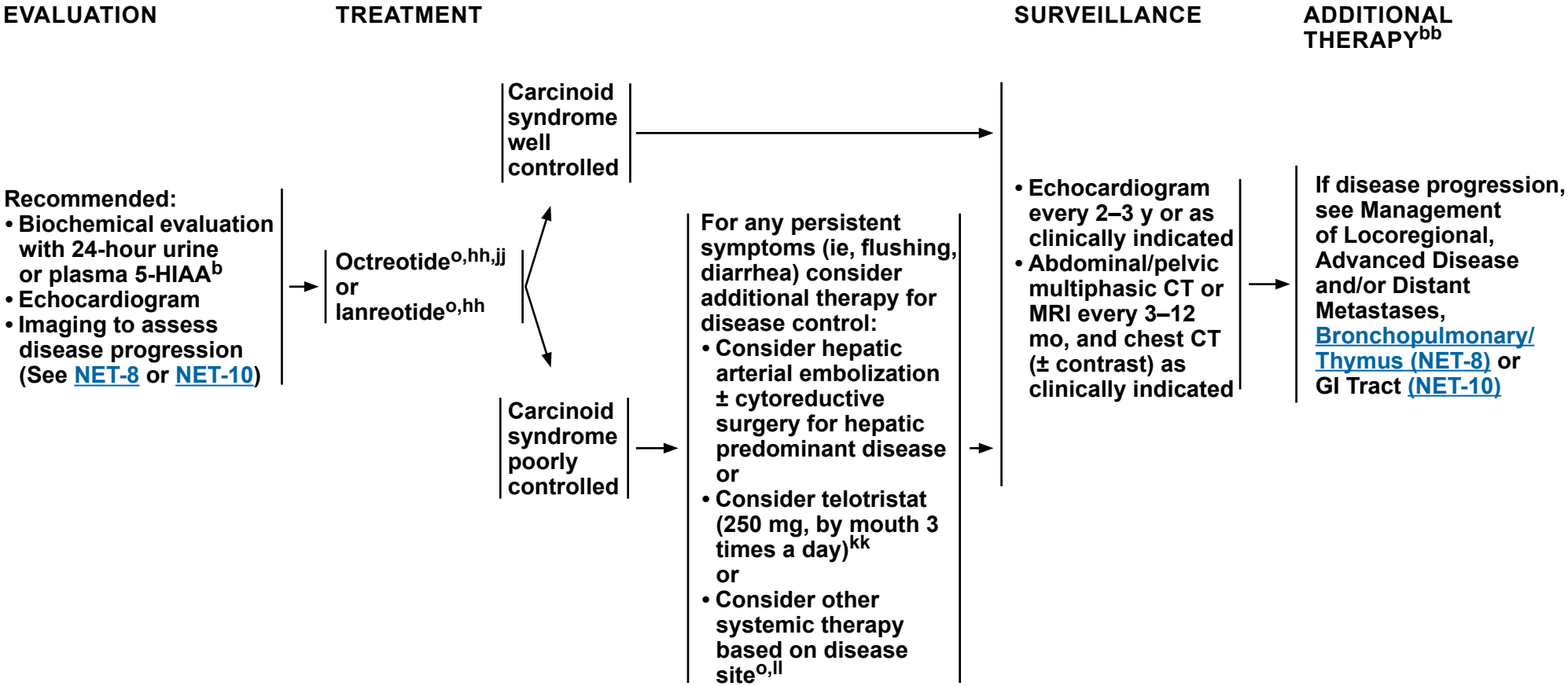
CARCINOID SYNDROME



[b] See Principles of Biochemical Testing (NE-B).
[o] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[bb] If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E.
[hh] Treatment with octreotide or lanreotide will likely only benefit those patients who are somatostatin receptor positive.
[jj] 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. For details on the administration of short-acting and/or long-acting octreotide with ^{177}Lu-dotatate, see NE-E.
[kk] Telotristat is not indicated for flushing due to poorly controlled carcinoid syndrome.
[ll] Safety and effectiveness of everolimus in the treatment of patients with carcinoid syndrome have not been established.

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NCCN Guidelines Version 4.2018
Neuroendocrine Tumors of the Pancreas

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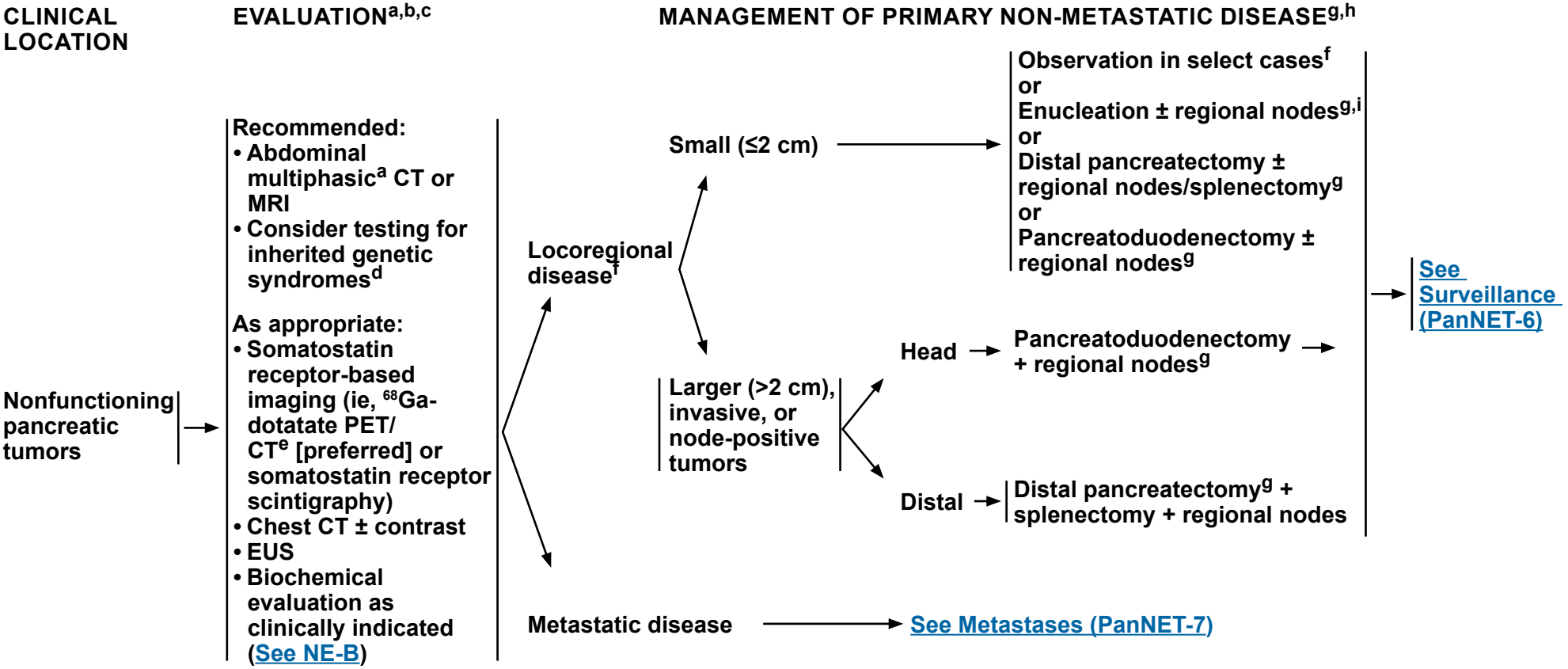

[a]Multiphasic imaging studies are performed with IV contrast.

[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 or other hereditary syndromes as appropriate. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).

[e] 68Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.

[f]Observation can be considered for small (<1 cm) low-grade, incidently discovered tumors. 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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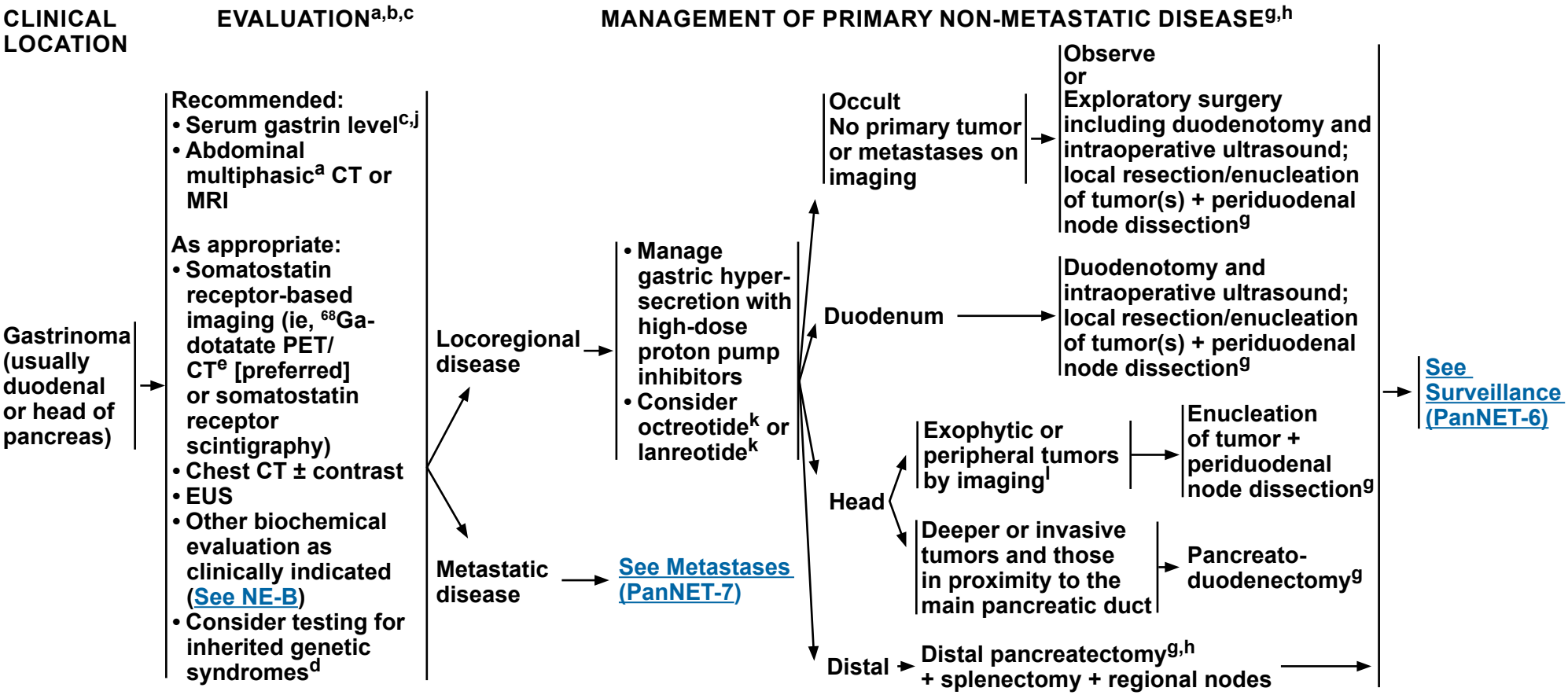

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[c]See Principles of Biochemical Testing (NE-B).
[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 or other hereditary syndromes as appropriate. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
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[g]See 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. To confirm diagnosis, 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.

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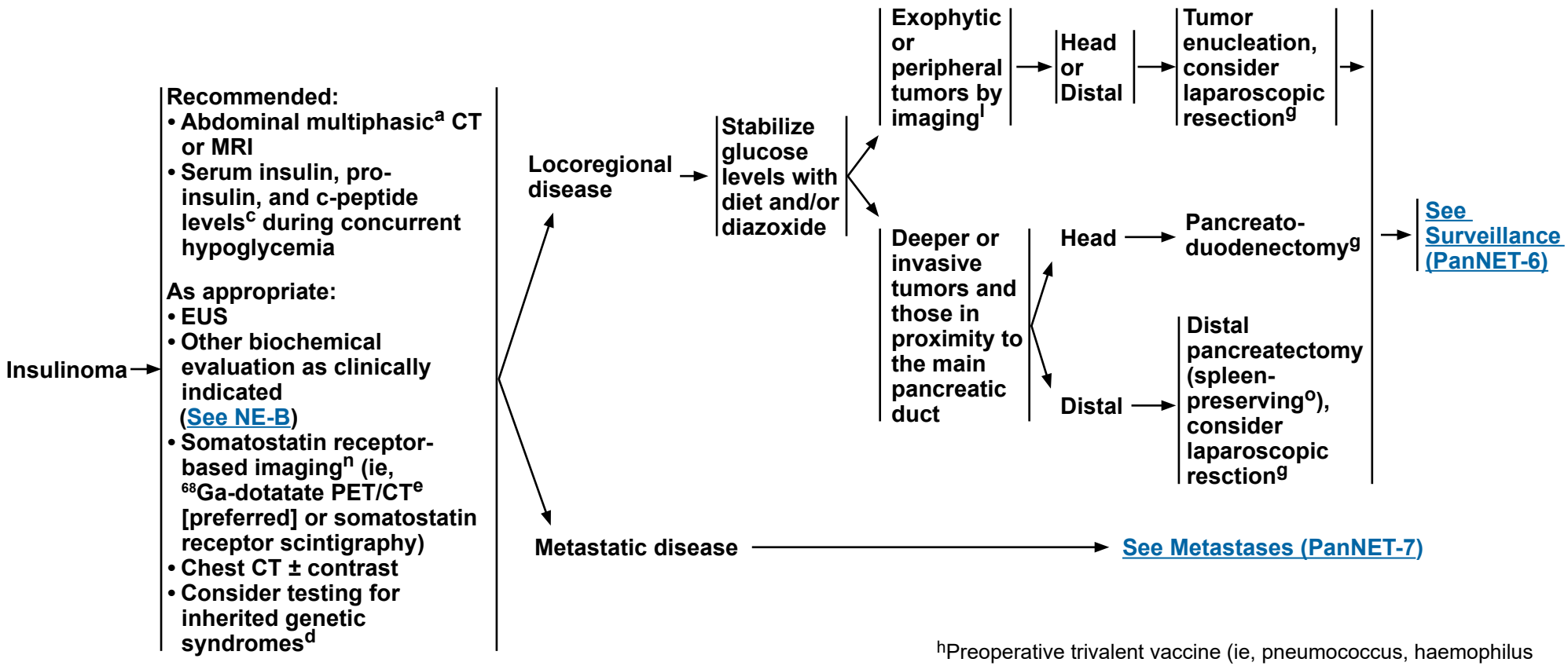

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[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 or other hereditary symptoms as appropriate. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
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[g]See 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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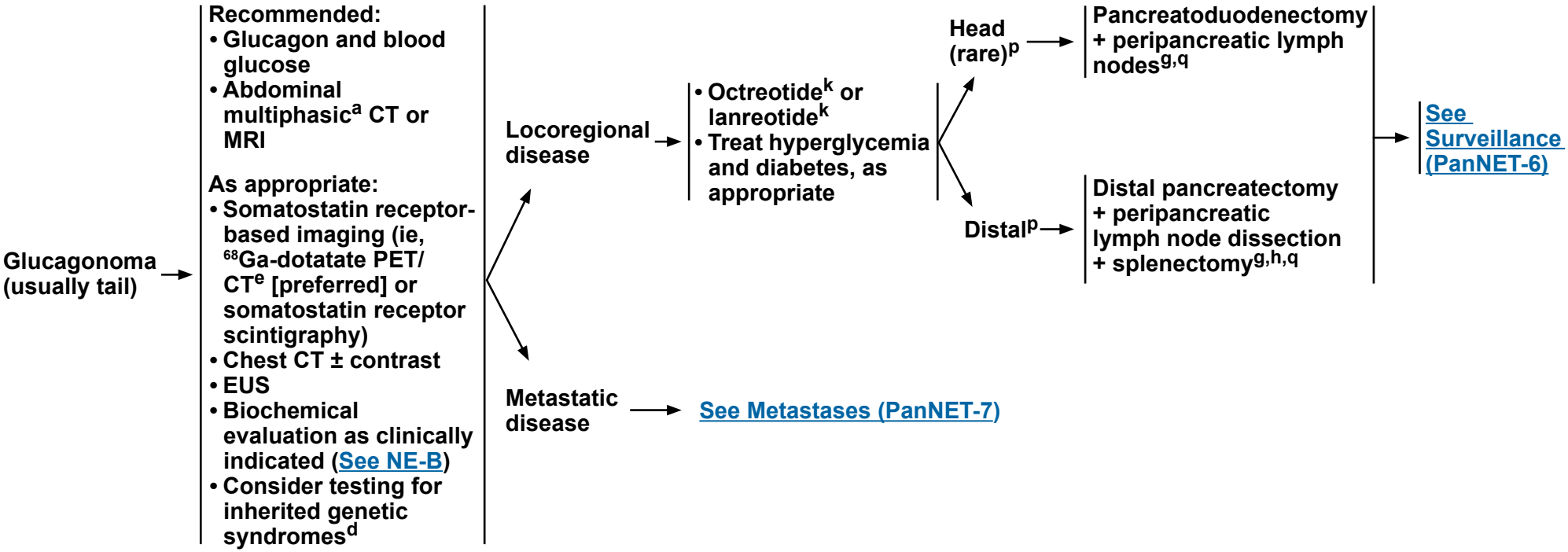

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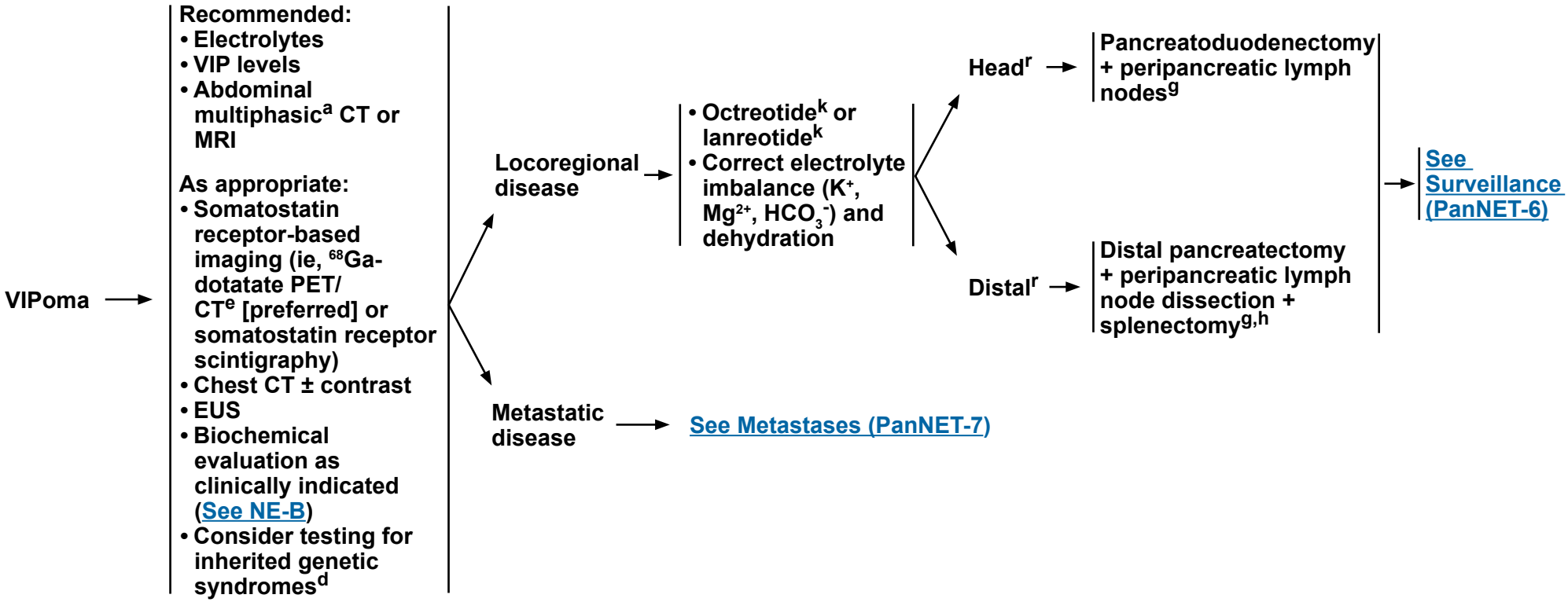
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)
[h]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[k]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[p]Small (<2 cm),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

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



[a]Multiphasic imaging studies are performed with IV 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 or other hereditary symptoms as appropriate. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1).
[e] 68Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.
[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 Advanced Disease and/or Distant Metastases (PanNET-7)

[a]Multiphasic imaging studies are performed with IV 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 ADVANCED DISEASE AND/OR DISTANT METASTASES[g]

EVALUATION

Locoregional advanced disease and/or distant metastases:
- **Abdominal/pelvic multiphasic[a] CT or MRI and chest CT (± contrast) as clinically indicated**
- **Somatostatin receptor-based imaging (ie, ^{68}Ga-dotatate PET/CT[e] [preferred] or somatostatin receptor scintigraphy)**
- **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 disease progression, 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
PRRT with ^{177}Lu-dotatate, if somatostatin receptor positive imaging[k,aa]
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[bb] (category 2B)**

[a]Multiphasic imaging studies are performed with IV contrast.

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

[e] ^{68}Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.

[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 should be continued in patients with functional tumors and may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E.

[aa]See Principles of PRRT with ^{177}Lu-Dotatate (NE-E).

[bb]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.

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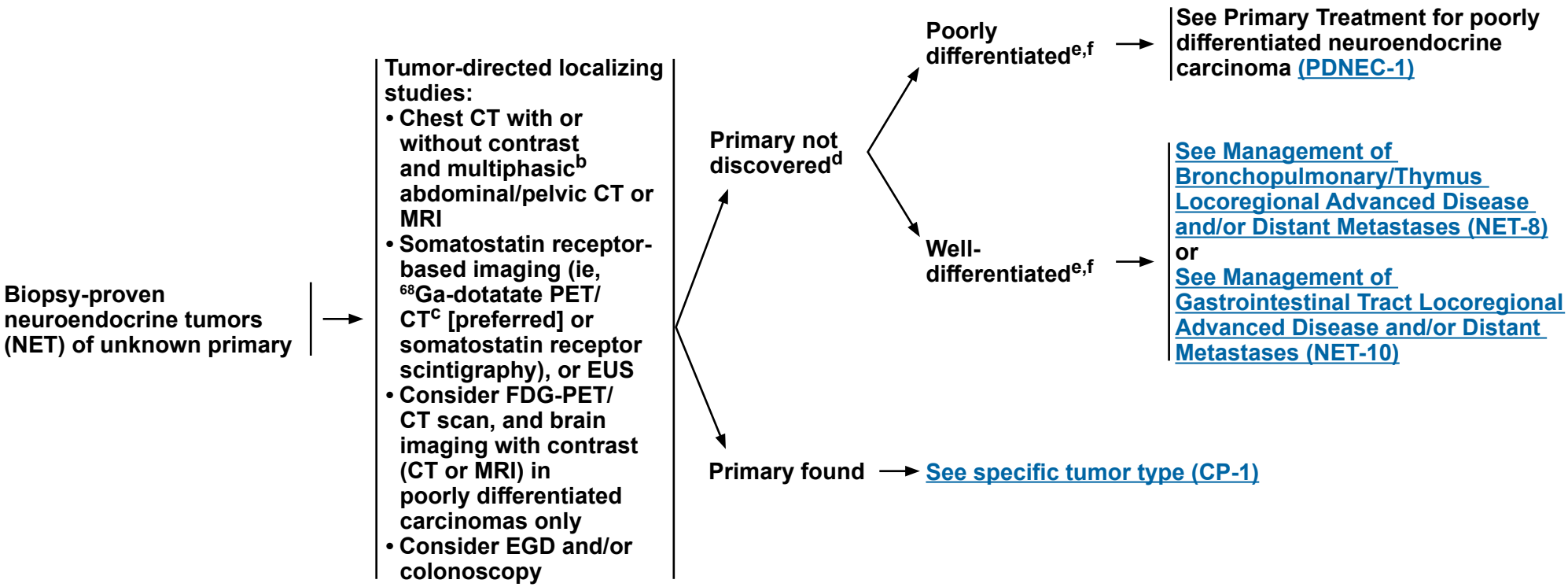
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

INITIAL WORKUP[a]



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] Multiphasic imaging studies are performed with IV contrast.
[c] 68Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.
[d] Consider small bowel primary tumor based on symptoms and associated radiologic findings.
[e] 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.
[f] See Principles of Biochemical Testing (NE-B).

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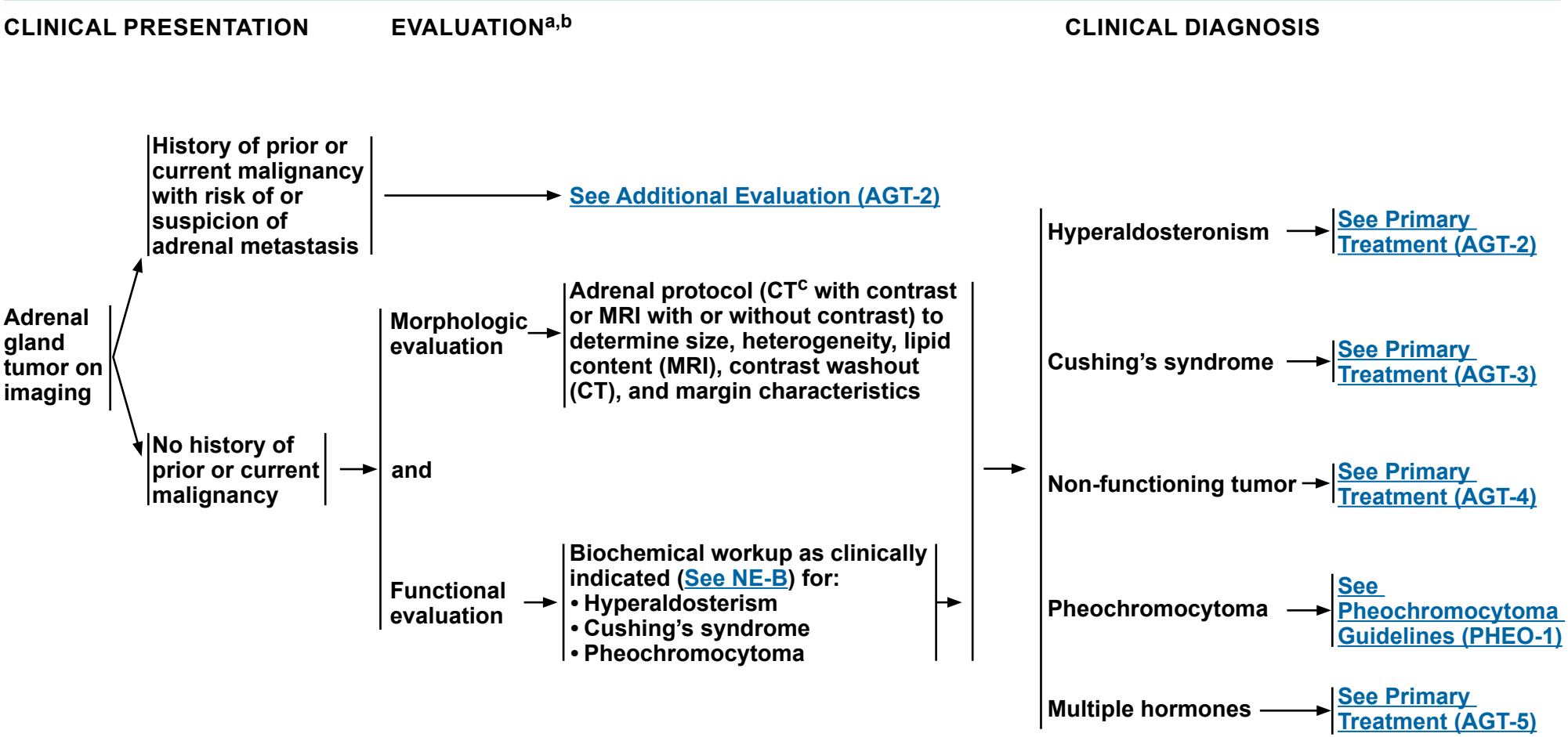

[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-B).
[c] If unenhanced is <+10 HU, then the tumor is probably benign. If unenhanced is >+10 HU, then use enhanced and washout. If >60% washout in 15 min, the tumor 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.)

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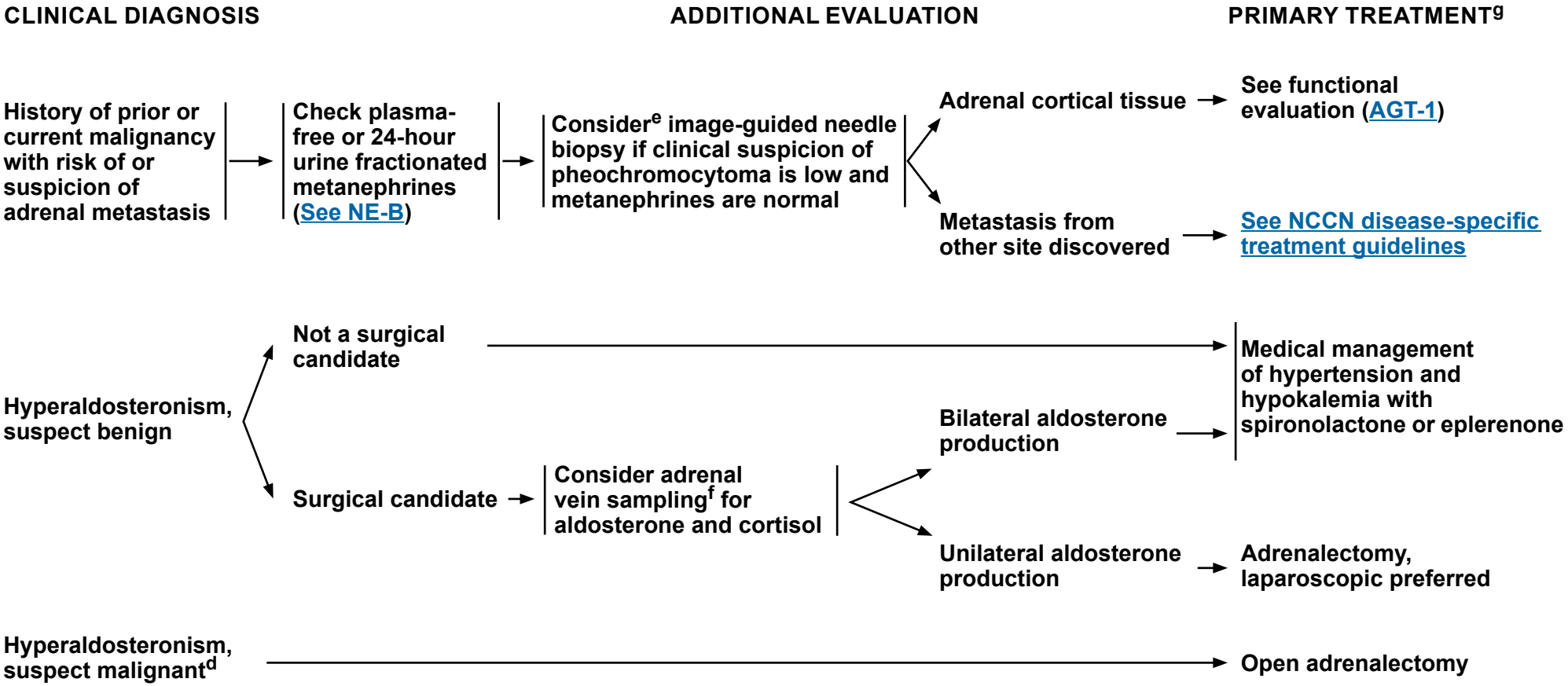

[d]Suspect malignancies with irregular/inhomogeneous morphology, lipid-poor, do not wash-out, tumor >4 cm, or secretion of more than one hormone.
[e]False negatives are possible; may consider proceeding directly to surgery in selected cases.
[f]Adrenal vein sampling can be considered for distinguishing 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.
[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

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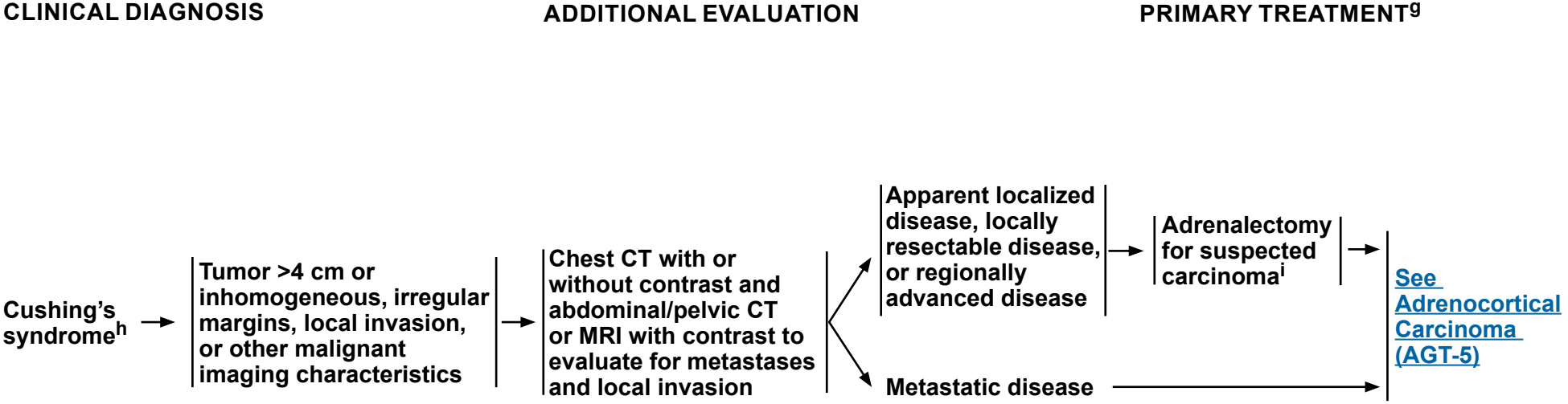

[g]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[h]For benign-appearing lesions, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome: Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831.
[i]May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.

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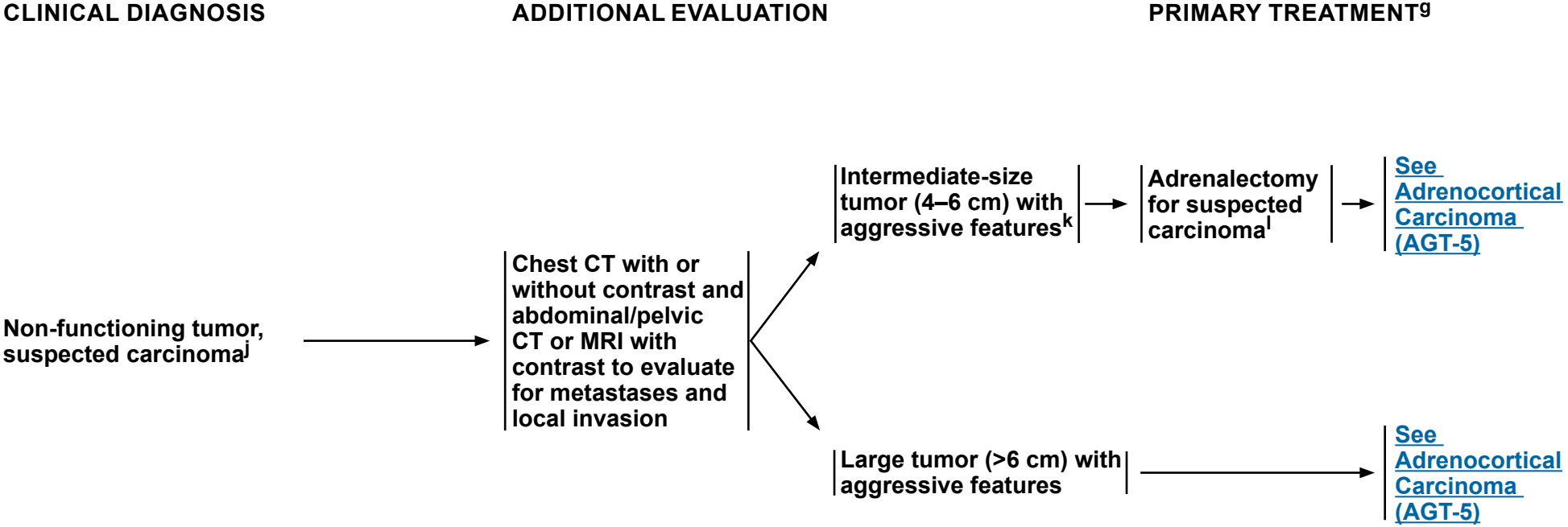

[g] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[j] For benign-appearing lesions, refer to the AACE/ACE guidelines for the management of adrenal incidentalomas: Zeiger MA, Thompson GB, Duh QY, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2009;15 Suppl 1:1-20.

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

[l] 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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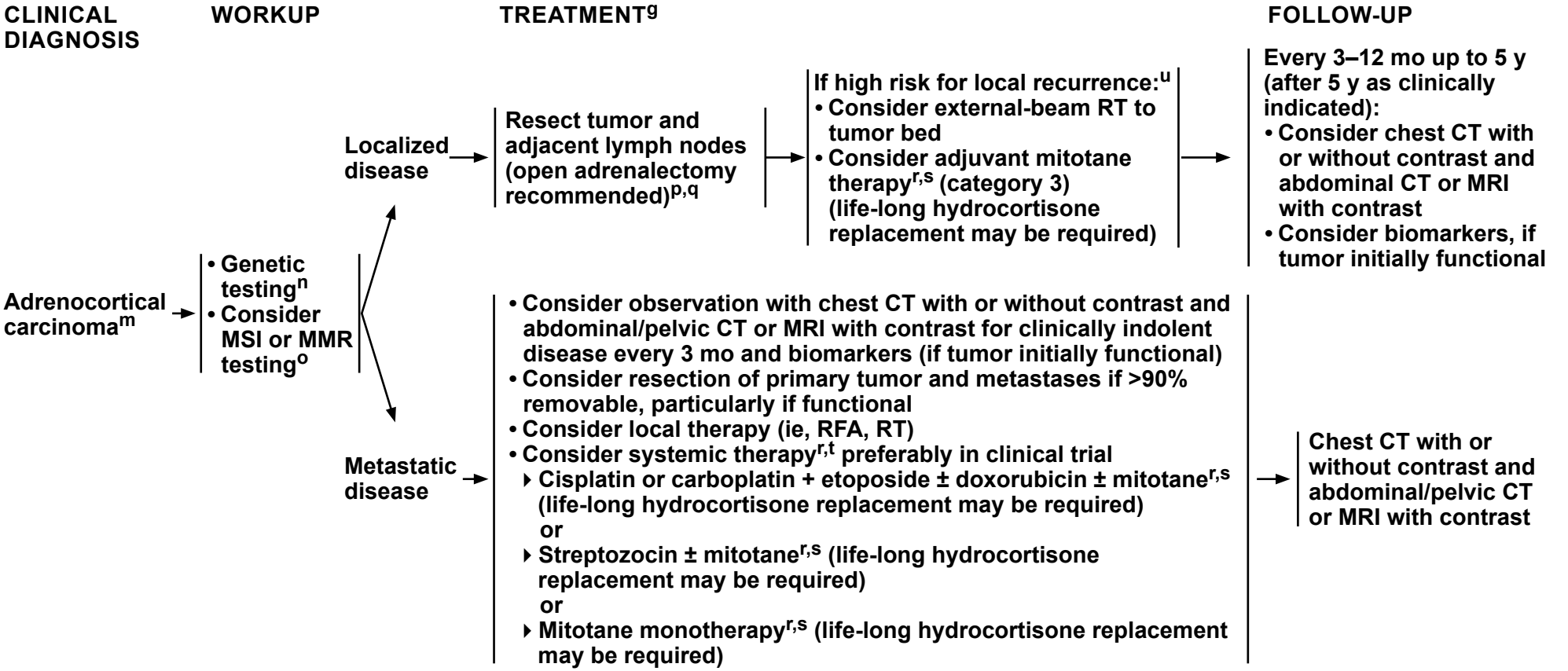

[g] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[m] 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.

[n] Testing for gene mutations associated with Lynch syndrome.

[o] Pembrolizumab should be considered for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.

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

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

[r] 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

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

[t] 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)

[u] 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, ^{68}Ga-dotatate PET/CT[g] [preferred] or somatostatin receptor scintigraphy)** • **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] ^{68}Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.

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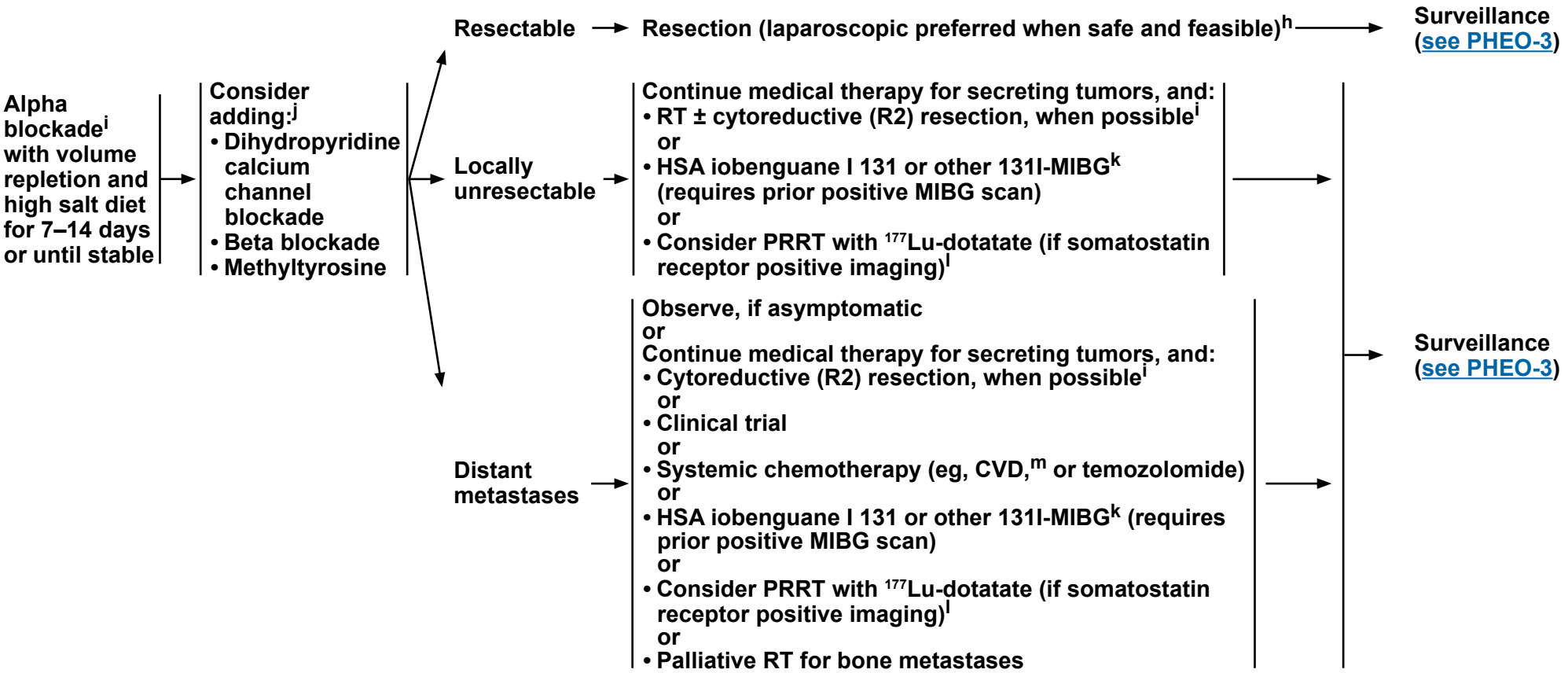
PRIMARY TREATMENT[h]



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

[i] 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.

[j] 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.

[k] HSA iobenguane I 131 is an FDA approved option.

[l] See Principles of PRRT with 177Lu-Dotatate (NE-E).

[m] CVD = cyclophosphamide, vincristine, and dacarbazine

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SURVEILLANCE[f]

Resectable disease (post-resection) →

3–12 mo postresection:[n]
- **H&P, blood pressure, and markers[b]**
- **Consider chest CT ± contrast and abdominal/pelvic CT or MRI with contrast or FDG-PET/CT**

>1 y postresection up to 10 y:
- **H&P, blood pressure, and markers[b]**
  - **Years 1–3: every 6–12 mo[m]**
  - **Years 4+ up to 10 y: annually[m]**
- **Consider chest CT ± contrast and abdominal/pelvic CT or MRI with contrast or FDG-PET/CT**

Locally unresectable disease or Distant metastases →

Every 3–12 mo:[n]
- **H&P, blood pressure, and markers[b]**
- **Consider imaging:**
  - **Chest/abdominal/pelvic CT with contrast**
    or
  - **Chest CT (± contrast) and abdominal/pelvic MRI without contrast (if risk for hypertensive episode)**
    or
  - **FDG-PET/CT**

[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)
[n] Earlier, if symptoms.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Poorly Differentiated Neuroendocrine Carcinoma/ Large or Small Cell

NCCN Guidelines Index
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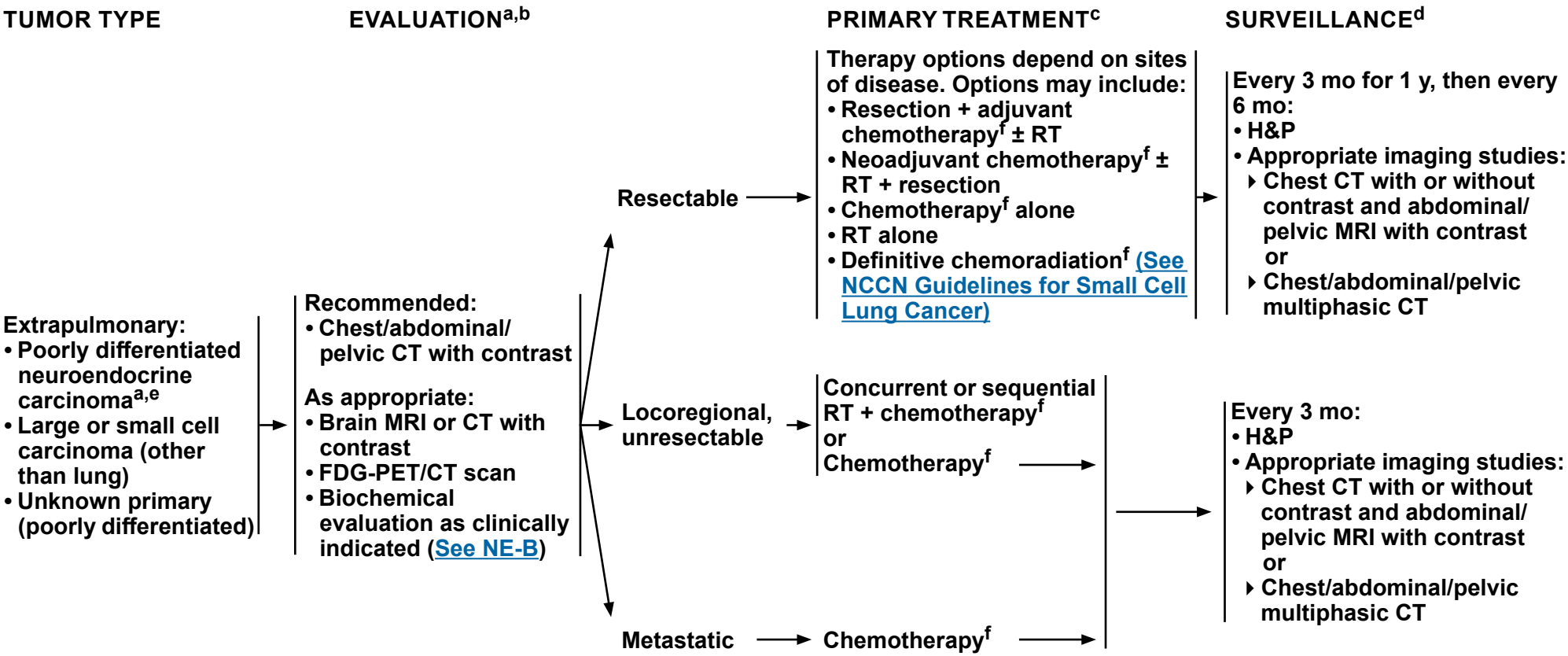
Discussion



[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-differentiated/ 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-10.

[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-10.

[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]Chemotherapy options include small cell lung cancer regimens, FOLFOX, FOLFIRI, and temozolomide ± capecitabine. 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 in a single patient: 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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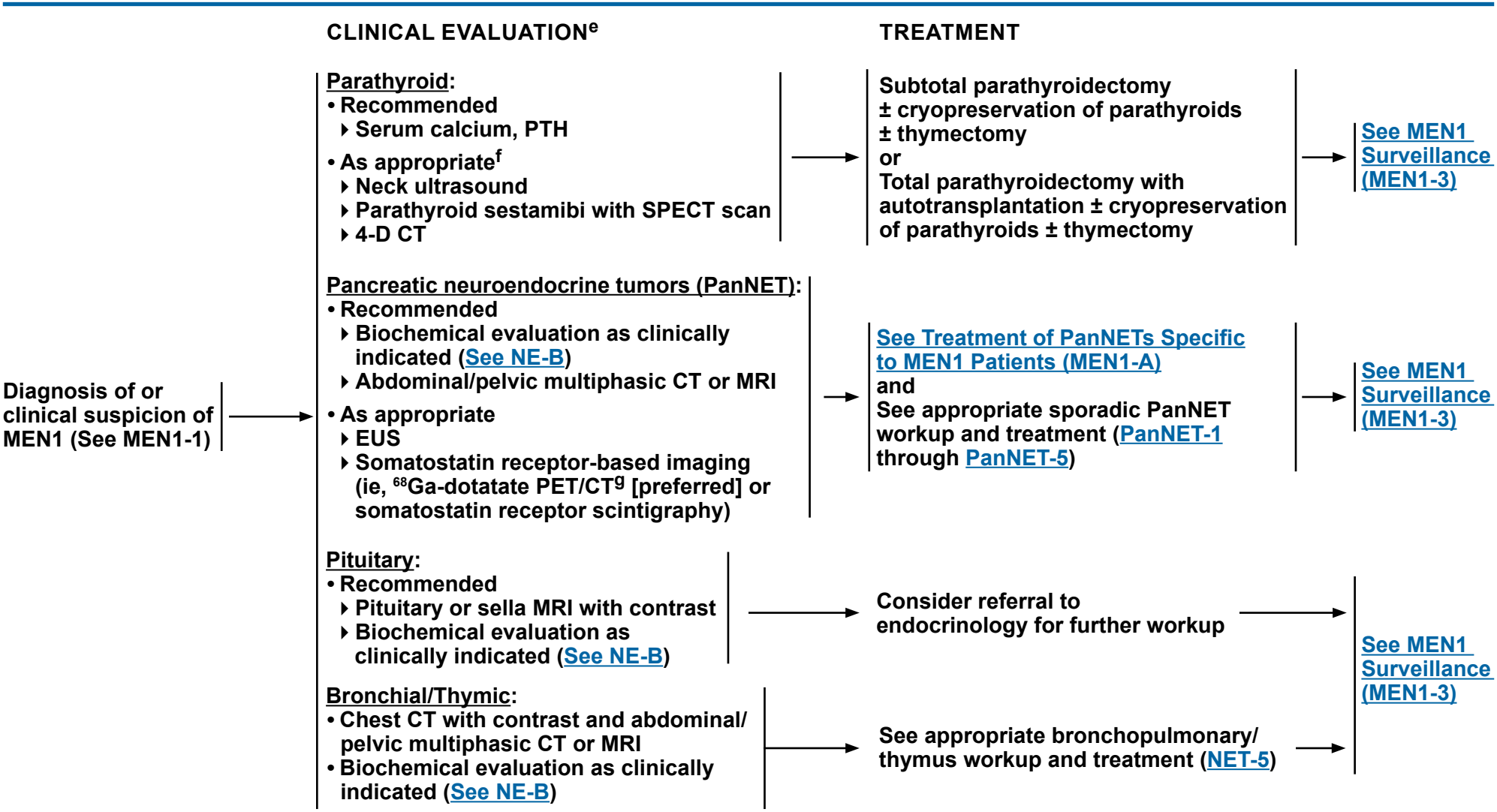

[e]For *MEN1* genetic testing recommendations, see MEN1-1.
[f]Preference of scan will depend on institutional practice/protocol.
[g] 68Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. PET/CT of skull base to mid-thigh; CT with IV contrast when possible. Data are limited on the optimal timing of scans following administration of somatostatin analogs.

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

Parathyroid:
- Calcium and PTH annually

→
- If calcium rises:
  - 25-OH vitamin D
  - Reimage with neck ultrasound and/or parathyroid sestamibi with SPECT scan or 4-D CT
  - Consider neck CT or MRI with contrast[j]

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

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

Pituitary:
- Pituitary or sella 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 or MRI[j] with contrast every 1–3 y

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

[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.
[i]Consider referral to an endocrinologist.
[j]For prolonged surveillance, studies without radiation are preferred.

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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.

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

DIAGNOSIS OF OR CLINICAL SUSPICION OF MEN2

- **MEN2 is subdivided into MEN2A and MEN2B. Medullary thyroid cancer (MTC) occurs in nearly all patients with MEN2A and MEN2B and is often the first manifestation of the syndrome.**
  - **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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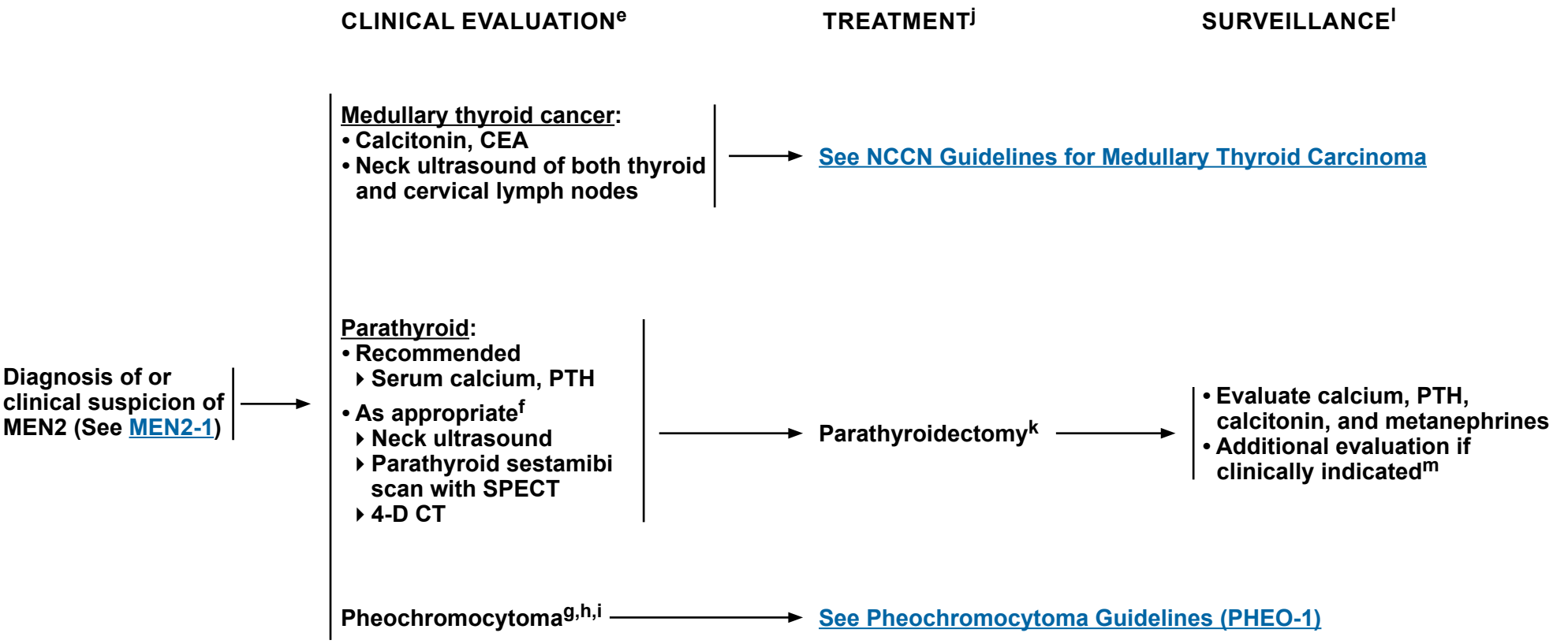

[e]For RET genetic testing recommendations, see MEN2-1.
[f]Preference of scan will depend on institutional practice/protocol.
[g]Evaluation of pheochromocytoma should be done before the administration of any anesthetic or invasive procedure.
[h]More likely to be multifocal.
[i]For synchronous bilateral pheochromocytomas, a bilateral adrenalectomy is recommended
[j]For the treatment of synchronous tumors, surgical resection of pheochromocytoma should take priority over thyroidectomy for medullary thyroid cancer.
[k]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.
[l]Earlier, if symptoms.
[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
- 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[a]

Differentiation	Grade	Gastrointestinal NET (excluding pancreas)	Pancreatic NET[b]	Lung and Thymus
Well-differentiated	Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis
	Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index	2–20 mitoses/10 HPF OR 3%–20% Ki-67 index	2–10 mitoses/10 HPF AND/OR foci of necrosis
	High Grade (G3)		>20 mitoses/10 HPF OR >20% Ki-67 index	
Poorly differentiated	High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>20 mitoses/10 HPF OR >20% Ki-67 index	>10 mitoses/10 HPF

[a]Adapted with permission 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; and Lloyd RV, Osamaru RY, Klöppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. IARC, Lyon, 2017.
[b]Similar classification for GI NET is expected.

Continued

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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.

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 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.[3-11] The most recent WHO classification system is suggested for GEP NETs and represents an attempt to unify European and American approaches.[9] 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.[1,12]

Mitotic rate

- Mitotic rate should be based on counting mitoses 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.[4,5]
- 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.[12]
- 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.[13]
- 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.

References

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PRINCIPLES OF BIOCHEMICAL TESTING[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 or plasma 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[a]**

[a]Basal, stimulated as indicated.

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Continued
References

PRINCIPLES OF BIOCHEMICAL TESTING[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[c]** • **Cervical paragangliomas: consider serum or urine dopamine or methoxytyramine (the metabolite of dopamine)[c]**
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[b]	**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**

[b]For additional information on biochemical testing for Cushing's syndrome, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome: Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(8):2807-2831.

[c]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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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, serial imaging is recommended and lymph node resection should be considered. For prolonged surveillance, imaging studies without radiation are preferred.**
- **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.**

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

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

- **Systemic therapy may not be appropriate for every patient with locoregionally advanced 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-10. For management of carcinoid syndrome, see NET-11.**

Options for Locoregionally Advanced and/or Metastatic NET of the Gastrointestinal Tract[a,b]	• **Octreotide[c] LAR 30 mg intramuscular injection, monthly[1]** • **Lanreotide[c] 120 mg deep subcutaneous injection, monthly[2]** • **Everolimus[d,3,4]** • **PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive imaging and progression on octreotide/lanreotide) (category 1 for mid-gut tumors)[e]** • **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.)** ▸ **Interferon alfa-2b[5] (category 3)**
Options for Incompletely Resected, Locoregionally Advanced, and/or Metastatic NET of the Lung/Thymus[a,b]	• **See NET-8. Depending on tumor burden and grade, options may include:** ▸ **Octreotide[c] LAR 30 mg intramuscular injection, monthly[1]** ▸ **Lanreotide[c] 120 mg deep subcutaneous injection, monthly[2]** ▸ **Everolimus[d]** ▸ **PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive imaging and progression on octreotide/lanreotide)[e]** ▸ **Temozolomide[f]** ▸ **Cisplatin + etoposide[f]** ▸ **Carboplatin + etoposide[f]**

[a]Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (eg, Ki-67). There are 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.

[b]If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the systemic therapy options. For details on the administration of octreotide or lanreotide with ^{177}Lu-dotatate, see NE-E.

[c]Somatostatin analog dosing also applicable for locoregional disease.

[d]Safety and effectiveness of everolimus in the treatment of patients with carcinoid syndrome have not been established.

[e]See Principles of PRRT with ^{177}Lu-Dotatate (NE-E).

[f]For primary therapy, cisplatin/etoposide, carboplatin/etoposide, or temozolomide 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

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregionall Advanced and/or Metastatic Pancreatic Neuroendocrine Tumors

- **Systemic therapy may not be appropriate for every patient with locoregionally advanced 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.**
- **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 PanNETs.**
- **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 Locoregionally Advanced and/or Metastatic Pancreatic Neuroendocrine Tumors

- **Somatostatin analogues (somatostatin analog dosing also applicable for locoregional disease)**
  - **Octreotide[g,h] 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**
- **PRRT with ^{177}Lu-dotatate (if somatostatin receptor positive imaging and progression on octreotide/lanreotide)[e]**
- **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]**

[e] See Principles of Peptide Receptor Radionuclide Therapy (NE-E).

[g] 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.

[h] 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]

References

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

PRINCIPLES OF PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) WITH ^{177}LU-DOTATATE[1-4]

Lutetium Lu 177-dotatate (^{177}Lu-dotatate) is a radiolabled somatostatin analog used as PRRT. It is approved by the FDA for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (NET), including foregut, midgut, and hindgut NET in adults.

Key Eligibility:

- Low or intermediate grade NET (Ki-67 ≤ 20%)
- Somatostatin receptor expression of NET as detected by somatostatin receptor-based imaging (ie, ^{68}Ga-dotatate PET/CT [preferred] or somatostatin receptor scintigraphy)
- Adequate bone marrow, renal and hepatic function

Preparing Eligible Patients for ^{177}Lu-Dotatate

- Do not administer long-acting somatostatin analogs (such as lanreotide, octreotide) for 4-6 weeks prior to each ^{177}Lu-dotatate treatment. Administer short-acting octreotide as needed for symptom control of carcinoid syndrome; discontinue at least 24 hours prior to initiating ^{177}Lu-Dotatate.
- Counsel patients about the risks of:
  - Radiation exposure to themselves and others
  - Myelosuppression
  - Secondary Myelodysplastic Syndrome (MDS) and Leukemia
  - Renal Toxicity
  - Hepatic Toxicity
  - Embryo-Fetal Toxicity
  - Infertility
  - Neuroendocrine hormonal crisis or carcinoid crisis: flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms
  - Nausea/vomiting (related to amino acid infusion required as part of therapy)
- Discuss radiation safety precautions during and after ^{177}Lu-dotatate.
- Verify pregnancy status in females of reproductive potential.
- Advise on use of effective contraception for up to 7 months (females) and 4 months (males) after last dose of ^{177}Lu-dotatate.

Continued

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

PRINCIPLES OF PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) WITH ^{177}LU-DOTATATE[1-4]

Dose and Administration

- ^{177}Lu-dotatate is administered intravenously (IV) via peripheral IV at dose of 200 mCi over 30-40 minutes every 8 weeks for a total of 4 treatments.
- Amino acid solution:
  - IV infusion of amino acids is a critical part of ^{177}Lu-dotatate therapy for nephroprotection.
  - Amino acids are administered 30 mins before, concurrently with, and 3 hours after ^{177}Lu-dotatate.
  - Commercial amino acid formulations infused at high rates are more emetogenic than compounded amino acids.
  - Solutions containing only arginine/lysine are only available through compounding pharmacies, but are much less emetogenic than commercial amino acid solutions. Options for amino acids are as follows:
    - ◊ Arginine 2.5%/lysine 2.5% in 1000 mL NaCl infused at 250 mL/hour for 4 hours.
    - ◊ Commercial amino acid formulation (typically containing approximately 20 amino acids) mixed in sterile water for total volume of approximately 2000 mL. Infusion rate can be increased to roughly 300-500 mL/hr, as tolerated. Recommend starting at low rate of 50 mL/hr and increasing by 10 mL/hr every 10 minutes as tolerated based on symptoms such as nausea. ^{177}Lu-dotatate infusion should begin after at least 250 mL of amino acids have been infused.
- Aggressive anti-emetic prophylaxis is recommended with a 5HT3 receptor antagonist with or without a NK1 receptor blocker. See NCCN Guidelines for Antiemesis.

Post-treatment instructions

- Detailed instructions on post-treatment radiation-risk reduction strategies should be provided per institutional radiation safety guidelines.
- Complete blood counts, serum chemistry including renal and hepatic functions should be monitored.
- SSAs (octreotide or lanreotide) can be administered 4-24 hours after each ^{177}Lu-dotatate treatment.

Timing of Somatostatin Analogs (SSAs) (Octreotide or Lanreotide) in relation to ^{177}Lu-dotatate

- Most patients treated with PRRT will have progressed on a first-line SSAs.
- Generally, patients with hormonally functional tumors should continue octreotide or lanreotide along with ^{177}Lu-dotatate. It is unclear whether patients with nonfunctional tumors benefit from continuation of SSA treatment during and after ^{177}Lu-dotatate treatment.
- There are theoretical concerns regarding the competition between SSAs and ^{177}Lu-dotatate for somatostatin receptor binding. Therefore, the following is recommended:
  - Do not administer long-acting SSAs for 4-6 weeks prior to each ^{177}Lu-dotatate treatment.
  - Stop short-acting SSAs 24 hours before each ^{177}Lu-dotatate treatment.
  - SSAs (short- and long-acting) can be resumed 4-24 hours after each ^{177}Lu-dotatate treatment.

Continued

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

PRINCIPLES OF PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) WITH ^{177}LU-DOTATATE REFERENCES

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

American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Stomach (gastric "carcinoid" tumors [NET G1 and G2, and rare well-differentiated G3]) (8th ed., 2017)

Table 1. **Definitions for T, N, M**

Stomach

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1*	Invades the lamina propria or submucosa and less than or equal to 1 cm in size
T2*	Invades the muscularis propria or greater than 1 cm in size
T3*	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4*	Invades visceral peritoneum (serosal) or other organs or adjacent structures

Note*: For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1–4 and # = number of primary tumors identified]; for multiple tumors with different Ts, use the highest.

***Example:* If there are two primary tumors, one of which penetrates only the subserosa, we define the primary tumor as either T3(2) or T3(m).

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

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 2. **AJCC Prognostic Stage Groups**

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

Continued

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Duodenum and Ampulla of Vater (8th ed., 2017)

Table 3. **Definitions for T, N, M**

Duodenum/Ampulla

T	**Primary Tumor**
TX	Primary tumor not assessed
T1	Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors); Tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors)
T2	Tumor invades the muscularis propria or is >1 cm (duodenal); Tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary)
T3	Tumor invades the pancreas or peripancreatic adipose tissue
T4	Tumor invades the visceral peritoneum (serosa) or other organs

Note: Multiple tumors should be designated as such (and the largest tumor should be used to assign the T category):
- If the number of tumors is known, use T(#); e.g., pT3(4)N0M0.
- If the number of tumors is unavailable or too numerous, use the suffix m —T(m)—e.g., pT3(m)N0M0.

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 4. **AJCC Prognostic Stage Groups**

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

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Jejunum and Ileum (small bowel "carcinoid" tumors [NET G1 and G2, and rare well-differentiated G3] arising in the jejunum and ileum.) (8th ed., 2017)

Table 5. **Definitions for T, N, M**
Jejunum/Ileum

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1*	Invades lamina propria or submucosa and less than or equal to1 cm in size
T2*	Invades muscularis propria or greater than 1 cm in size
T3*	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4*	Invades visceral peritoneum (serosal) or other organs or adjacent structures

Note:* For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1–4, and # = number of primary tumors identified]; for multiple tumors with different T, use the highest.
***Example:* If there are two primary tumors, only one of which invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal), we define the primary tumor as either T3(2) or T3(m).

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement metastasis has occurred
N1	Regional lymph node metastasis less than 12 nodes
N2	Large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 6. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1, N2	M0
	T2	N1, N2	M0
	T3	N1, N2	M0
	T4	N0	M0
	T4	N1, N2	M0
Stage IV	Any T	Any N	M1

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Colon and Rectum (colonic and rectal "carcinoid" tumors [neuroendocrine tumor G1 and G2, and rare well-differentiated G3]) (8th ed., 2017)

Table 7. **Definitions for T, N, M**
Colon and Rectum

T*	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades the lamina propria or submucosa and is ≤2 cm
T1a	Tumor <1 cm in greatest dimension
T1b	Tumor 1–2 cm in greatest dimension
T2	Tumor invades the muscularis propria or is >2 cm with invasion of the lamina propria or submucosa
T3	Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4	Tumor invades the visceral peritoneum (serosa) or other organs or adjacent structures

Note:* For any T, add "(m)" for multiple tumors [TX(#) or TX(m), where X = 1-4 and # = number of primary tumors identified]; for multiple tumors with different T, use the highest.
***Example:* If there are two primary tumors, only one of which invades through the muscularis propria into the subserosal tissue without penetration of the overlying serosa, we define the primary tumor as either T3(2) or T3(m).

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

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 8. **AJCC Prognostic Groups**

	T	N	M
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N1	M0
Stage IV	TX, T0	Any N	M1
	T1	Any N	M1
	T2	Any N	M1
	T3	Any N	M1
	T4	Any N	M1

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Pancreas [well-differentiated neuroendocrine tumors arising in the pancreas] (8th ed., 2017)

Table 9. **Definitions for T, N, M**
Pancreatic

T	**Primary Tumor**
TX	Tumor cannot be assessed
T1	Tumor limited to the pancreas,* <2 cm
T2	Tumor limited to the pancreas,* 2−4 cm
T3	Tumor limited to the pancreas,* >4 cm; or tumor invading the duodenum or common bile duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)

**Limited to the pancreas* means there is no invasion of adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of tumor into peripancreatic adipose tissue is NOT a basis for staging.

Note: Multiple tumors should be designated as such (the largest tumor should be used to assign T category):
- If the number of tumors is known, use T(#); e.g., pT3(4) N0 M0.
- If the number of tumors is unavailable or too numerous, use the *m* suffix, T(m); e.g., pT3(m) N0 M0.

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 10. **AJCC Prognostic Stage Groups**

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

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors of the Appendix (carcinoid) [NET G1 and G2, and rare well-differentiated G3] (8th ed., 2017)

Table 11. **Definitions for T, N, M**
Appendiceal Neuroendocrine Tumors

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but less than or equal to 4 cm
T3	Tumor more than 4 cm or with subserosal invasion or involvement of the mesoappendix
T4	Tumor perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), e.g., abdominal wall and skeletal muscle
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Table 12. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IV	TX, T0	Any N	M1
	T1	Any N	M1
	T2	Any N	M1
	T3	Any N	M1
	T4	Any N	M1

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Adrenal – Neuroendocrine Tumors [Pheochromocytoma and paraganglioma] (8th ed., 2017)

Table 13. **Definitions for T, N, M**
Adrenal

T	Primary Tumor
TX	Primary tumor cannot be assessed
T1	PH <5 cm in greatest dimension, no extra-adrenal invasion
T2	PH ≥5 cm or PG-sympathetic of any size, no extra-adrenal invasion
T3	Tumor of any size with local invasion into surrounding tissues (e.g., liver, pancreas, spleen, kidneys)

PH: within adrenal gland
PG Sympathetic: functional
PG Parasympathetic: nonfunctional, usually in the head and neck region
Note: Parasympathetic Paragaglioma are not staged because they are largely benign.

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

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis to only bone
M1b	Distant metastasis to only distant lymph nodes/liver or lung
M1c	Distant metastasis to bone plus multiple other sites

Table 14. **AJCC Prognostic Stage Groups**
Pheochromocytoma/Sympathetic Paraganglioma

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

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Adrenal Cortical Carcinoma (8th ed., 2017)

Table 15. **Definitions for T, N, M**
Adrenal Cortical Carcinoma

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤5 cm in greatest dimension, no extra-adrenal invasion
T2	Tumor >5 cm, no extra-adrenal invasion
T3	Tumor of any size with local invasion but not invading adjacent organs
T4	Tumor of any size that invades adjacent organs (kidney, diaphragm, pancreas, spleen, or liver) or large blood vessels (renal vein or vena cava)

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

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

G	**Histologic Grade**
LG	Low grade (≤20 mitoses per 50 HPF)
HG	High grade (>20 mitosis per 50 HPF); *TP53* or *CTNNB* mutation

Table 16. **AJCC Prognostic Stage Groups**

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

Continued

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Lung (8th ed., 2017) [carcinomas of the lung, including non–small cell and small cell carcinomas, and bronchopulmonary carcinoid tumors].

Table 17. **Definitions for T, N, M**
Lung

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 *in situ* Squamous cell carcinoma i*n situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm 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)*
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor 2 ≤1 cm or less in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor >1 cm but 3 ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor more than >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Lung (8th ed., 2017) [carcinomas of the lung, including non–small cell and small cell carcinomas, and bronchopulmonary carcinoid tumors].

Table 17. **Definitions for T, N, M *(continued)***

Lung

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 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 or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

Table 18. **AJCC Prognostic Stage Groups**

	T	N	M
Occult	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi, T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a, T1b, T1c	N1	M0
	T2a, T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a, T1b, T1c	N2	M0
	T2a, T2b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a, T1b, T1c	N3	M0
	T2a, T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Continued

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Thymus (8th ed., 2017) [including thymoma, thymic carcinoma, thymic neuroendocrine tumors, combined thymic carcinoma]

Table 19. **Definitions for T, N, M**

Thymus

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	Tumor with no mediastinal pleura involvement
T1b	Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes

M	**Distant Metastasis**
M0	No pleural, pericardial, or distant metastasis
M1	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Table 20. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1a, b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
	Any T	N0, N1	M1a
Stage IVB	Any T	N2	M0, 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 indicated.

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Overview

Neuroendocrine tumors are thought to arise from cells throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are in the gastrointestinal (GI) tract, lungs and bronchi [so-called bronchopulmonary], thymus, and pancreas. Sites of origin within the GI tract include the stomach, small intestine, appendix, and rectum.[1,2] 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 6.98 cases per 100,000 people in the year 2004.[1,2] 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 170,000.[1,2] Other independent analyses of the SEER database also found that the incidence of GI neuroendocrine tumors increased from 1975 to 2008.[3,4] The reasons for this increase are unclear, although it seems likely that improved diagnosis and classification is one factor.[5]

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.[6] 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.[7]

Neuroendocrine tumors have also been associated with von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.[8,9]

Patients with neuroendocrine tumors may or may not have symptoms attributable to hormonal hypersecretion. These symptoms include intermittent flushing and diarrhea in patients with GI neuroendocrine tumors,[10] hypertension in patients with pheochromocytoma,[11] and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic neuroendocrine tumors.[12] 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 and adrenal 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 *High-Grade or Poorly Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas or Unknown Primary*, 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 published in the field since the previous Guidelines update, 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 peer-reviewed biomedical literature.[13]

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 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 at www.NCCN.org.

Histologic Classification and Staging of Neuroendocrine and Adrenal 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 and tumor grade (grades 1–3). Most neuroendocrine tumors fall into 3 to 4 broad histologic categories: well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); poorly differentiated, high-grade (G3); and a fourth category for pancreatic neuroendocrine tumors: well-differentiated, high grade (G3).[14]

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.[12,14-16] Numerous studies have confirmed that increased mitotic rate and high Ki-67 index are associated with a more aggressive clinical course and worse prognosis.[17-20] In most cases for GI and pancreatic neuroendocrine tumors, 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. 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.[21-23] 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 neuroendocrine tumors 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 (intermediate grade, 2–10 mitosis/10 HPF and/or foci of necrosis), using histologic criteria.[24]

High-grade, poorly differentiated lung and thymus neuroendocrine carcinomas are of either small cell or large cell cytology, with greater than 10 mitoses/10 HPF and extensive foci of necrosis.[23,25-27]

Considerable debate remains as to the most appropriate Ki-67 proliferative threshold for the determination of tumor grade and consequent treatment decisions.[28,29] 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%.[30] 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.[31] 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.[32]

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.[33] The T and N definitions and other staging definitions were revised in the 8th edition of the AJCC Cancer Staging Manual. [34] The 8th edition also added the first staging system for thymic tumors and adrenal-neuroendocrine tumors (including staging for pheochromocytoma and paraganglioma).[34] Neuroendocrine tumors of the stomach, duodenum/ampulla, jejunum/ileum, appendix, colon/rectum, and pancreas have separate staging systems. The association of tumor stage with prognosis has been confirmed in analyses of the SEER database and the National Cancer Database.[35-41] An 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.[32] 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.[29] Similar results were reported in a separate analysis of 6792 small intestine neuroendocrine tumors in the SEER database, which found that outcomes were similar for patients with T1 and T2 tumors.[42] These results have been supported in additional analyses, confirming that the presence of lymph node and distant metastases have the strongest effect on survival.[43,44]

Neuroendocrine tumors 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 neuroendocrine tumors of the lungs and bronchi is associated with worse prognosis. [33,34]

The TNM staging system for the classification of pancreatic neuroendocrine tumors in the 8th edition of the AJCC Cancer Staging Manual is separate from exocrine pancreatic carcinoma.[33,34] 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 the AJCC 2017 classification system, with 5-year overall survival (OS) rates of 92%, 84%, 81%, and 57% for stages I through IV, respectively ($P < .001$).[45] 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.[46,47] 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%.[47]

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.[48,49]

Whether or not tumors are associated with symptoms of hormone hypersecretion (”functioning” or “non-functioning”), these symptoms are, in general, a part of the clinical rather than histologic diagnosis. Thus, functional status is usually not included in the pathology 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 OS in 195 neuroendocrine tissue samples (15% were located in the pancreas; 85% were GI carcinoids).[50] Small bowel carcinoid (neuroendocrine) tumors have been found to have recurrent mutations in the cyclin-dependent kinase inhibitor, CDKN1B (p27),[51] and loss of CDKN1B expression has been reported to be an adverse prognostic factor in gastroenteropancreatic neuroendocrine tumors.[52] 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 OS in patients with varyingly pre-treated metastatic neuroendocrine tumors from various primary sites.[53]

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.[54]

Sporadic Neuroendocrine Tumors

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

Approximately one-third of neuroendocrine (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.[1,2] The prognosis for patients with neuroendocrine tumors varies according to the stage at diagnosis, histologic classification, and

primary site of the tumor (see *Histologic Classification and Staging of Neuroendocrine and Adrenal 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.[55,56] 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.[57] Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.[58]

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,[59,60] 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 neuroendocrine tumors of the GI tract, lung, and thymus: 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 neuroendocrine tumors of the GI tract, lung, or thymus 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 overexpress high-affinity receptors for somatostatin,[57,61] a peptide hormone generated by the hypothalamus that blocks the release of growth hormones,[62] 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. A major advance in imaging neuroendocrine tumors came with the 2016 FDA approval of PET/CT imaging using the radiolabeled somatostatin analog gallium-68 (^{68}Ga) dotatate. Several studies have shown the diagnostic utility, safety, specificity, and high sensitivity of ^{68}Ga-dotatate PET/CT.[63-67] One study even showed that it was able to more correctly identify patients for peptide receptor radiotherapy than ^{111}Indium-diethylenetriaminepentaacetic acid (^{111}In-DPTA) scintigraphy.[68] The 2018 Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors recommends the use of somatostatin receptor PET over ^{111}In-DPTA scintigraphy.[69] However, the 2018 Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors recommends the use of somatostatin receptor PET over ^{111}In-DPTA scintigraphy.[69] 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.[63-65] Unless otherwise indicated, somatostatin receptor-based imaging in this discussion includes imaging with either ^{68}Ga-dotatate PET/CT

(preferred) or somatostatin receptor scintigraphy. ^{68}Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status. Data are limited on whether long-acting somatostatin receptor inhibition interfere with ^{68}Ga-dotatate PET/CT scans, but one study[70] showed that timing doesn't make a difference. The Panel does not currently include specific recommendations on the optimal timing of scans following somatostatin analog administration.

Additional imaging 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; endorectal ultrasound for rectal neuroendocrine tumors; and bronchoscopy as appropriate for bronchopulmonary 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 or plasma collection for 5-hydroxyindoleacetic acid (5-HIAA), is generally recommended in patients with metastatic lung or GI neuroendocrine 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,[71] 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.[72]

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 neuroendocrine tumors of the GI tract, lung, and thymus. 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. Octreotide and lanreotide also may be considered for tumor control in patients with locoregional disease who have somatostatin receptor-positive imaging (see *Management of Locoregional Advanced and/or Distant Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract Neuroendocrine Tumors* or *of the Bronchopulmonary or Thymus Neuroendocrine Tumors*, 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).[73] 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).[73] 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 neuroendocrine 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.[74] Endoscopic resection should be reserved for small (<1 cm), superficial, low-grade tumors.

Thymic Neuroendocrine Tumors

Localized (stage I–II) and locoregional (stage III A/B) neuroendocrine tumors in the thymus are generally treated with surgical resection without adjuvant therapy if they have been completely resected with negative margins. There are 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.[75,76] Observation may be considered for patients with incomplete resection and/or positive margins, or in the setting of locally unresectable, low-grade (typical) disease.[77] Systemic therapy alone may be considered for patients with locally unresectable disease. Radiation therapy (RT) is considered in select cases by some panel members to be an option for low-grade (typical) tumors (category 3) with or without systemic therapy. If tumors are intermediate grade (atypical), treatment with RT with or without systemic therapy is generally more recommended given evidence that radiation and chemotherapy appear to have greater efficacy in tumors with higher mitotic and proliferative indices. For atypical or intermediate disease, the data are extrapolated from small cell lung cancer recommendations.

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, observation or adjuvant therapy (category 2B) in the presence or absence of radiotherapy (category 2B) may be considered. Systemic therapy regimens may include cisplatin/etoposide, carboplatin/etoposide, or temozolomide. There are limited data on the effectiveness of adjuvant therapy in this setting. Response rates in small studies with less than 40 patients with atypical carcinoid (neuroendocrine tumors) found a 19% to 22% response rate when patients were treated with any chemotherapy.[78-80] Otherwise, efficacy has been extrapolated from small cell lung cancer trials.[81-83]

There are limited data on the efficacy of chemoradiation for unresectable IIIA or IIIB lung neuroendocrine tumors; however, some panel members consider chemoradiation in this situation. If surgical resection is not medically feasible for patients with low-grade, stage IIIA or stage IIIB disease, then observation or systemic therapy may be considered. Additionally, RT (category 3) with or without chemotherapy (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 systemic therapy, or systemic therapy alone are generally recommended. Chemoradiation is thought to have the most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices.[78,79]

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.[84,85]

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.[86] 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 (neuroendocrine) tumors, small-vessel invasion was a risk factor for metastases in patients with tumors <2 cm.[87]

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 intravenous (IV)

contrast. Chest CT scans with contrast and biochemical evaluations may be performed as appropriate or as clinically indicated. To make an unequivocal diagnosis, somatostatin receptor-based imaging may be considered if there are equivocal CT findings. If no distant disease is identified, patients 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 with negative margins may be sufficient, but for resection with indeterminate margins and low grade (G1), endoscopy at 6 to 12 months by endoscopy is recommended to assess for residual disease. If endoscopy results determine residual disease or intermediate grade after endoscopy, or if the small incidental tumors have indeterminate margins and intermediate grade (G2), the pathway for all other rectal tumors should be followed. All other rectal lesions should be staged using rectal MRI or endorectal ultrasound. 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 (EUA) 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.[88]

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.[89]

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 12 to 24 months for up to 10 years. If initial scans are negative, the frequency of follow-up scans may decrease. For high-grade tumors, more frequent surveillance may be appropriate.

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.[90,91] 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; $P < .001$).[92] 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-HIAA, a metabolite of serotonin, in a 24-hour urine or plasma 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 neuroendocrine 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 18F-fluorodeoxyglucose (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 and negative margins, prognosis is excellent and no follow-up is usually required. Follow-up endoscopies with rectal MRI or endorectal ultrasound are recommended for rectal tumors that are small (<1 cm) with indeterminate margins and residual disease or intermediate grade, or 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,[93-95] 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 Advanced Disease 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.[96,97] The most common sites of metastases from intestinal neuroendocrine

tumors include regional/mesenteric lymph nodes, liver, and bones. When evaluating locoregional advanced and/or metastatic neuroendocrine tumors of the GI tract, lung, and thymus, or for suspected carcinoid syndrome, abdominal/pelvic multiphasic CT or MRI scans with IV contrast and chest CT scans with contrast are recommended. Chest CT scans may be performed with or without contrast when evaluating for metastases from primary tumors in other sites.

Somatostatin receptor-based imaging, if not already done, is recommended to assess the somatostatin receptor status of locoregional advanced 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;[98] therefore, FDG-PET/CT may be considered for neuroendocrine tumors that are poorly differentiated or have atypical histology. If carcinoid syndrome is suspected, a cardiology consultation and echocardiogram is recommended to assess whether the patient has carcinoid heart disease, and somatostatin receptor-based imaging may be considered to assess the somatostatin receptor status of neuroendocrine tumors.[99]

Baseline levels of chromogranin A (category 3) or 24-hour urine or plasma 5-HIAA may also be considered, and then repeated over time to monitor subsequent disease progression. As previously mentioned, if carcinoid syndrome is suspected, evaluation of serotonin secretion, using a 24-hour urine or plasma 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;[100] 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 Advanced 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.[101] 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 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.[102-104]

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 GI neuroendocrine tumors, gastrinomas, or tumors secreting vasoactive intestinal polypeptide (VIPomas).[105-109] 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.[110] 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 may be considered for persistent symptoms (eg, diarrhea). Telotristat is not indicated for

flushing due to poorly controlled carcinoid syndrome. 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.[111,112] 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. The TELESTAR study was 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.[113] 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 ($P < .001$).[113] Compared to placebo, treatment with telotristat at either dosage did not result in a statistically significant change in the number of observed flushing episodes;[113] therefore, additional options should be considered to manage other symptoms associated with carcinoid syndrome. Additional therapies that may be considered to achieve disease control are hepatic arterial embolization with or without cytoreductive surgery for hepatic-predominant disease or other systemic therapy based on disease site.

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,[101] or as clinically indicated. Cardiac heart disease is frequent in patients with carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation.[114,115] 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.[116] To monitor disease control and/or progression, surveillance imaging of the abdomen and pelvis using multiphasic CT or MRI every 3 to 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 LAR or lanreotide is recommended to potentially control tumor growth if they are not already receiving it. The recommendation to consider octreotide LAR 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 (proliferative index, Ki-67, up to 2%), which showed median times to tumor progression of 14.3 and 6 months in the octreotide LAR and placebo groups, respectively ($P = .000072$).[117] 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[118] found that 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; $P = .51$).[119] However, post-study treatment included octreotide LAR 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 (proliferative index, Ki-67, up to 10%) 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; $P < .001$).[120] Subsequent data from a pre-planned interim analysis of the open-label extension of the CLARINET study estimated PFS in patients treated with lanreotide at 32.8 months (95% CI, 30.9–68.0).[121] The difference in the reported median PFS between the PROMID and CLARINET studies is likely explained by a difference in the study populations, as the majority of the patients enrolled in the CLARINET trial had stable disease in the 3 to 6 months before randomization. [120]

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 OS rate was 50.4%.[122] A recent systematic review reported 5-year OS rates ranging from 41% to 100% in patients undergoing hepatic resection.[123] Most patients with resected metastatic disease, however, will eventually experience recurrence.[124,125] 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.[123] However, taking a careful history is recommended as surgery may be an option for asymptomatic patients with previous, intermittent obstructions. A recent retrospective study did not find a survival improvement of resecting asymptomatic primary small bowel tumors.[126] 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.[101]

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

For patients with locoregional advanced, hepatic-predominant, progressive disease or patients with poorly controlled carcinoid syndrome, hepatic-directed therapies are recommended, mainly with the palliative goals of extending life and relieving hormonal symptoms.[127-130]

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).[131-135] Ablative

therapy in this setting is non-curative. Data on the use of these interventions are emerging. For unresectable liver metastases, hepatic regional therapy (arterial embolization,[136] chemoembolization,[137-139] or radioembolization [category 2B])[139-146] is recommended. No single modality of embolization therapy has been shown to be superior to another, but there is a difference in both long-term and short-term toxicities among the different modalities.

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

For patients with progressive metastatic GI tract neuroendocrine tumors or intermediate grade (atypical) bronchopulmonary neuroendocrine tumors, everolimus is a recommended treatment option. However, the safety and effectiveness of everolimus in the treatment of patients with carcinoid syndrome have not been established. Everolimus is an inhibitor of mTOR and was well tolerated and showed evidence of antitumor effect in patients with advanced neuroendocrine tumors when given with octreotide LAR in a phase II trial.[147] 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.[148] 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. An open-label extension of the RADIANT-2 trial allowed patients who had progressed or completed the double-blind core phase to take everolimus plus octreotide LAR. The median OS was not statistically different for patients receiving everolimus plus octreotide LAR (29.2 months) or placebo plus octreotide LAR (during the open-label extension; 35.2 months) at the final cutoff date.[149] Adverse events associated with everolimus included stomatitis, rash, fatigue, and diarrhea.[148,149] Other side effects have also been described.[150-152]

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.[153] 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 real-world 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.[154] An increased risk of adverse events in patients who had received previous radiolabeled peptide therapy or chemotherapy was noted. A recent exploratory analysis of a subgroup of patients with advanced, progressive, well-differentiated, non-functional lung neuroendocrine tumors from RADIANT-4 reported improved PFS by central review (HR, 0.50; 95% CI, 0.28–0.88) in the everolimus arm (9.2 months) compared to the placebo arm (3.6 months).[155] Additionally, a secondary endpoint analysis of RADIANT-4 found that health-related quality-of-life outcomes were maintained in patients receiving everolimus and placebo, with no significant difference between them.[156]

The panel distinguishes the recommendations for everolimus for advanced disease. Everolimus is an option that may be considered for patients with locoregional advanced bronchopulmonary/thymic disease

and/or distant metastases who have clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical). However, everolimus is recommended as a treatment option for patients with progressive metastatic GI tract neuroendocrine tumors.

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 neuroendocrine tumors appear, at best, to be modest. Tumor response rates are generally low, and no PFS benefit has been clearly demonstrated.[157]

Capecitabine was tested in patients with metastatic carcinoid (neuroendocrine) tumors in a phase II trial; no objective responses were reported, although 13 of 19 patients were reported to have experienced stable disease.[158] 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.[159] 5-FU was assessed in the phase III E1281 trial in combination with streptozocin or doxorubicin.[160] 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 (neuroendocrine tumors) are rare.[161]

A phase II trial assessed bevacizumab plus capecitabine and included 49 patients with advanced and/or metastatic GI neuroendocrine tumors.[162] A PFS of 23.4 months was reported, with 18% of patients achieving a partial response and 70% achieving stable disease. Similar results were seen in 2 small trials of FOLFOX (fluorouracil, leucovorin, oxaliplatin) and CAPOX (capecitabine, oxaliplatin) combined with bevacizumab where a PFS of 19.3 months and 16.7 months, respectively, was reported.[163] However, these findings have not been confirmed in phase III studies.

The panel lists cytotoxic chemotherapy (namely 5-fluorouracil [5-FU], capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide) for progressive neuroendocrine tumors of the GI tract as a category 3 recommendation. While some panelists believe the toxicity of systemic therapy does not warrant its widespread 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.[78,164] In a retrospective study of 31 patients with progressive metastatic bronchial neuroendocrine tumors, temozolomide monotherapy was associated with partial responses in 14% of patients.[164]

Alpha Interferon: Use of interferon in the setting of advanced GI tract neuroendocrine tumors is a category 3 recommendation. In several large, non-randomized series, interferon alpha has been shown to be associated with an antitumor effect in patients with advanced GI neuroendocrine tumors.[103,165-168] In a recent, large randomized study led by the Southwest Oncology Group, treatment with interferon alpha-2b (5 million units 3 d/wk) was compared to treatment with bevacizumab (15 mg/kg administered every 21 days) in 427 patients with progressive neuroendocrine tumors.[169,170] Treatment with octreotide was included in both arms of this study. 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.[169,170] Because of its potential side

effects, interferon is usually not initiated until failure of somatostatin analog treatment.[157]

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

Several early studies initially reported that treatment with radiolabeled somatostatin analogs was associated with tumor responses in patients with advanced neuroendocrine tumors.[171-175] A prospective phase II study of radiopeptide therapy in 90 patients with metastatic neuroendocrine tumors refractory to octreotide showed that treatment was associated with improvement in symptoms; radiographic regression, however, was relatively uncommon.[176] Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.[177-179]

A recent phase III study, NETTER-1, randomized 229 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).[180] Objective tumor responses were observed in 18% of patients who received ^{177}Lu-dotatate versus 3% in the control group ($P <$ .001).[180] Another recent study examined the long-term efficacy, survival, and toxicity of ^{177}Lu-dotatate in a group of 610 Dutch patients with metastatic gastroenteropancreatic and bronchial neuroendocrine tumors.[181] PFS and OS for all patients were 29 months [95% CI, 26–33 months] and 63 months (95% CI, 55–72 months), respectively.[181] Other smaller studies also found improved OS (58.8 months, n = 114)[182] and median PFS (20.1 months with typical disease and 15.7 months with atypical disease; n = 34)[183] with peptide receptor radionuclide therapy (PRRT) treatment in patients with advanced bronchopulmonary neuroendocrine tumors.

PRRT with ^{177}Lu-dotatate was approved by the FDA in January 2018 for the treatment of adult patients with unresectable, low- or intermediate-grade, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors.[184] NCCN recommends considering PRRT with ^{177}Lu-dotatate as a treatment option for some patients with advanced and/or metastatic GI tract, bronchopulmonary, and thymic neuroendocrine tumors that are somatostatin receptor positive with imaging. Treatment with ^{177}Lu-dotatate is recommended for patients with unresectable GI neuroendocrine tumors that have progressed if there was somatostatin receptor-positive imaging (category 1 for mid-gut tumors). Treatment with ^{177}Lu-dotatate may also be considered for patients with bronchopulmonary or thymic neuroendocrine tumors, somatostatin receptor-positive imaging, and disease progression while taking octreotide or lanreotide, if the tumor is either low grade (typical) with clinically significant tumor burden, or intermediate grade (atypical). Please see *Principles of Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-dotatate* in the algorithm for practical guidance and information, including patient eligibility, patient preparation for treatment, dose and administration of ^{177}Lu-dotatate, post-treatment instructions, and timing of somatostatin analogues.

Use of Somatostatin Analogs with ^{177}Lu-Dotatate

Most patients treated with PRRT will have progressed on first-line somatostatin analog treatment. Patients with hormonally functional tumors should continue octreotide or lanreotide along with ^{177}Lu-dotatate. It is unclear whether patients with nonfunctional tumors benefit from continuation of somatostatin analog treatment during and after ^{177}Lu-dotatate treatment. A recent study looked at whether ^{68}Ga-dotatate uptake before or after long-acting somatostatin analog treatment was affected in patients with neuroendocrine tumors and found that the uptake in the primary tumor and metastatic sites were not

compromised.[70] However, there are still theoretical concerns regarding the competition between somatostatin analogs and ^{177}Lu-dotatate for somatostatin receptor binding. Somatostatin analog treatment interruption may not be necessary, but the panel recommends the following adjustments. Concomitant use of long-acting somatostatin analogs such as lanreotide and octreotide is not recommended in the 4 to 6 weeks prior to each treatment with ^{177}Lu-dotatate. Additionally, short-acting somatostatin analogs should be stopped 24 hours before each ^{177}Lu-dotatate treatment. Somatostatin analogs (short- and long-acting) can be resumed 4 to 24 hours after each ^{177}Lu-dotatate treatment. IV infusion of amino acids is a critical part of ^{177}Lu-dotatate therapy for nephroprotection.

Liver Transplantation Considered Investigational 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.[185-190] Results from a multicenter database of 85 patients at 28 centers who underwent liver transplantation for neuroendocrine tumors were also reported.[191] A recent meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.[192] 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 Advanced 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 neuroendocrine tumors to intermediate-grade atypical neuroendocrine tumors.[193] 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. The phase 3 RADIANT-2 trial included 44/429 patients with lung neuroendocrine tumors and only 9 of these were atypical carcinoids.[80] However, this study did not stratify according to the type of tumor; 33 patients received octreotide LAR + everolimus and 11 patients received octreotide LAR + placebo. 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. If patients are asymptomatic, observation may be appropriate.

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[164]; or initiation of treatment with carboplatin or cisplatin and etoposide. Cisplatin/etoposide, carboplatin/etoposide, or temozolomide may be considered for tumors on the higher end of the atypical category with respect to Ki-67, mitotic index, and grade, especially for tumors that are poorly differentiated histologically.[78] These treatments may be given with or without octreotide or lanreotide. Observation may be considered for patients with tumors on the lower end of the proliferative index-defined spectrum. If disease progression is observed on first-line therapy, the panel recommends considering changing the therapeutic intervention.

Although rare, some patients may present with multiple lung nodules or tumorlets and widespread peripheral airway neuroendocrine cell hyperplasia. In this case, a diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) can be made.[193] This condition is generally indolent, and patients can be observed with chest CT scans without contrast every 12 to 24 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.[194] 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.[194,195] 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.[47] An estimated 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional. The remainder manifest with clinically evident hormonal symptoms.[12,47] Consistent with these numbers, analysis of the NCCN Neuroendocrine Tumors Outcomes Database found that 22% of patients with pancreatic neuroendocrine tumors have a hormonal syndrome.[59] 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.[195] The remaining rare pancreatic neuroendocrine tumors include VIPoma and cholecystokinin-producing tumors (CCKomas).[196]

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.[197]

Evaluation of Neuroendocrine Tumors of the Pancreas

The recommended evaluation also includes an abdominal multiphasic CT or MRI scan with contrast. A chest CT scan with or without contrast may be included as appropriate. Somatostatin receptor-based imaging and EUS can also be considered if additional imaging is needed.[198] Consideration of genetic testing for inherited genetic syndromes is recommended for all patients with pancreatic neuroendocrine tumors. Personal and family history should also be evaluated in patients with pancreatic neuroendocrine tumors for the possibility of MEN1 (see

Multiple Endocrine Neoplasia, below) or other hereditary syndromes as appropriate.

Hormone-secreting tumors, even when very small, may result in significant clinical symptoms, and lesion identification can be difficult.[199] These cases often require additional imaging, such as EUS and somatostatin scintigraphy.

Because many pancreatic neuroendocrine tumors secrete hormones, biochemical evaluation should also be considered in patients with pancreatic neuroendocrine tumors.[195] Biochemical evaluation is generally guided by the presence of symptoms that might indicate excess hormone secretion. Screening for hormones in asymptomatic individuals is not routinely recommended. However, chromogranin A is non-specific and is often elevated in all neuroendocrine tumors. 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 peptic ulcers. Glucagonomas are associated with the development of hyperglycemia or diabetes mellitus and/or migratory necrolytic erythema. Patients with somatostatinomas may also present with hyperglycemia or diabetes mellitus and/or diarrhea/steatorrhea. VIPomas are characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) from secretion of VIP. The guidelines describe appropriate tests for each of these situations. Non-functioning tumors are not accompanied by any symptoms or hormone secretion, but often have elevated pancreatic polypeptide (PP; category 3) and chromogranin A (category 3), which can be tested.

Chromogranin A levels are elevated in 60% or more of patients with either functioning or nonfunctioning pancreatic endocrine tumors.[200-202] 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; $P < .001$).[92] Chromogranin A was also found to be a prognostic factor in a prospective study of patients treated with everolimus.[203] 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 serum gastrin levels.[204] 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 confirm diagnosis, gastrin levels must be measured after the patient is off PPI therapy for at least 1 week.[205]

Imaging with abdominal multiphasic CT/MRI scan with IV contrast is recommended. Other tests, such as somatostatin receptor-based imaging, chest CT scan with or without contrast, EUS, and other biochemical tests, such as chromogranin A levels (category 3), may be performed as appropriate. Approximately 70% of patients with MEN1 and gastrinoma have tumors situated in the duodenum.

Evaluation of Insulinomas

Insulinomas should be suspected in people who have hypoglycemia (generally fasting or nocturnal) and a pancreatic mass. However, some insulinomas can be small and not visible on imaging and so should be suspected in persons presenting with hypoglycemia. Evaluation with a 72-hour fast, which tests serum insulin, pro-insulin, and C-peptide during concurrent hypoglycemia, is the gold standard.[206] 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 is suspicious for insulinoma.[206] Other biochemical tests, such as chromogranin A levels (category 3), may be performed as appropriate. Other causes of hypoglycemia, such as adrenal insufficiency, malnutrition, and other causes of non–insulin-mediated hypoglycemia should be ruled out prior to performing a 72-hour fast. The *Endocrine Society Guidelines on Hypoglycemia* have details regarding the general workup for hypoglycemia.[206]

Imaging with abdominal multiphasic CT with contrast or MRI is recommended to localize insulinomas. Some insulinomas are too small to be imaged with CT or MRI, and in those cases EUS can be useful. If imaging is negative, then insulinomas can often 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).[207] Most experts recommend this test only for patients with persistent or recurrent insulin-mediated hypoglycemia and when other localization tests are equivocal or negative.

Ninety percent of insulinomas pursue an indolent course and can be cured surgically. To rule out metastatic disease, chest CT scans with or without contrast and somatostatin receptor-based imaging can also be done. However, 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).[208]

Evaluation of Glucagonomas and VIPomas

For patients with recent-onset diabetes, cachexia, and/or a necrolytic erythematous skin rash and a pancreatic mass, the panel recommends a blood test for glucagon and blood glucose. For suspected VIPomas with characteristic watery diarrhea, testing for VIP and electrolytes is recommended. For both glucagonomas and VIPomas, abdominal multiphase contrast-enhanced CT or MRI scans with IV contrast is recommended to identify the primary tumors. Chest CT scans with or without contrast can be performed. Somatostatin receptor-based imaging and EUS can be performed as appropriate if the tumor is not able to be localized or there is concern for metastatic disease.

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.[101] 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.[208] Octreotide and lanreotide should not be used in patients with insulinoma who have a negative result by somatostatin receptor-based imaging.

In addition, specific measures are often recommended based on symptoms. For insulinomas, it is important to stabilize glucose levels with diet and/or diazoxide. For gastrinomas, gastrin hypersecretion may be treated with high-dose PPIs. For patients with glucagonoma, treatment of hyperglycemia and diabetes is necessary, especially to control blood sugars prior to surgery. 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.[209,210] 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.[211-213] Other retrospective studies suggest that nonoperative management can be safe for nonfunctioning pancreatic neuroendocrine tumors <1.7 cm or <3 cm.[214,215] Based on these limited data, the panel includes observation alone as a recommended option for selected cases of incidentally discovered, small (<1 cm), low-grade 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. Serial imaging is recommended and lymph node resection should also be considered for tumors of 1 to 2 cm, because there is a small but real risk of lymph node metastases.[216,217] For prolonged surveillance, imaging studies without radiation are preferred.

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 and splenectomy. Gastrinomas in some cases may be associated with lymph node metastases,[218] which are removed with 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 tumor location 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.[219]

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.[220,221] Therefore, perioperative anticoagulation can be considered because of the increased risk of pulmonary emboli.

Surgical Management of VIPomas

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

Surgical Management of Other Pancreatic Neuroendocrine Tumors

The treatment recommendations for tumors secreting hormones such as somatostatinoma, ACTH, parathyroid hormone-related peptide (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.[222-224] Higher lymph node ratio and Ki-67 status may indicate a higher chance of recurrence.[222] 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.[225] In select cases, including resectable locoregional or oligometastatic recurrence, surgical resection may be considered.

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

To evaluate the extent of locoregional advanced disease and/or distant metastases, multiphasic CT or MRI scans with IV contrast of the abdomen and pelvis should be performed. Somatostatin receptor-based imaging is also recommended. 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 patient population.[123] 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.[226] Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence.[124,125] 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 OS rate of 50.4%.[122]

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.[101]

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 targeted agents (everolimus, sunitinib, or peptide receptor radionuclide therapy; 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; $P < .001$).[120] 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 (neuroendocrine) tumors of the midgut.[117] 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.[227] 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.[228-230] Everolimus can also be considered to stabilize glucose levels for patients with insulinomas.[231] Adverse events associated with everolimus include stomatitis, hyperglycemia, and, in rare cases, pneumonitis.[227] Other side effects have also been described.[150-152] 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.[154] 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.[232] 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%.[232] A large proportion of patients on the placebo arm subsequently received sunitinib at progression, and no significant difference in OS was observed between the arms.[233] Adverse events associated with sunitinib include fatigue and, in rare cases, congestive heart failure.[234] Other side effects have also been described, including diarrhea, mucositis, and weakness.[235-237]

Cytotoxic Chemotherapy for Advanced Pancreatic Neuroendocrine Tumors

Cytotoxic chemotherapy is another option for patients with locoregional advanced 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.[238] A retrospective review from MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin.[239] A phase II trial assessed bevacizumab combined with 5-FU and streptozocin.[240] A PFS of 23.7 months was reported, with 56% of patients achieving a partial response and 44% achieving stable disease.

Oral temozolomide-based therapy is also used in patients with advanced pancreatic neuroendocrine tumors. Temozolomide has been administered using different schedules, either alone or in combination with other agents.[161,241-244] 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.[244] Another retrospective review of the temozolomide and capecitabine combination reported a 61% response rate in 18 patients, with 1 surgically proven complete pathologic response.[245] A small retrospective study (7 patients) reported a response rate of 43%.[246]

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).[241] 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.[247]

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.[160] 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.[248,249] 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.[159]

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.[171-175] Numerous large, non-randomized cohort analyses have also reported encouraging survival rates with this approach.[178,179,181] Most recently, the study of ^{177}Lu-dotatate in a group of 610 Dutch patients with metastatic gastroenteropancreatic neuroendocrine tumors and bronchial neuroendocrine tumors included 133 patients with pancreatic neuroendocrine tumors.[181] Patients with a primary neuroendocrine tumor in the pancreas had the longest OS (71 months) and 6 patients had a complete response.[181] In general, these studies have enrolled only patients with evidence of high tumoral somatostatin receptor expression. A randomized study of high-dose octreotide versus ^{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.[180,250] Prospective, randomized studies of radiolabeled somatostatin analogs have not yet been completed in patients with advanced pancreatic neuroendocrine tumors. [251]

The panel recommends PRRT with ^{177}Lu-dotatate as a treatment option for patients with locoregional advanced pancreatic neuroendocrine tumors and/or distant metastases who have symptomatic disease, clinically significant tumors burden, or clinically significant progressive disease, and disease progression with positive somatostatin receptor imaging.

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.[129] The panel lists cytoreductive surgery or ablative therapy (ie, RFA,[135] cryotherapy, microwave[132,134]) as category 2B recommendations for these patients. Although some groups report that the risks of cytoreductive surgery outweigh its benefits,[252] others have reported good outcomes.[253,254]

Additional options include hepatic regional therapies including bland hepatic arterial embolization,[136] radioembolization (category 2B),[140-146] and chemoembolization.[255] Whereas embolization in general is considered an effective approach in patients with hepatic-predominant disease,[127,128,130] only limited data compare the various embolization techniques, and the optimal embolization approach remains uncertain.

Liver Transplantation Considered Investigational

Several series have now reported the results of liver transplantation in patients with pancreatic neuroendocrine tumors whose metastases are confined to the liver.[185-190,256] A meta-analysis showed that, while 5-year survival rates are encouraging, the majority of patients undergoing liver transplantation ultimately develop recurrence.[192] 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

A SEER database analysis reported high incidence rates for neuroendocrine tumors with an unknown primary site of 0.84 per 100 000 persons.[1,2] 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.[257,258] If the primary tumor cannot be identified, treatment decisions are generally guided by tumor histology (see *Histologic Classification and Staging of Neuroendocrine and Adrenal Tumors*, above). Many of these tumors are poorly differentiated and aggressive.[259]

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.[64,260] 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.[261] It is not uncommon for small bowel neuroendocrine 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.[261]

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

Adrenal Gland Tumors

Adrenocortical carcinomas (ACCs) are rare (incidence, 0.7–2 per million).[262,263] ACC has a bimodal age distribution, with peak incidences in early childhood and the fourth to fifth decades of life. Women are more frequently affected (55%–60%).[262,264] Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beckwith-

Wiedemann syndrome, MEN1, Lynch syndrome, and familial adenomatous polyposis.[6,265-270] 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[271,272]) and alterations at the 11p15 locus (site of the *IGF2* gene[273,274]) seem to occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.[263] 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, dorsocervical fat pad and 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.[263] 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.[263] 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, dorsocervical fat pad and 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.[263] 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.[263]

Evaluation and Treatment of Adrenal Gland Tumors

All patients with adrenal gland tumors need biochemical evaluation and appropriate imaging. Biochemical evaluation to evaluate for hyperaldosteronism, hypercortisolemia, and pheochromocytoma should be done with every adrenal mass. Comprehensive guidelines for the workup of adrenal tumors, adrenal incidentalomas, hyperaldosteronism, Cushing's syndrome, and pheochromocytoma and paraganglioma are published through the Endocrine Society[275-277] and the European Society of Endocrinology (ESE).[278,279]

NCCN recommends doing a morphologic evaluation of adrenal nodules with adrenal protocol CT with contrast, or MRI with or without contrast, to determine the size, heterogeneity, lipid content (with MRI), contrast washout (with CT), and margin characteristics. Functional evaluation should be done as noted above. Most adrenal cortical carcinomas express multiple hormones; therefore, if imaging is suspicious for adrenal cortical carcinoma, evaluation for sex steroid in addition to the above evaluation is indicated. If several hormones are over-secreted, adrenal cortical carcinomas are more likely.

History of cancer in another site raises the question of metastatic disease. In these patients, an image-guided needle biopsy can be considered only if clinical suspicion for pheochromocytoma is low and plasma or urine fractionated metanephrines are normal. False-negative biopsies are possible; therefore, proceeding directly to surgery should be considered in some 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.

Evaluation and Treatment of Hyperaldosteronism

When hyperaldosteronism (also called *primary aldosteronism*) is suspected, serum aldosterone and plasma 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.[277] Confirmatory testing is often recommended 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.[277]

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 4 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.[279]

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 two causes of benign hyperaldosteronism and should be considered if the patient is a surgical candidate, because CT imaging is not always reliable in differentiating between the two. It may be reasonable, however, to exclude adrenal vein sampling in patients younger than 35 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 one 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.[276,280] Elevated levels of cortisol are indicative of Cushing's syndrome. If there is evidence of hypercortisolemia, then ACTH should be checked to determine if it is ACTH-mediated. Adrenal masses that secrete cortisol are non–ACTH-mediated. Endocrinology referral should be considered for the biochemical workup and localization of hypercortisolemia.

Cushing's syndrome can be associated with either benign adrenal tumors (adrenal adenoma) or malignant adrenal tumors. Malignancy should be suspected if the tumor is larger than 4 cm or is inhomogeneous with irregular margins and/or has 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 are 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. It is important that patients who have cortisol-secreting adrenal tumor receive perioperative glucocorticoids. For more details, please see the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome.[281]

Treatment of Nonfunctioning, Benign Adrenal Tumors

Adrenal tumors that do not secrete hormones are often discovered incidentally during scans for unrelated reasons (*incidentalomas)*. It is still important to evaluate for biochemical secretion of hormones for hyperaldosteronism, Cushing's syndrome, and pheochromocytoma and paraganglioma as listed above to confirm they are non-secreting. Please refer to the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AACE/AAES) guidelines[282] and the ESE guidelines[279] for the management of adrenal 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 Adrenocortical Carcinoma

ACC should be strongly suspected in nonfunctioning tumors larger than 4 cm with irregular margins or that are internally heterogeneous.[263] On CT scans with IV 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.[263] 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.[283] MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.[263] 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 undergo genetic testing for mutations associated with Lynch syndrome.[269] Patients with ACC may also consider microsatellite instability (MSI) or mismatch repair (MMR) testing.

Treatment and Surveillance of Nonmetastatic Adrenocortical Carcinoma

Surgical resection of the tumor with removal of adjacent lymph nodes is recommended in patients with localized ACC, 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.[284]

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.[285] A recent systematic review and meta-analysis of the benefits of mitotane after resection of ACC in patients without distant metastasis included 5 retrospective studies reporting on 1249 patients.[286] The meta-analysis found benefit of adjuvant mitotane, with significantly longer recurrence-free survival and OS, 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. For monometastatic or polymetastatic disease, local therapy may be considered (ie, RFA, RT).

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.[287-289] Partial response rates are thought to be 10% to 30% at most.[290]

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.[291] Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%.[292] 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 OS (14.8 vs. 12.0 months; HR, 0.79; 95% CI, 0.61–1.02; *P* = .07).[293] However, response rates and PFS were improved with the 4-drug regimen and an OS 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 two 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.[290] 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 sympathetic and para-aortic sympathetic ganglia are called paragangliomas.[275] 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.[294] Approximately 10% to 15% of pheochromocytomas and paragangliomas are malignant, but it could be up to 40%.[278,295] Pheochromocytomas release catecholamines (epinephrine and norepinephrine) and their metabolites metanephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. About 40% of paragangliomas secrete catecholamines. Head and neck paragangliomas only secrete catecholamines about 5% of the time and often it is dopamine.

The peak incidence of occurrence for pheochromocytomas is between the third and fifth decades 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.[296] 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.[297] For those without metastases, the rate of identification of these mutations was still high, at 64.7%. The OS of patients with pheochromocytomas and paragangliomas can be heterogeneous, but a systematic review and meta-analysis of 7 studies of 738 patients reported survival be 63% at 5 years.[298] Predicting who will go on to develop metastasis is difficult, but some studies have reported that almost half of patients have not progressed a year after diagnosis.[299] Delays at a median of 5.5 years with a range from 0.3 to 53.4 years between initial diagnosis and metastasis have been reported in a retrospective study spanning 55 years of patients with pheochromocytomas or paragangliomas, and many such patients

survive long term after treatment of metastatic disease.[300] 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, and chromogranin A level. Elevated levels of metanephrines or normetanephrines are suggestive of pheochromocytoma or paraganglioma. In general, adrenal pheochromocytomas more commonly secrete metanephrines and paragangliomas secrete normetanephrines, with a few exceptions.[275] Concurrent medications should be reviewed before metanephrine/normetanephrine 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.[301] Elevations in metanephrine levels that are 3 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.[302] Measurement of serum and/or 24-hour urine fractionated catecholamines for dopamine levels can be considered for cervical or head and neck 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 (ie, ^{68}Ga dotatate, PET/CT [preferred], somatostatin receptor scintigraphy), 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.[294,303] Pheochromocytomas occur in patients with MEN2A, MEN2B, and other familial diseases such as neurofibromatosis, von Hippel-Lindau syndrome, Osler-Weber-Rendu syndrome, and polycythemia-paraganglioma-somatostatinoma syndrome. In addition to germline mutations associated with these syndromes (ie, *RET, NF1*, *VHL*, *SMAD4, ENG, ALK1, EPAS1*), germline mutations in *SDHB*, *SDHA*, *SDHAF2*, *SDHD*, *SDHC*, *TMEM127*, *MAX*, *FH, HIF2A*, and *MDH2* have also been associated with an increased incidence of pheochromocytomas and paragangliomas.[295,303-309] *SDHB* gene mutations are associated with a 40% to 60% risk of developing metastatic disease.[295] 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.[309] Because a significant proportion of patients with a pheochromocytoma or paraganglioma have a heritable mutation,[303] 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.[275]

Individuals with known germline mutations associated with pheochromocytomas and paragangliomas should undergo lifelong biochemical and clinical surveillance, beginning around ages 6 to 8 years.[309] 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.[310-312]

For locally unresectable tumors, RT can be considered with cytoreductive resection, when possible. Alternatively, if tumors are positive on MIBG scan,[313,314] treatment with high-specific-activity (HSA) iobenguane ^{131}I or other iodine-131-MIBG therapy is recommended. If tumors are somatostatin receptor positive upon imaging, PRRT with ^{177}Lu-dotatate may be considered. The panel advises diligence to ensure that the maximum cumulative radiation dose is not reached for these patients. In addition, medical therapy should be continued for unresectable secreting tumors.

A study of 20 patients with high somatostatin receptor expressing pheochromocytoma or paraganglioma treated with ^{177}Lu-dotatate measured the effectiveness of PRRT in controlling hypertension.[315] Most patients receiving PRRT saw no increase or reduction in medication to treat hypertension. The median PFS was 39 months and median OS was not reached with a median follow-up time of 28 months.

An ENETS Centre study with 22 patients with progressive or metastatic pheochromocytomas or paragangliomas were treated with PRRT with either ^{90}Y-dotatate or ^{177}Lu-dotatate, and ^{131}I-MIBG treatment.[316] Patients treated with PRRT had increased PFS and treatment response compared to ^{131}I-MIBG treatment, but no significant differences were seen in OS. Other case studies have been presented at conferences[317-319] or published[320,321] that have also shown improvements in patients with high somatostatin receptor expressing pheochromocytoma or paraganglioma treated with ^{177}Lu-dotatate.

When distant metastases are present, observation is recommended if asymptomatic and medical therapy should be continued for secreting tumors. For the latter, cytoreductive resection is recommended when possible. Other options for treating unresectable, metastatic disease include: 1) clinical trial; 2) systemic chemotherapy (eg, cyclophosphamide/vincristine/dacarbazine [CVD] or temozolomide)[242,322-325]; 3) HSA iobenguane ^{131}I or other iodine-131-MIBG therapy after positive MIBG scan;[313,314,326,327] 4) considering PRRT with ^{177}Lu-dotatate (if somatostatin receptor-positive imaging); or 5) 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.[323] 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.[328] 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.[329] Partial and complete responses were seen in 27% and 3% of patients, respectively.

The results of a phase 2, open-label, multicenter study investigating HSA iobenguane ^{131}I to treat patients with malignant, recurrent, and/or unresectable pheochromocytoma or paraganglioma were recently presented.[326,327] The primary endpoint was reduction in antihypertension medication by at least half, which was met by 25% of all patients who received at least one therapeutic dose (n = 68), and 32% of patients who received 2 therapeutic doses (n = 50). The objective tumor response was evaluated as a secondary endpoint. Overall 23% of patients had partial response, which went up to 30% in 15/50 patients who received 2 therapeutic doses, and 68% of patients had stable disease. The median OS was 37 months. The most commonly reported side effects in patients who received any dose of HSA iobenguane ^{131}I were nausea, myelosuppression, and fatigue. In 2018, HSA iobenguane ^{131}I became an FDA-approved option for patients who have an MIBG positive scan; have unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma; and require systemic anticancer therapy.

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 then 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 or Unknown Primary

Although rare, extrapulmonary poorly differentiated neuroendocrine carcinomas can 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. Gastrointestinal tumors with mixed histology of poorly differentiated adenocarcinoma can be treated according to the NCCN Guidelines for Colon Cancer (available at www.NCCN.org).

Results from a SEER database analysis of neuroendocrine carcinomas found that 9% were extrapulmonary.[330] The median survival of patients with GI neuroendocrine carcinomas was 7.5 months, with patients with small intestine tumors doing better (25.1 months) than patients with pancreatic tumors (5.7 months). The median survival for patients with unknown primary neuroendocrine carcinomas was 2.5 months.

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

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 or Unknown Primary

For resectable poorly differentiated/large or small cell neuroendocrine carcinomas or poorly differentiated of unknown primary, treatment options depend on the disease site. Surgical resection and adjuvant chemotherapy with or without radiotherapy, neoadjuvant chemotherapy with or without radiation and resection, chemotherapy alone, RT alone, and definitive chemoradiation according to the NCCN Guidelines for Small Cell Lung Cancer are options that may be considered (see NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org). For unresectable locoregional disease, concurrent or sequential radiotherapy in combination with chemotherapy, or chemotherapy alone are recommended. If metastatic tumors are present, chemotherapy alone is recommended.

Small cell lung regimens, such as FOLOFOX, FOLFIRI, and temozolomide with or without capecitabine, 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%).[30] 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. Systemic options as described for the management of locoregional advanced or metastatic bronchopulmonary, thymic, and GI tract disease may be considered as appropriate, particularly for high-grade tumors that are well-differentiated. 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 or Unknown Primary

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) 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 an 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 hyperparathyroidism (most commonly 4-gland hyperplasia), pituitary adenomas, and pancreatic neuroendocrine tumors; MEN1 may also be associated with neuroendocrine 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 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),[331] 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.[332] Somatic mutation of the *MEN1* gene is also the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial neuroendocrine tumors.[6] Somatic *RET* mutations are found in sporadic MTC.[333]

MEN1

MEN1 (or Wermer syndrome) is typically characterized by tumors of the parathyroid and pituitary glands; neuroendocrine tumors of the pancreas, thymus, bronchi, or gastrointestinal tract; adrenal tumors; and/or 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.[6] About 30% to 40% 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.[334] Approximately 2% of patients with MEN1 develop thymic or bronchopulmonary neuroendocrine tumors.[335] Approximately 30% of patients with MEN1 die from the neuroendocrine tumor.[335]

Examples of functional syndromes include hypercalcemia related to parathyroid hyperplasia; 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 neuroendocrine tumor of the pancreas, thymus, bronchus, or by an 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 neuroendocrine tumors 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 neuroendocrine

tumors of the pancreas or 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 an individual patient has 2 or more MEN1-associated tumors (ie, multi-gland parathyroid hyperplasia, enteropancreatic neuroendocrine tumors, pituitary tumors).[335] 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 parathyroid hormone (PTH) is recommended if hyperparathyroidism is suspected.

Imaging of parathyroids is less helpful in MEN1 because of the multiple gland hyperplasia.[335] Imaging of the parathyroid glands using neck ultrasound, 4-D CT, and/or sestamibi scanning with single photon emission CT (SPECT) is optional but may aid in identifying ectopically situated parathyroids. Preference of scan will depend on institutional practice/protocol.

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 and 4-gland hyperplasia. 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.[336,337] Tc^{99m} sestamibi with SPECT can improve sensitivity and specificity compared to planar scan.[338]

4D-CT is a method of multiphase CT imaging that uses a fourth dimension of changes in contrast attenuation over time and is increasingly used for preoperative imaging.[339] It has 60% to 87% sensitivity and allows for more robust diagnostic accuracy than traditional sonography or nuclear scintigraphy techniques. Three- or four-phase CT scanning protocols consist of precontrast, arterial, early-delayed, and late-delayed phases.

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 if equivocal CT findings 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 *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 insulin-like growth factor 1 (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 and 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.[334,335] 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 neuroendocrine 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.[340-342] A randomized, prospective trial compared these surgical approaches in 32 patients with MEN1 and hyperparathyroidism.[343] 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.[344] 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 Advanced 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.[101] 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* 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.[345] Consider referral to an endocrinologist. The patients are also more likely to have or develop new parathyroid carcinomas, pancreatic neuroendocrine tumors, pituitary tumors, and/or bronchial/thymic tumors. Carcinoid (neuroendocrine) tumors occur in approximately 3% of patients with MEN1.[335] Bronchial neuroendocrine tumors occur more frequently in women, while thymic neuroendocrine tumors occur more frequently in men. In addition, smokers appear to be at increased risk for the development of thymic neuroendocrine tumors.[335]

The panel recommends annual calcium and serum PTH levels to screen for parathyroid tumors. If calcium levels rise, 25-OH vitamin D should be measured and imaging with neck ultrasound and/or parathyroid sestamibi with SPECT scan or 4D-CT should be performed. Cross-sectional CT or MRI with contrast of the neck can also be considered. For prolonged surveillance, studies without radiation are preferred.

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 pituitary or sella 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 of bronchial or thymic neuroendocrine tumors, the panel suggests that cross-sectional chest CT or MRI with contrast be considered every 1 to 3 years. For prolonged surveillance, studies without radiation are preferred.

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.[195] Patients with MEN2A may also have or develop pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%).[195] 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%).[195] 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*.[7,346]

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 Medullary 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.[347,348] 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.[347,348] 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, PTH, and 25-OH vitamin D determinations. A neck ultrasound, sestamibi scan with SPECT, or 4D-CT can also be performed as appropriate. Preference of scan will depend on institutional practice/protocol.

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).[347,348] 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.[347,348] 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.[348]

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.[347] 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,[347,349-351] as detailed in the NCCN Guidelines for Medullary 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 Medullary 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 parathyroidectomy of abnormal glands. 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%).[352] 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 Medullary 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, PTH, calcitonin, and metanephrine 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[353]:

- 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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