



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Neuroendocrine Tumors

Version 1.2011

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NCCN Guidelines™ Version 1.2011 Panel Members Neuroendocrine Tumors

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

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical_trials/physician.html](#)

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#)

[Staging \(ST-1\)](#)

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2011.

**Updates in Version 1.2011 of the NCCN Guidelines from Version 2.2010 include:****General**

- CT or MRI was clarified as “multiphasic CT or MRI” throughout the guidelines.

Carcinoid tumors

- Surveillance of carcinoid tumors, for > 1 y postresection, “annual thereafter” was changed to *6-12 mo thereafter*. Also for PancNET-4.

CARC-1

- “Duodenal” was added as a separate clinical location with the corresponding workup and clinical presentation and “jejunal and ileal” were added to colon.

CARC-2

- Rectal, “consider 5-HIAA” was removed from surveillance.

CARC-4

- Clinical location “bronchial” was clarified as “bronchopulmonary”.

CARC-5

- Title was modified from “Management of recurrent or unresected disease” to “management of locoregional unresectable disease and/or distant metastases” and the page was extensively revised by organizing recommendations based on disease status rather than based on sites of metastasis (liver, lung, bone, regional/mesenteric lymph nodes).
 - The management is based on the following disease statuses: if complete resection; asymptomatic low tumor burden; locally symptomatic from primary tumor; clinically significant tumor burden; carcinoid syndrome.
 - Upon clinically significant disease progression, the recommendations are:
 - ◊ Octreotide, if not already receiving and
 - ◊ Consider hepatic regional therapy or
 - ◊ Consider cytoreductive surgery (category 2B) or
 - ◊ Consider everolimus (10 mg/d) (category 3) or
 - ◊ Consider cytotoxic chemotherapy (category 3), if no other options feasible.
- Footnote m, “Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated” was added.

Pancreatic Endocrine Tumors (Islet Cell Tumors)**PancNET-1**

- Nonfunctioning pancreatic tumors:
 - Management of locoregional disease was modified by adding “Subtotal pancreatectomy and distal pancreatectomy”.
 - Footnote g, “Risks and benefits of surgical resection should be carefully weighed in patients with small lesions” is new to the page.
- Gastrinoma management:
 - “Consider octreotide” was added.
 - Occult, no primary tumor or metastases on imaging,
 - ◊ Modified by adding “Exploratory surgery with” to “enucleation of ...”
 - ◊ Category 2B was removed from “observe”.
 - Head, exophytic or peripheral tumors by imaging and surgical removal feasible, for management “with duodenotomy” was removed from “enucleation of tumor.”
 - Distal, “± splenectomy” was added to distal pancreatectomy and “spleen preserving” was removed.

PancNET-2

- Insulinoma evaluation:
 - “Transgastric ultrasound” was changed to “endoscopic ultrasound”.
 - “72-hour observed fast” was removed from “insulin/glucose ratio”.
 - “Octreoscan” was added after metastatic disease with corresponding footnote “j”. Footnote “j” added to PancNET-5 also.
- Insulinoma management:
 - “Category 2B” was removed from “distal pancreatectomy”.
- Glucagonoma evaluation:
 - “Multiphasic contrast enhanced” was added to “CT/MRI”.
- Glucagonoma, management of locoregional disease
 - “Consider perioperative anticoagulant” was added as a footnote.
 - Footnote “Consider venacaval filter for patients at risk for deep vein thrombosis” was removed.

[Continued on next page](#)

**Updates in Version 1.2011 of the NCCN Guidelines from Version 2.2010 include:****PancNET-5**

- Management of locoregional unresectable disease and/or distant metastases was extensively revised by organizing recommendations based on disease status rather than based on sites of metastasis (liver, bone, lung).
 - ▶ The management is based on the following disease statuses: if complete resection possible; asymptomatic, low tumor burden and stable disease; symptomatic or clinically significant tumor burden or clinically significant progressive disease.
 - ▶ For symptomatic or clinically significant tumor burden or clinically significant progressive disease, the recommendations have been revised as:
 - ◊ Manage clinically significant symptoms as appropriate and
 - ◊ Everolimus (10 mg/d) or
 - ◊ Sunitinib (37.5 mg/d) or
 - ◊ Cytotoxic chemotherapy or
 - ◊ Hepatic regional therapy or
 - ◊ Cytoreductive surgery (category 2B) or
 - ◊ Consider octreotide, if not already receiving (category 2B)
 - ▶ The category designation for both everolimus and sunitinib were changed from a category 2B to a category 2A recommendation.
- Footnote n, “Staged or synchronous resection when possible. When performing staged pancreaticoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. *Ann Surg* 2010;252:142-148” was added.
- Footnote ‘q’ was modified by adding, “Octreotide can be used alone or in combination with other agents.”

Adrenal Gland Tumors**AGT-1**

- Clinical presentation was separated into “History of prior or current malignancy with risk of adrenal metastasis” and “No history of prior or current malignancy with risk of adrenal metastasis”.
- Footnote d, “Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation” is new to the page.

AGT-2

- History of prior or current malignancy with risk of adrenal metastasis: “Rule out functioning adrenal neoplasm” was moved from a footnote to before “image-guided needle biopsy”.
- Hyperaldosteronism was separated into “suspect benign” and “suspect malignancy” with a corresponding footnote e, “Suspect malignancies with irregular/inhomogeneous morphology, lipid-poor, does not wash-out, tumor > 3 cm, or secreting of more than one hormone” was added to the page.
- Footnote f, “Adrenal vein sampling is considered the standard for distinguishing single unilateral adenomas from bilateral hyperplasia. CT imaging is not always reliable. Some NCCN institutions recommend sampling in all cases of primary aldosteronism. Cortisol measurement in the catheterization samples is only used to confirm proper catheter placement” is new to the page.

AGT-4

- Non-functioning adenoma:
 - ▶ Treatment was separated by “Benign appearing by CT or MRI criteria or Myelolipoma by radiographic features (any size) without symptoms” and “Suspected lipid-rich adenoma of intermediate size (4-6 cm) by CT or MRI criteria” and “Suspect carcinoma”.
 - ◊ Suspected carcinoma was separated by “Intermediate tumor (4-6 cm) with aggressive features” and “Large tumor (> 6 cm) with aggressive features”.

AGT-5

- Footnote h, “May require removal of adjacent structures (liver, kidney, pancreas, spleen, diaphragm) for complete resection” is new to the page.
- Footnote “k” was modified as, “Increased risk for local recurrence *and peritoneal spread* when done laparoscopically”.
- Footnote l, “Monitor mitotane blood levels” is new to the page.

[Continued on next page](#)



Updates in Version 1.2011 of the NCCN Guidelines from Version 2.2010 include:

Pheochromocytoma

PHEO-1

- Footnote “d” was modified by adding “The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers.”

PHEO-2

- Distant metastases, 131I MIBG, “as compassionate use on clinical trial” was removed.

Multiple Endocrine Neoplasia, Type 1

- Trivalent vaccine was removed from the algorithms and the corresponding footnote, “Trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy” was added to the title, “management of primary non-metastatic disease”. Also for PancNET pages.

MEN1-1

- Occult gastrinoma with no primary found:
 - Modified by adding “or metastases on imaging”.
 - Treatment was modified by adding “Exploratory surgery with” to “enucleation and duodenotomy...”.

Immunohistochemical and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors

NE-A

- Immunohistochemical studies, Ki67 (MIB-1), “and/or mitotic rate” was added for clarification.
- Footnote 1 regarding VIP was modified by removing “This test should not be requested on patients who have recently received radioactive material.”

Surgical Principles for Management of Neuroendocrine Tumors

NE-B

- 4th bullet was modified by adding, “Resection of recurrent tumor or *previously* unresectable tumor that has regressed should be considered...”.

**DIAGNOSIS AND CLINICAL PRESENTATIONS****Carcinoid tumors^a****Clinical presentations:**

- Jejunal, ileal, Colon ([See CARC-1](#))
- Duodenal ([See CARC-1](#))
- Appendix ([See CARC-2](#))
- Rectal ([See CARC-2](#))
- Gastric ([See CARC-3](#))
- Bronchopulmonary, Thymus ([See CARC-4](#))
- Atypical lung carcinoid
- Recurrent or Metastatic disease ([See CARC-5](#))

Pancreatic endocrine tumors (Islet cell tumors)^a**Clinical presentations:**

- Nonfunctioning pancreatic tumors ([See PancNET-1](#))
- Gastrinoma ([See PancNET-1](#))
- Insulinoma, Glucagonoma ([See PancNET-2](#))
- VIPoma ([See PancNET-3](#))
- Recurrent disease ([See PancNET-4](#))
- Metastatic disease ([See PancNET-5](#))

Neuroendocrine unknown primary ([See NUP-1](#))^a**Adrenal gland tumors ([See AGT-1](#))^b****Pheochromocytoma/paraganglioma ([See PHEO-1](#))****Poorly differentiated (high grade or anaplastic)/****Small cell ([See ANAP-1](#))****Multiple endocrine neoplasia, type 1****Clinical presentations:**

- Hyperparathyroidism ([See MEN1-3](#))
- Gastrinoma ([See MEN1-1](#))
- Glucagonoma, Insulinoma ([See MEN1-2](#))
- VIPoma, Pancreatic polypeptidoma, Somatostatinoma, Nonfunctioning tumor ([See MEN1-3](#))
- Pituitary tumor ([See MEN1-4](#))
 - Prolactinoma
 - Cushing's disease
 - Acromegaly
 - TSH producing adenomas
 - Nonfunctioning adenoma
- Adrenal gland tumor ([See AGT-1](#))
- Bronchopulmonary Carcinoid, Thymus ([See CARC-4](#))
- Lipomas, skin angiomas

Multiple endocrine neoplasia, type 2**medullary thyroid carcinoma ([See MEN2-1](#))****Clinical presentations:**

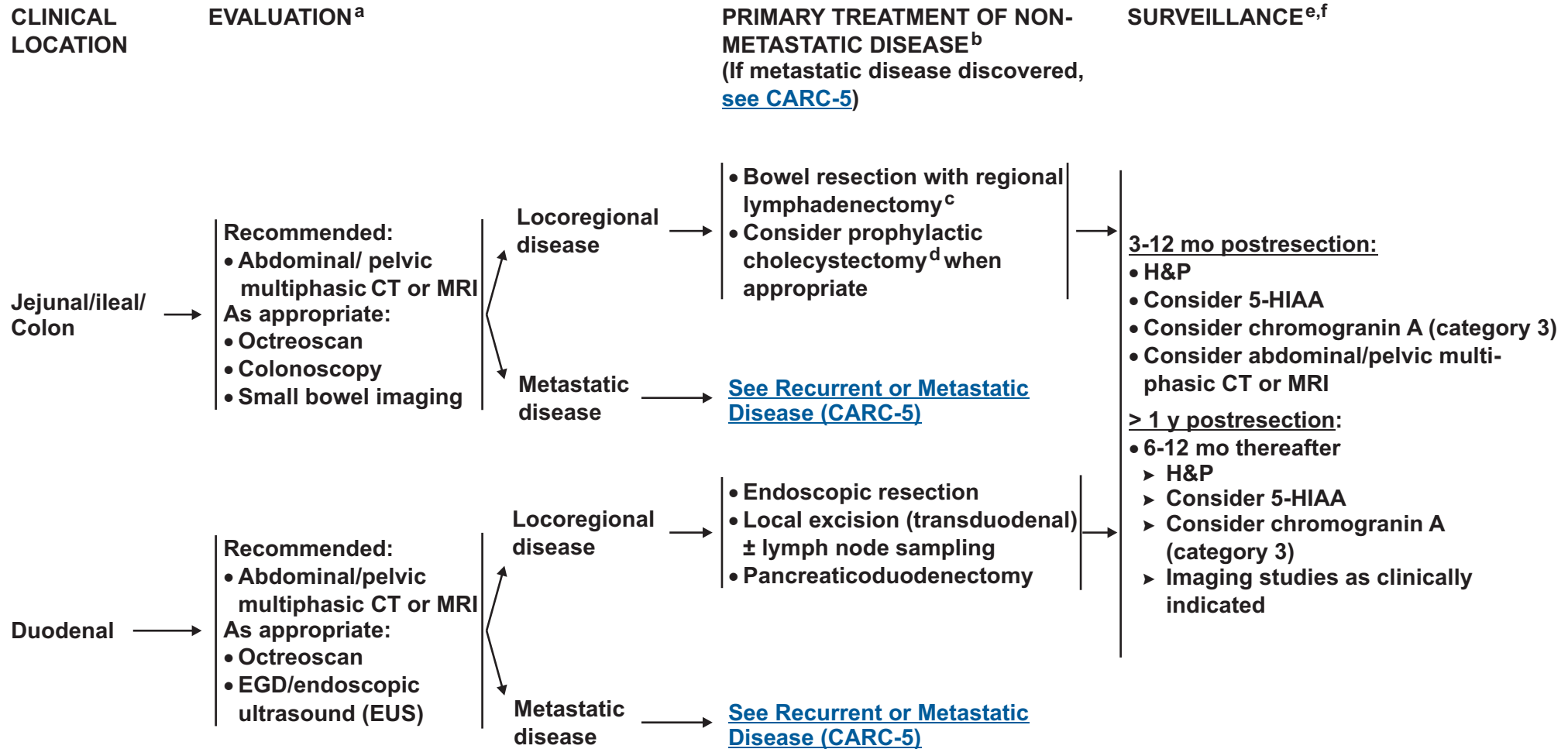
- Medullary thyroid cancer ([See NCCN Thyroid Carcinoma Guidelines](#))
- Pheochromocytoma
- Hyperparathyroidism (MEN2A)
- Marfanoid habitus (MEN2B)
- Mucosal neuromas (MEN2B)
- Lichen planus amyloidosis (MEN2A)

Merkel cell carcinoma ([See Merkel Cell Carcinoma Guidelines](#))^aGuidelines pertain to well and moderately differentiated tumors. For poorly differentiated/high grade/anaplastic or small cell carcinomas, [see ANAP-1](#).^bIncludes adrenal cortical tumors and incidentaloma.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



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Carcinoid Tumors



^a [See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)
^b [See Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\).](#)

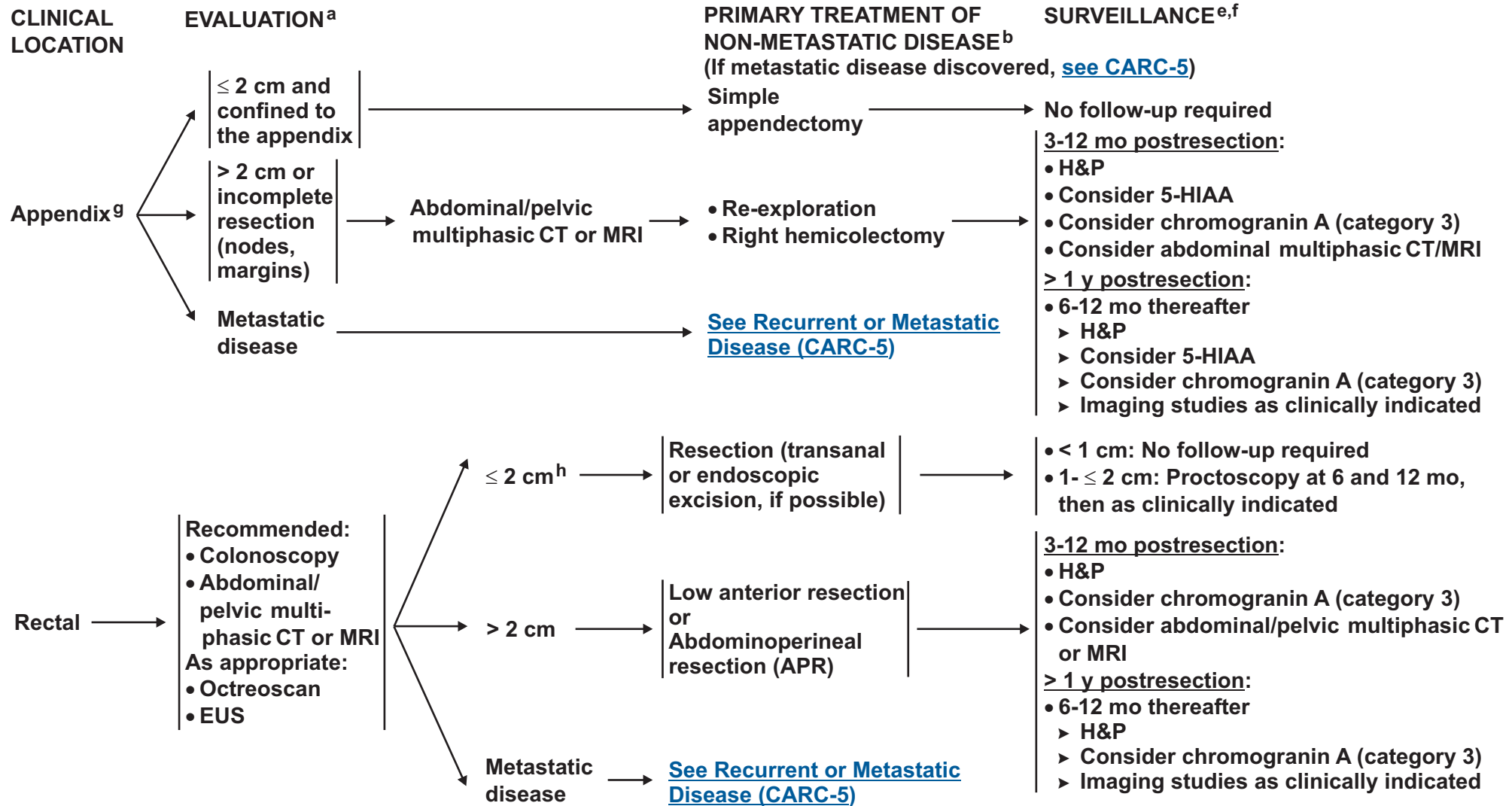
^c Should include careful examination of the entire bowel as multiple synchronous lesions may be present.
^d If possible future need for octreotide.
^e Earlier, if symptoms.
^f Octreoscan and PET scan not recommended for routine surveillance.

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Carcinoid Tumors



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^bSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^eEarlier, if symptoms.

^fOctreoscan and PET scan not recommended for routine surveillance.

^gIf histology is goblet cell or adenocarcinoid, manage as colon adenocarcinoma. [See NCCN Colon Cancer Guidelines](#).

^hFor 1-2 cm tumors, consider examination under anesthesia (EUA) with radical resection if muscularis propria invasion or node positive.

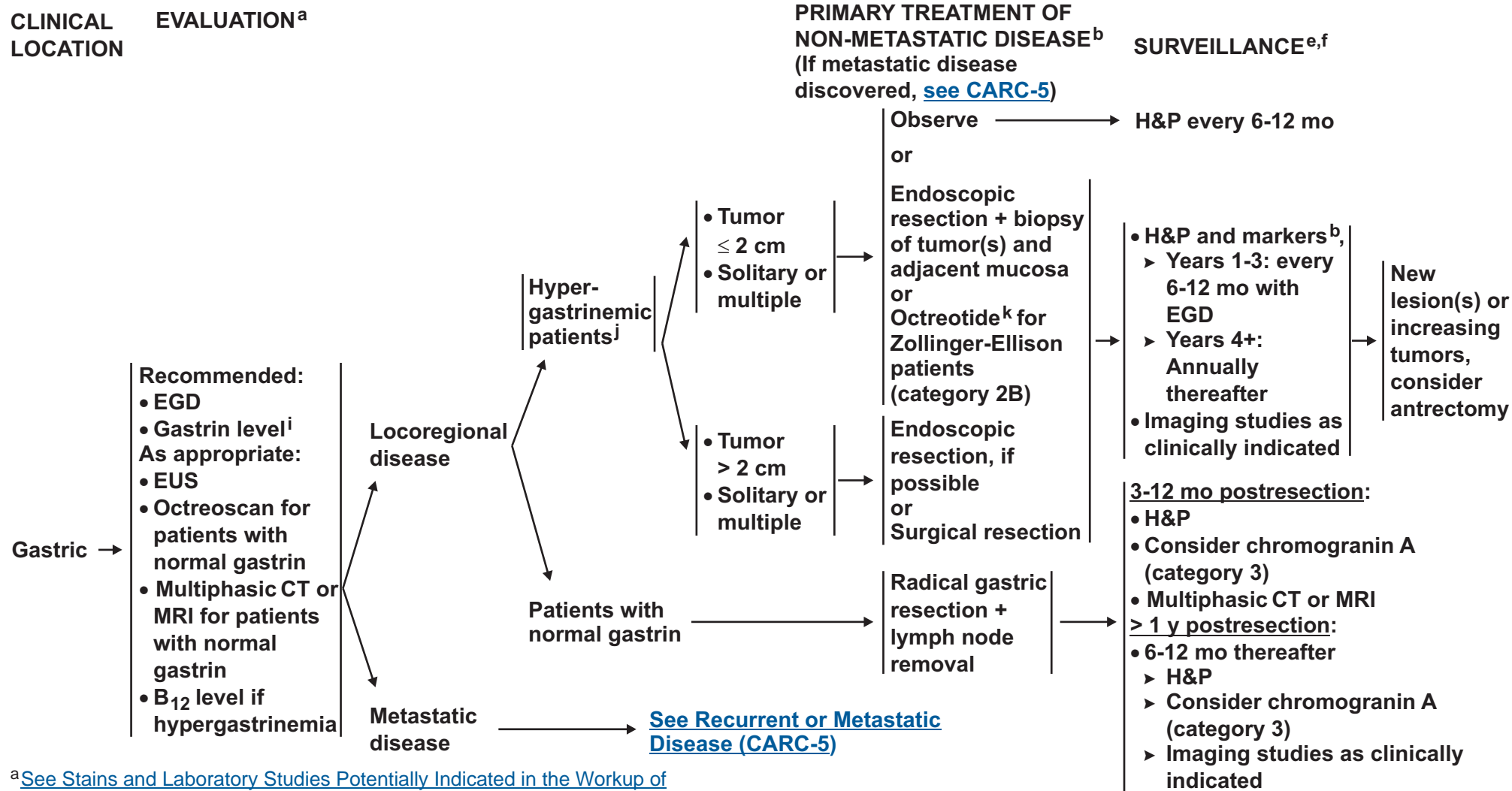
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Carcinoid Tumors



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^bSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^eEarlier, if symptoms.

^fOctreoscan and PET scan not recommended for routine surveillance.

ⁱGastrin levels needs to be completed while fasting and off protein pump inhibitors for 1 week.

^jIf gastric pH is low, see gastrinoma on [PancNET-1](#) or [MEN1-1](#).

^kOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

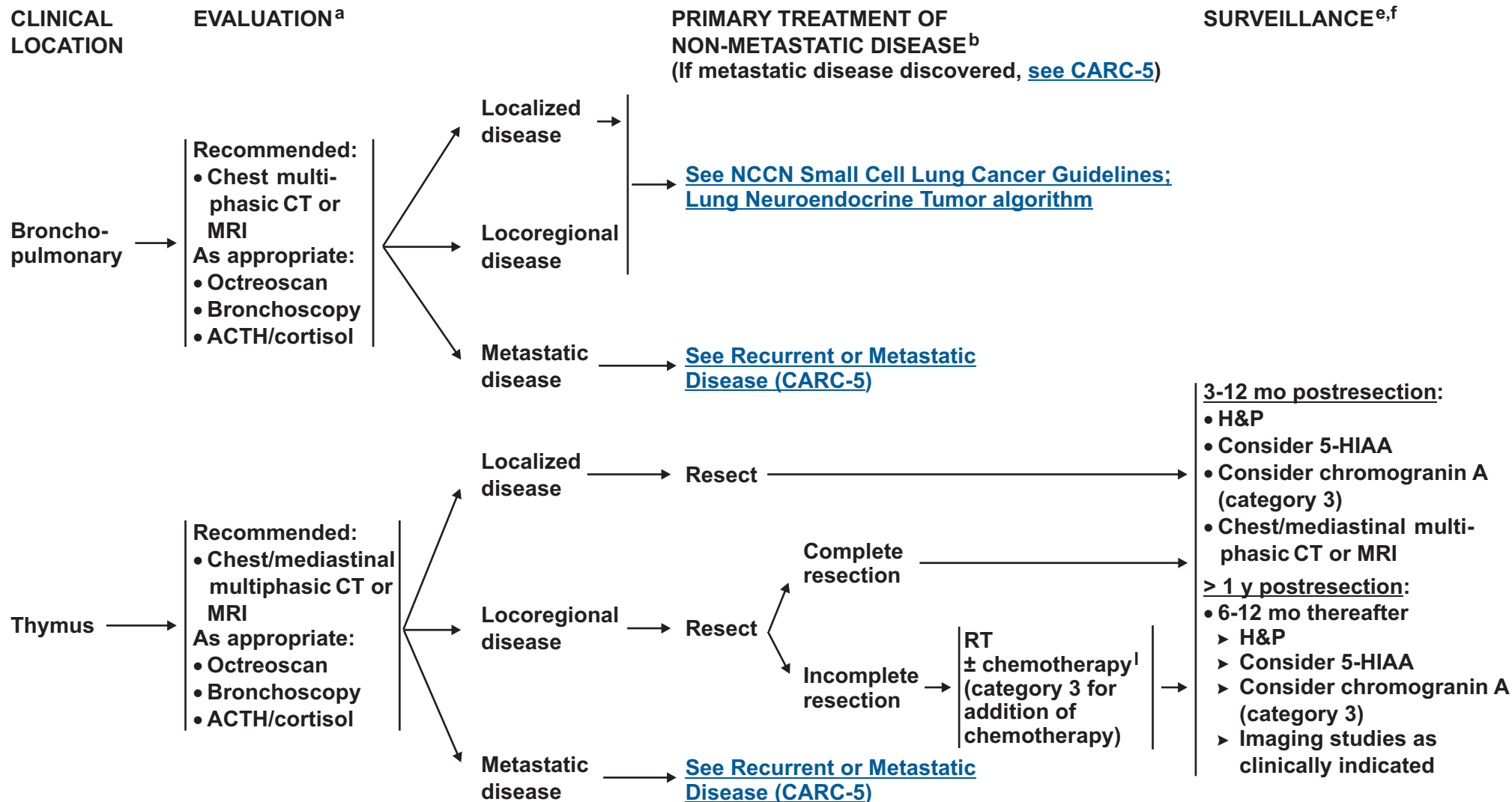
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Carcinoid Tumors



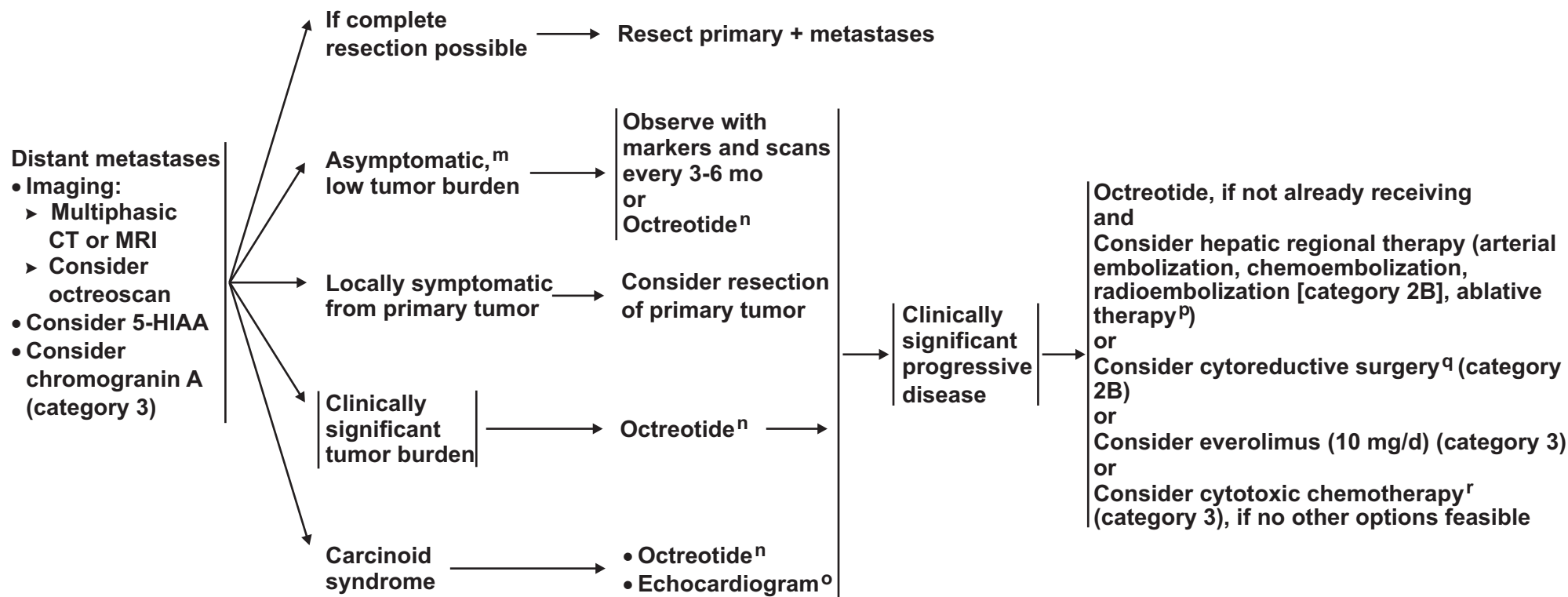
^a[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)
^b[See Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\).](#)
^eEarlier, if symptoms.

^fOctreoscan and PET scan not recommended for routine surveillance.
^lConsider 5-fluorouracil or capecitabine at radiosensitizing doses. Cisplatin or carboplatin with etoposide may be appropriate for patients with moderately differentiated or atypical tumors.

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MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^b



^bSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^mResection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

ⁿOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. See PROMID study: J Clin Oncol. 2009;27:4656-4663.

^oIf signs and symptoms of heart disease or planning major surgery.

^pIncludes 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.

^qOnly if near complete resection can be achieved.

^rAnticancer agents such as, capecitabine, dacarbazine, 5-fluorouracil, interferon, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a progression-free or overall survival benefit.

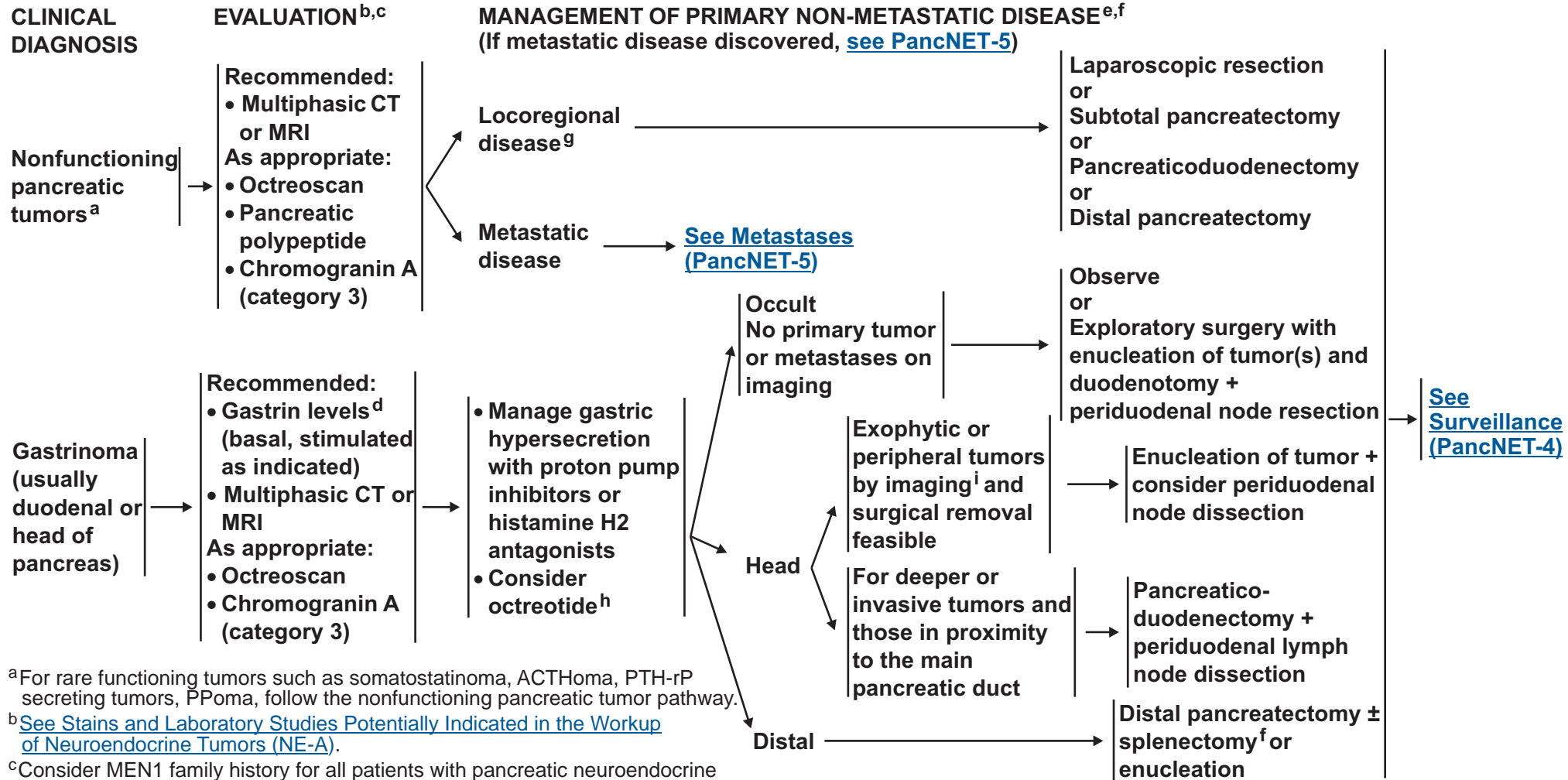
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Pancreatic Endocrine Tumors (Islet Cell Tumors)



^aFor rare functioning tumors such as somatostatinoma, ACTHoma, PTH-rP secreting tumors, PPoma, follow the nonfunctioning pancreatic tumor pathway.

^b[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)

^cConsider MEN1 family history for all patients with pancreatic neuroendocrine tumors.

^dGastrin levels needs to be completed while fasting and off proton pump inhibitors for 1 week.

^e[See Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\).](#)

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

^gRisks and benefits of surgical resection should be carefully weighed in patients with small lesions.

^hOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

ⁱNot adjacent to the main pancreatic duct.

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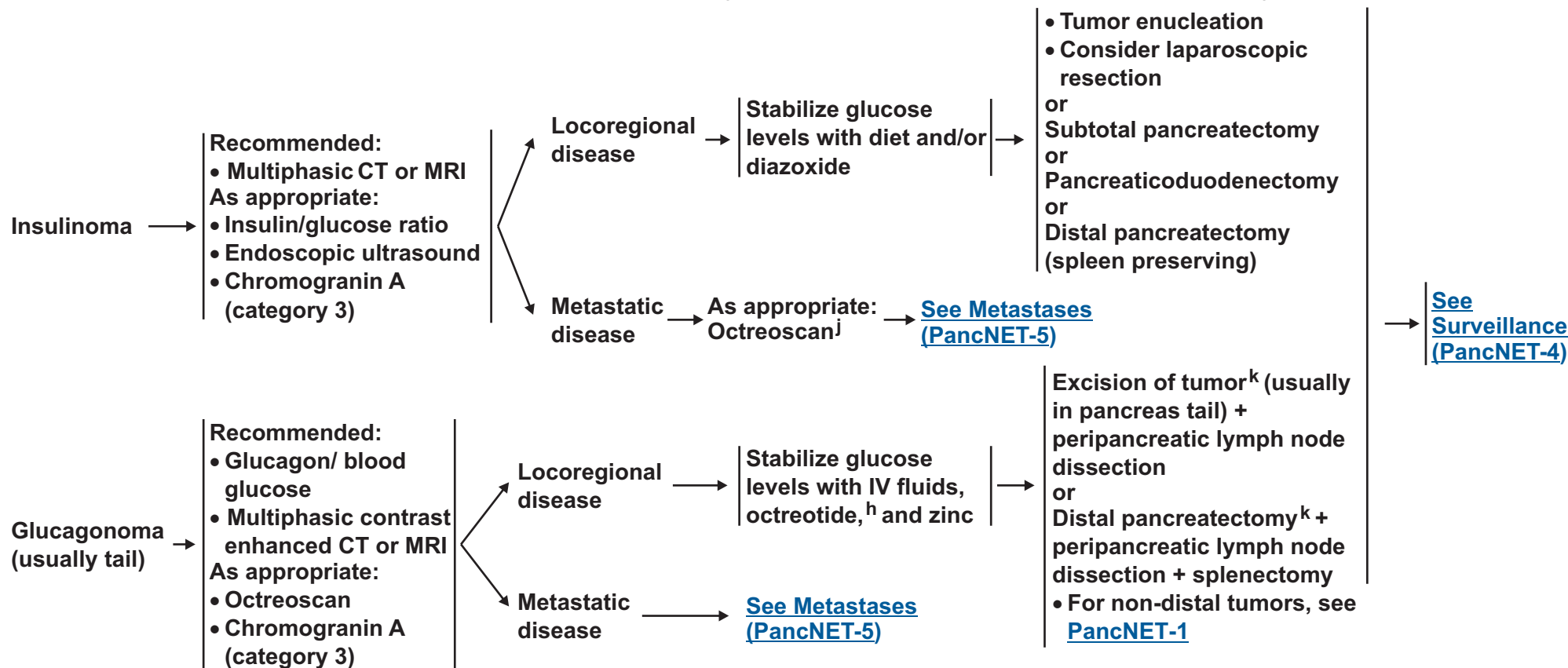
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Pancreatic Endocrine Tumors (Islet Cell Tumors)

CLINICAL DIAGNOSIS

EVALUATION^{b,c}

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE^{e,f} (If metastatic disease discovered, [see PancNET-5](#))



^b See [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^c Consider MEN1 family history for all patients with pancreatic neuroendocrine tumors.

^e See [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^f Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.

^h 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms

ⁱ Octreotide should be used with caution in patients with insulinoma as it may transiently worsen hypoglycemia (see discussion).

^k Consider perioperative anticoagulation.

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

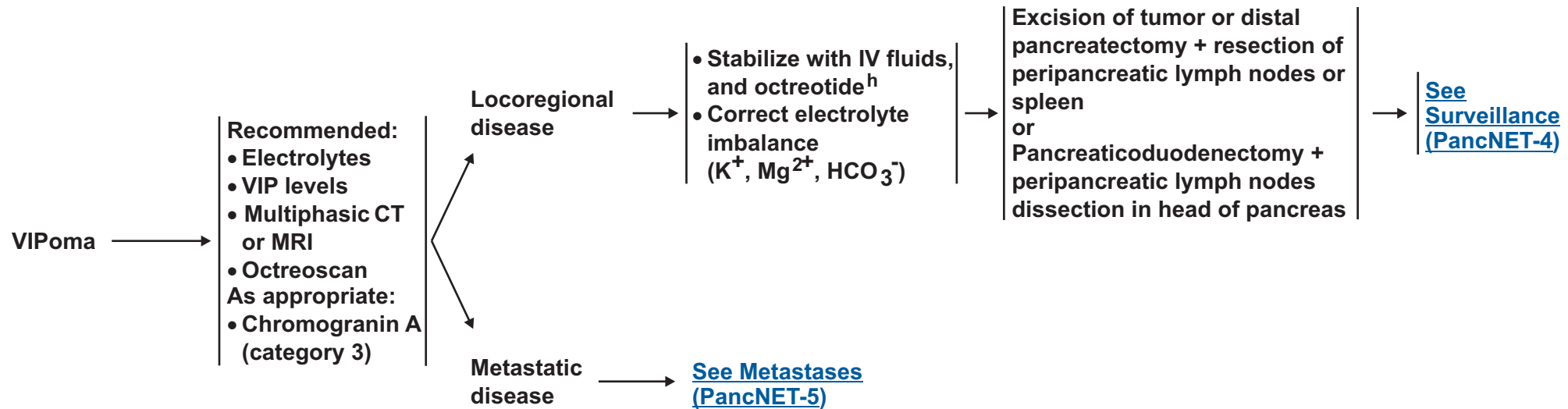
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**CLINICAL
DIAGNOSIS**

EVALUATION^{b,c}

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE^{e,f}
(If metastatic disease discovered, [see PancNET-5](#))



^b[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)

^cConsider MEN1 family history for all patients with pancreatic neuroendocrine tumors.

^e[See Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\).](#)

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

^hOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

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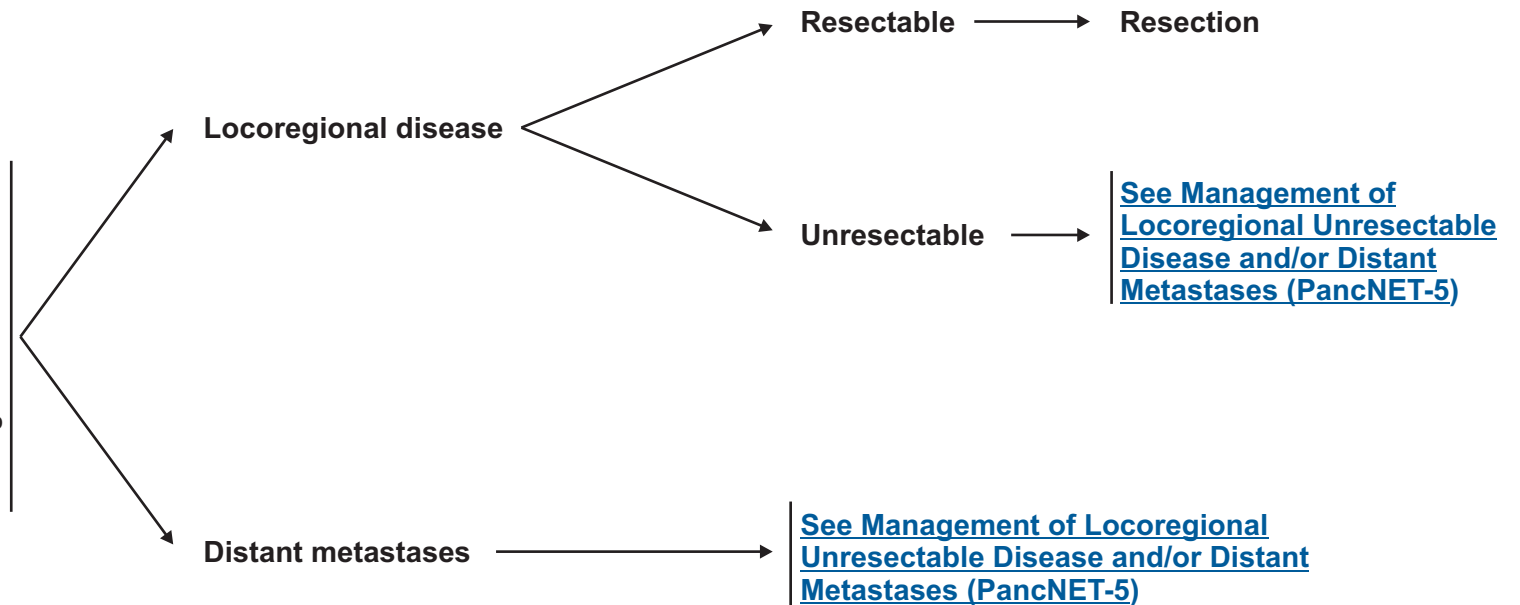


SURVEILLANCE^{l,m}

RECURRENT DISEASE

MANAGEMENT OF RECURRENT DISEASE^e

- 3-12 mo postresection:**
- H&P and consider markers from preoperative evaluation as indicated^b
 - Multiphasic CT or MRI
- > 1 y postresection:**
- 6-12 mo thereafter
 - ▶ H&P and consider markers^b
 - ▶ Imaging studies as clinically indicated



^bSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^eSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

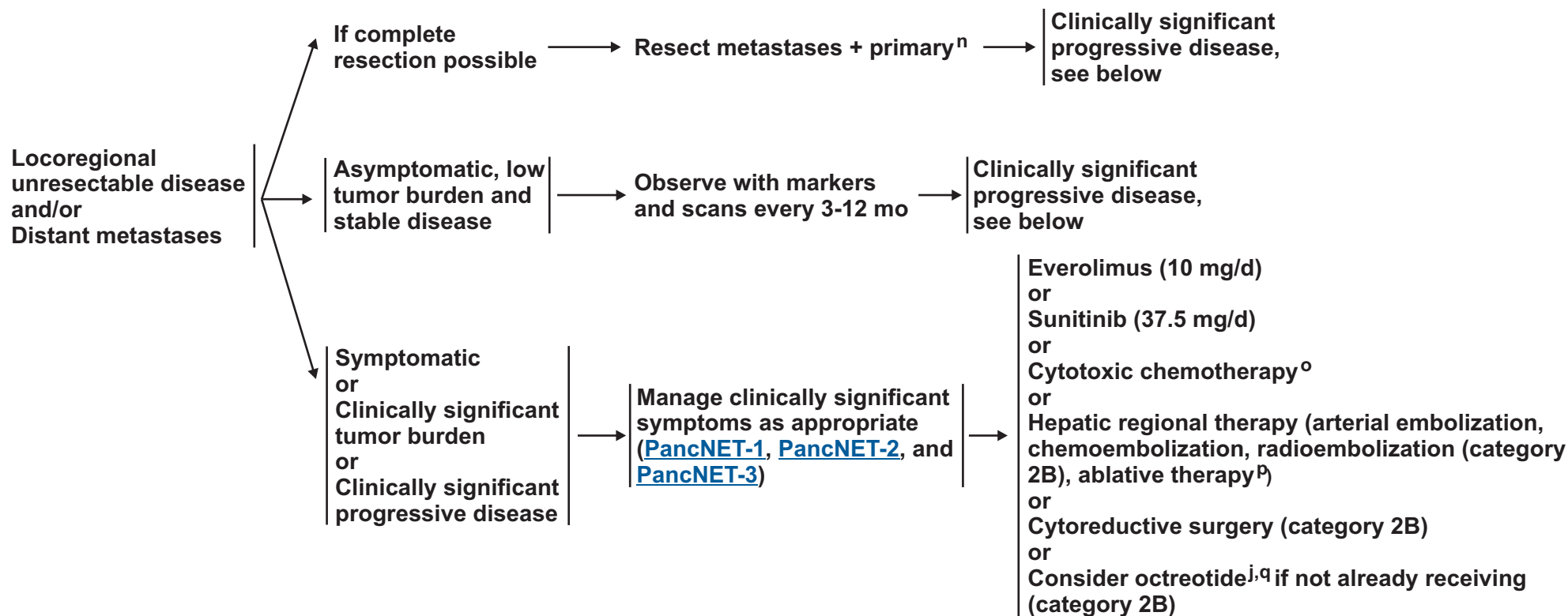
^lEarlier, if symptoms.

^mOctreoscan and PET scan not recommended for routine surveillance.

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MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^e



^eSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

ⁱOctreotide should be used with caution in patients with insulinoma as it may transiently worsen hypoglycemia (see discussion).

ⁿStaged or synchronous resection when possible. When performing staged pancreaticoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. *Ann Surg* 2010;252:142-148.

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

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

^qOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. Octreotide can be used alone or in combination with other agents.

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

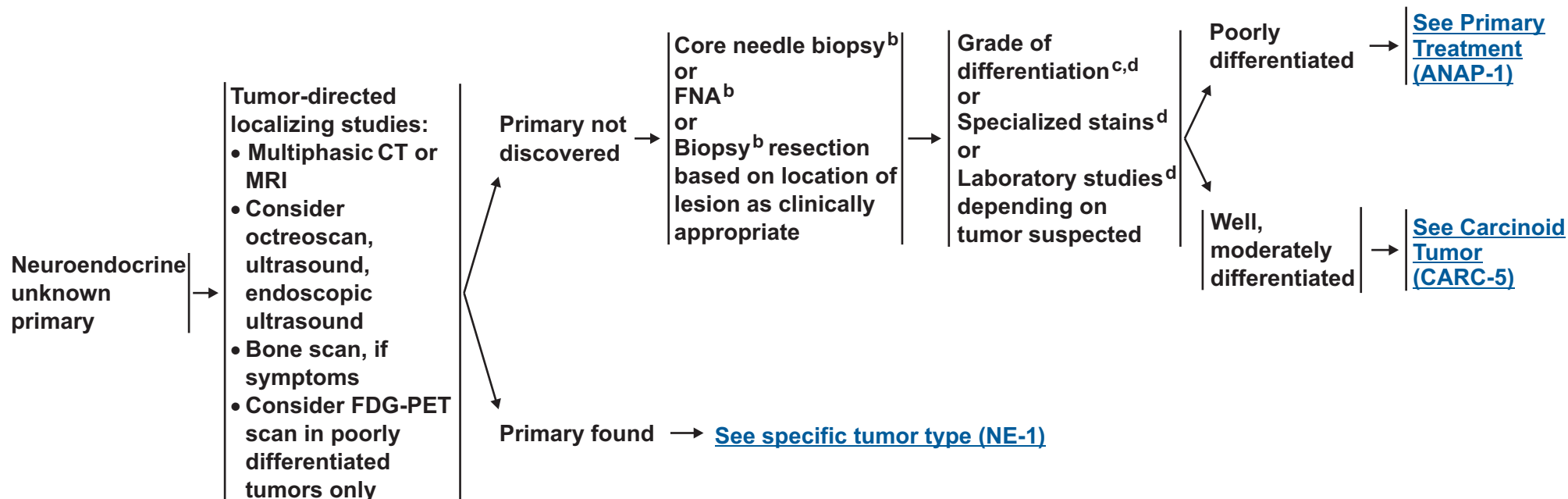
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NCCN Guidelines™ Version 1.2011 Neuroendocrine Unknown Primary

INITIAL WORKUP^a

ADDITIONAL WORKUP



^aSequence may vary.

^bRule out functioning adrenal neoplasms and suspected carcinoid tumor syndrome prior to biopsy. Alpha blockade required prior to biopsy or manipulation for suspected pheochromocytoma or paraganglioma ([See PHEO-1](#)). Octreotide premedication required before biopsy in suspected functioning carcinoid tumor.

^cWell, moderately, or poorly differentiated. Solcia E, Rindi G, Paolotti D, La Rosa S, Capella C, Fiocca R. Clinicopathological profile as a basis for classification of the endocrine tumors of the gastroenteropancreatic tract. *Ann Oncol* 1999;10 Suppl 2:S9-15.

^d[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

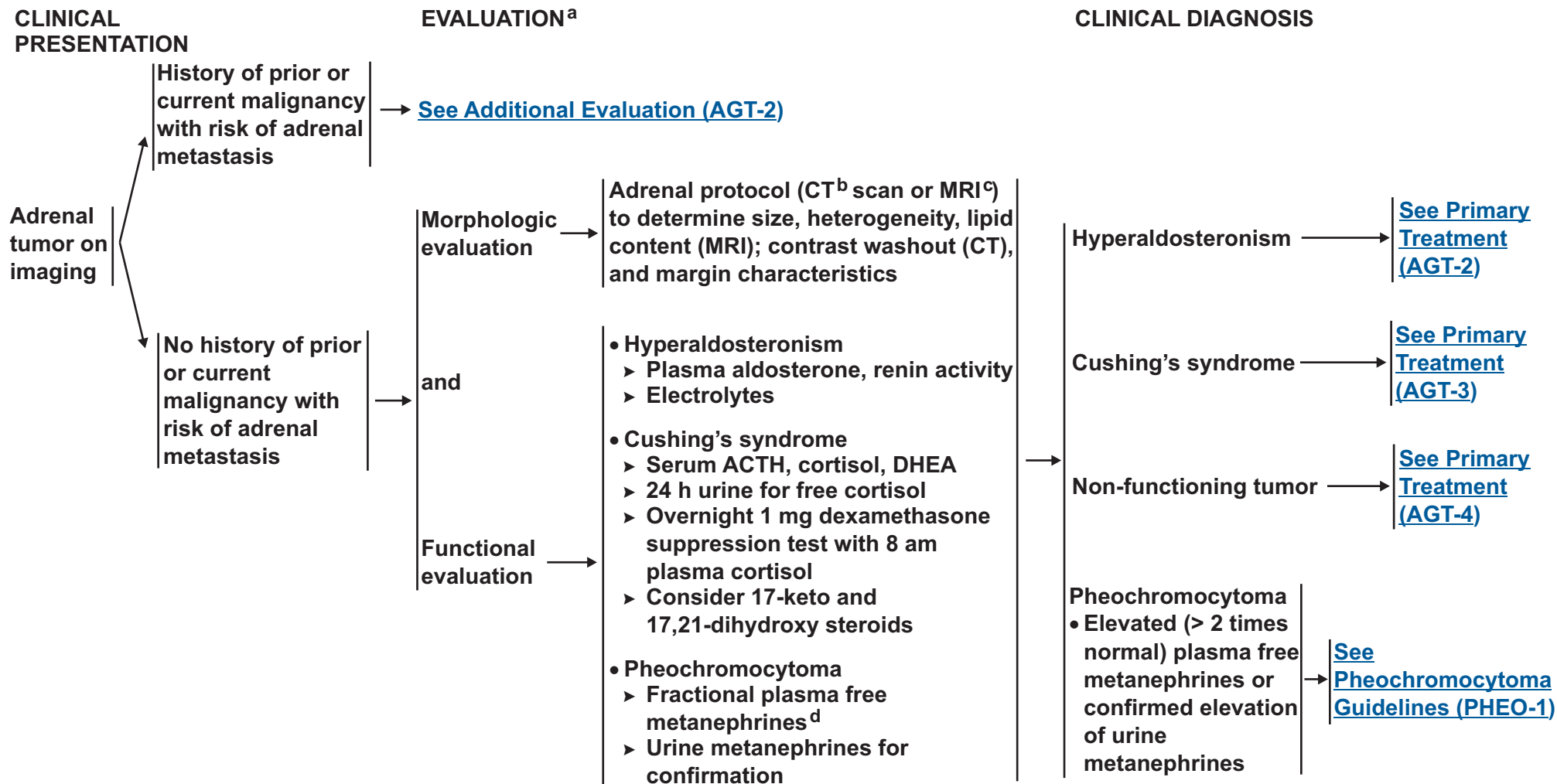
Note: All recommendations are category 2A unless otherwise indicated.

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



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Adrenal Gland Tumors



^a[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)

^bIf unenhanced is < +10 HU, then the tumor is probably benign. If unenhanced > +10 HU, then use enhanced and wash-out. If > 60% wash-out in 15 min, the tumor is likely to be benign, less than 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.)

^cChemical shift imaging.

^dReview concurrent medication(s) for those that may interfere with plasma metanephrines evaluation.

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



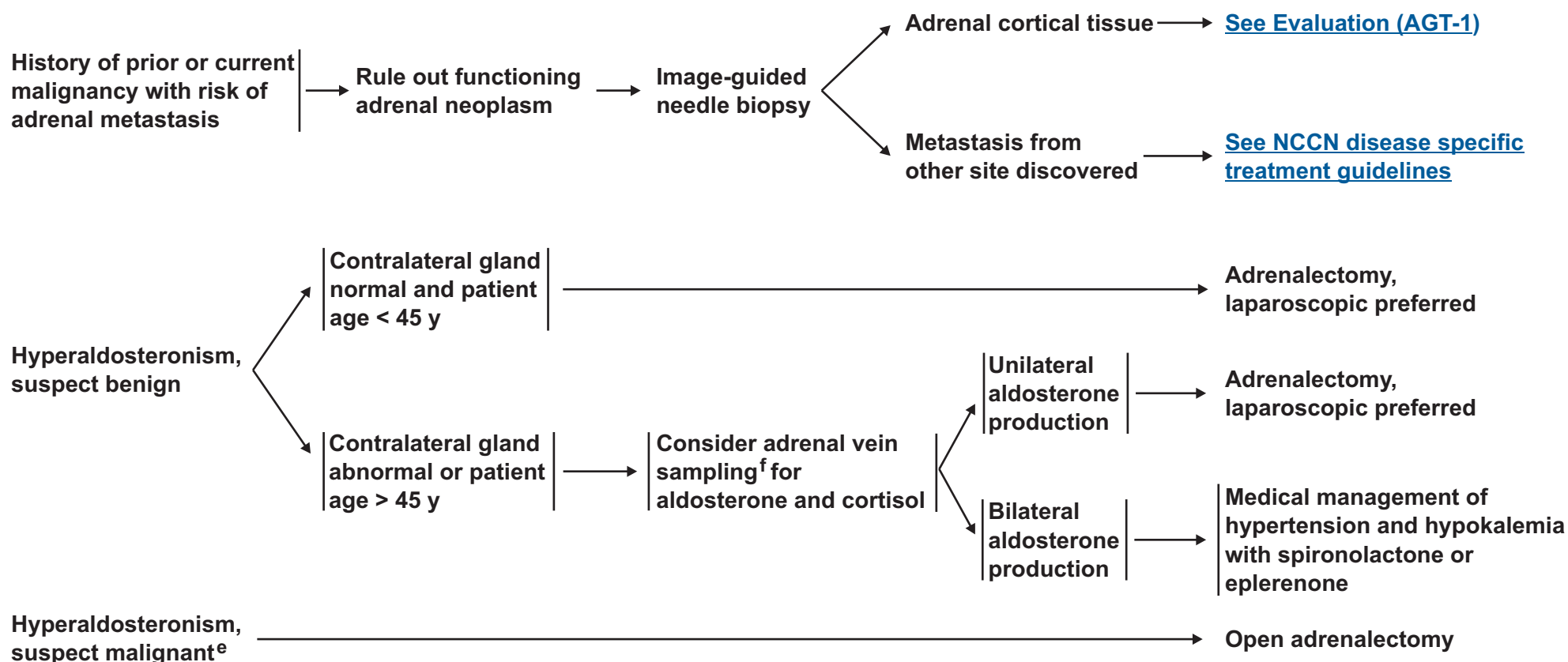
NCCN Guidelines™ Version 1.2011

Adrenal Gland Tumors

CLINICAL DIAGNOSIS

ADDITIONAL EVALUATION

PRIMARY TREATMENT⁹



^eSuspect malignancies with irregular/inhomogeneous morphology, lipid-poor, does not wash-out, tumor > 3 cm, or secreting of more than one hormone.

^fAdrenal vein sampling is considered the standard for distinguishing single unilateral adenomas from bilateral hyperplasia. CT imaging is not always reliable. Some NCCN institutions recommend sampling in all cases of primary aldosteronism. Cortisol measurement in the catheterization samples is only used to confirm proper catheter placement.

⁹See [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

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

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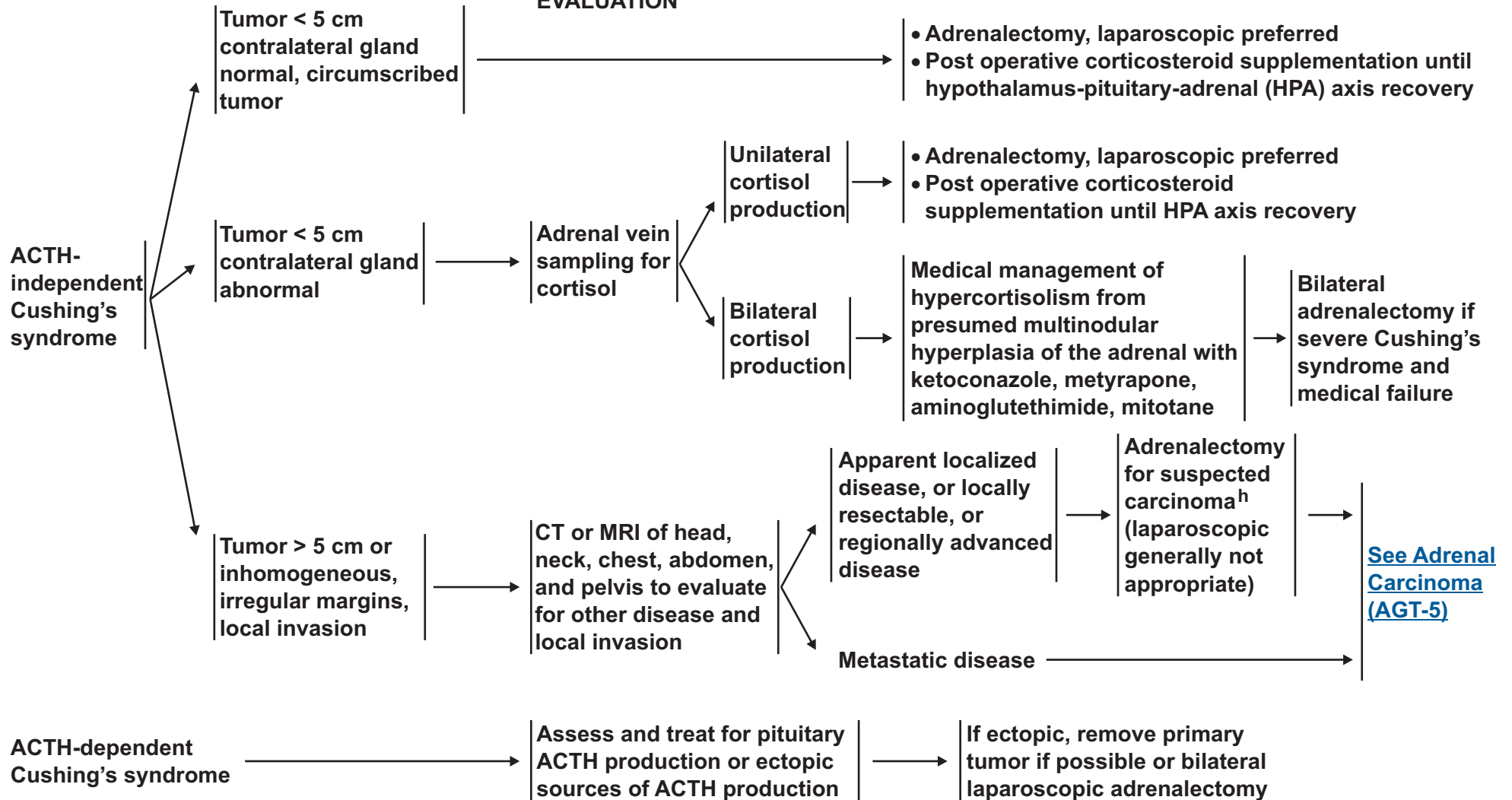


NCCN Guidelines™ Version 1.2011 Adrenal Gland Tumors

CLINICAL DIAGNOSIS

ADDITIONAL EVALUATION

PRIMARY TREATMENT^g



^gSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

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

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

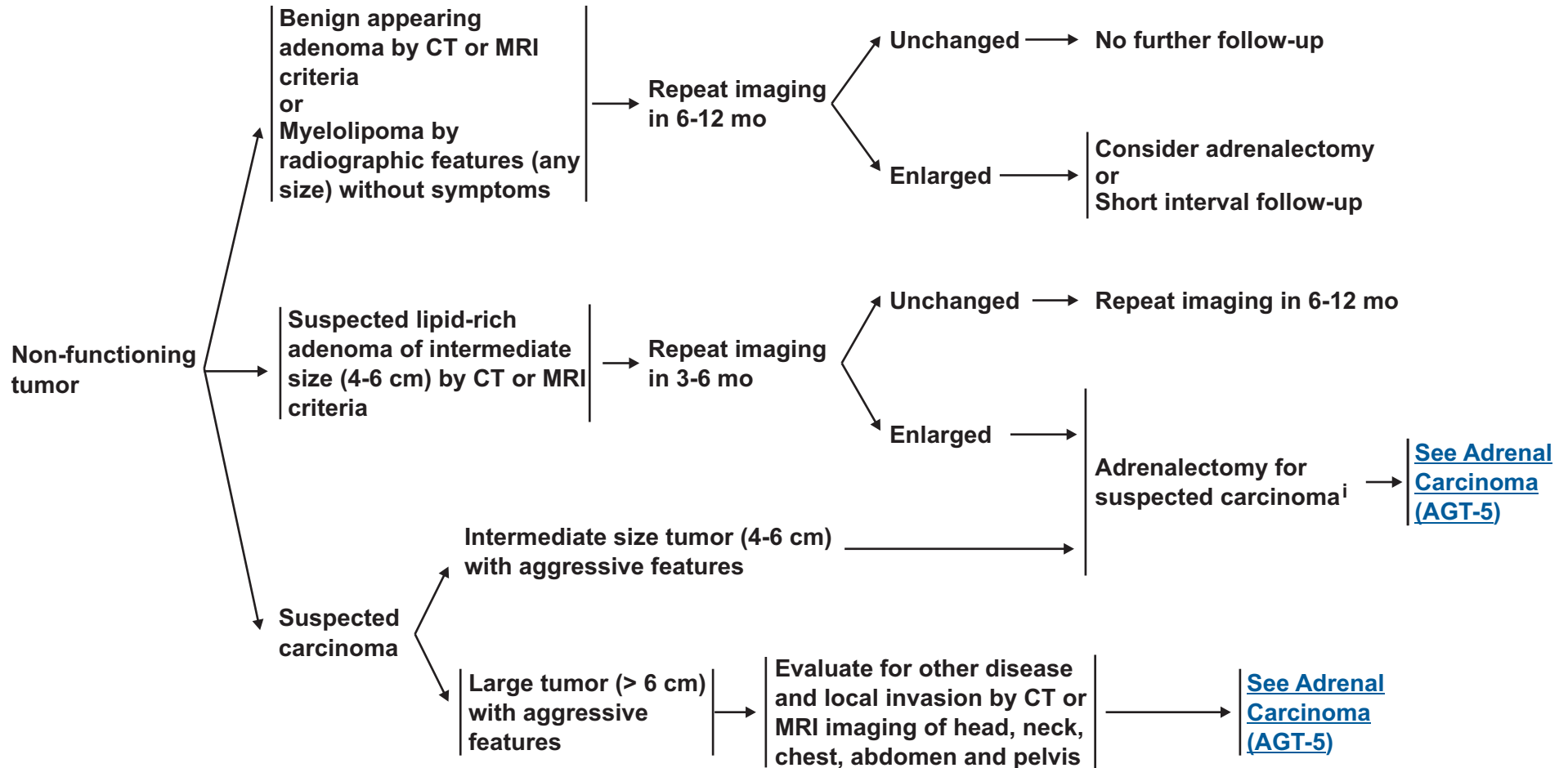
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



CLINICAL DIAGNOSIS

ADDITIONAL EVALUATION

PRIMARY TREATMENT⁹



⁹See [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

ⁱIf size resectable by laparoscopy, may explore laparoscopically with planned conversion for evidence of local invasion.

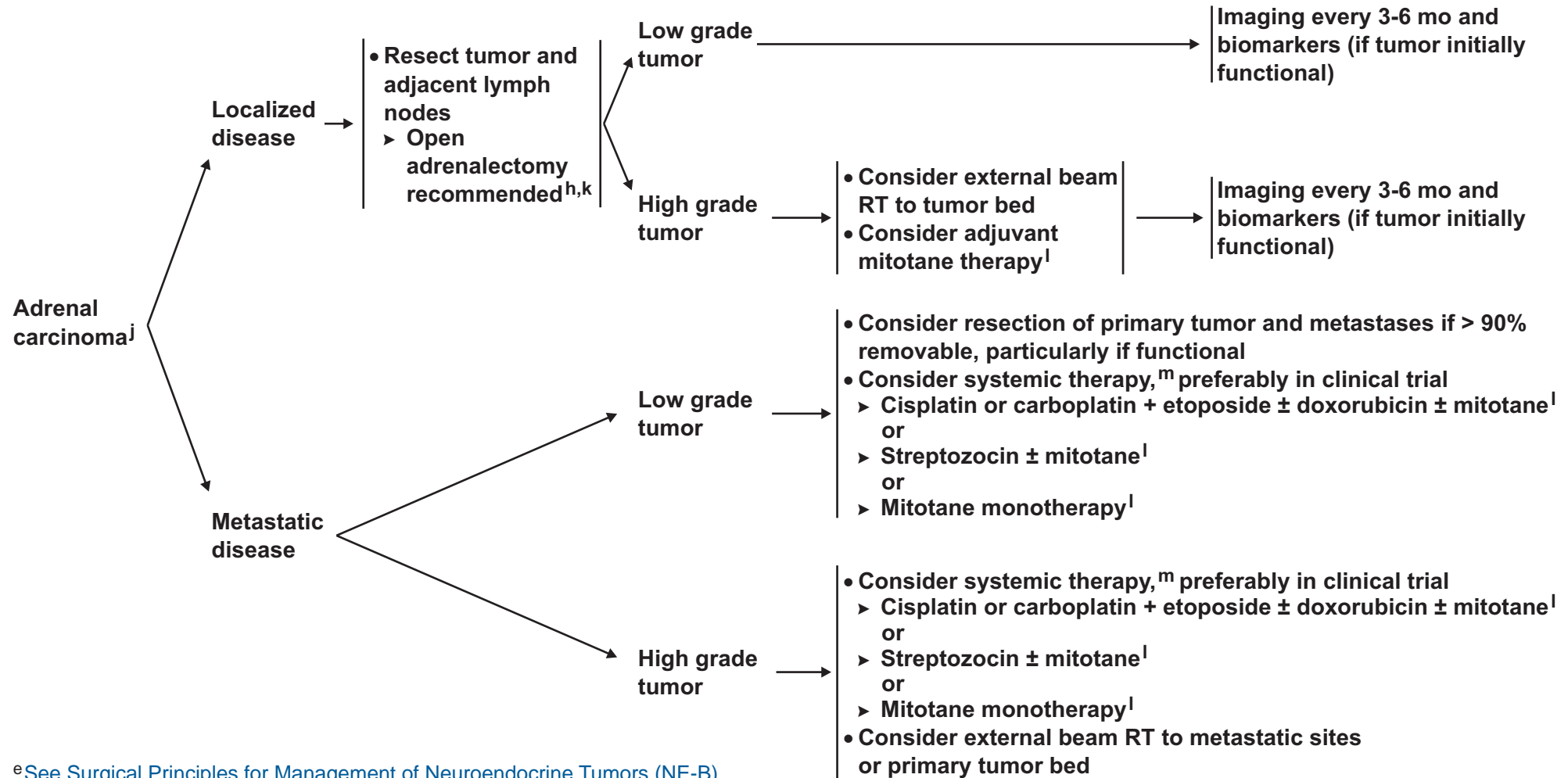
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



ADRENAL CARCINOMA

TREATMENT^e

FOLLOW-UP



^eSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

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

^jCross sectional imaging to stage disease.

^kIncreased risk for local recurrence and peritoneal spread when done laparoscopically.

^lMonitor mitotane blood levels.

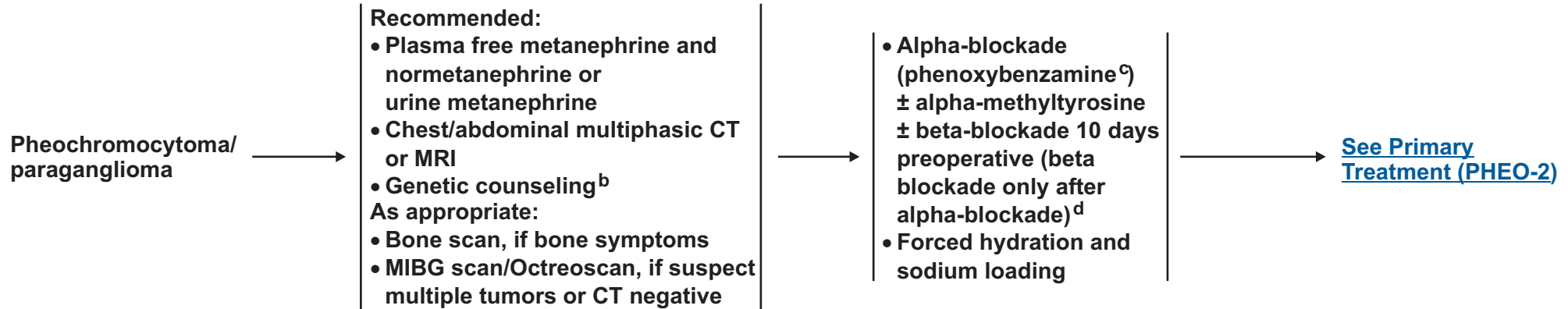
^mIGF-1 inhibitor may be useful. Consider a clinical trial.

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



TUMOR TYPE

EVALUATION^a



^a[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)

^bGenetic counseling may include genetic testing when appropriate.

^cPhenoxybenzamine: Initial dose of 10 mg PO twice a day, titrated up to control hypertension and starting therapy at least 7 days prior to planned procedure: side effects include postural hypotension and dry mucous membranes. Please refer to the FDA prescribing information on www.fda.gov.

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

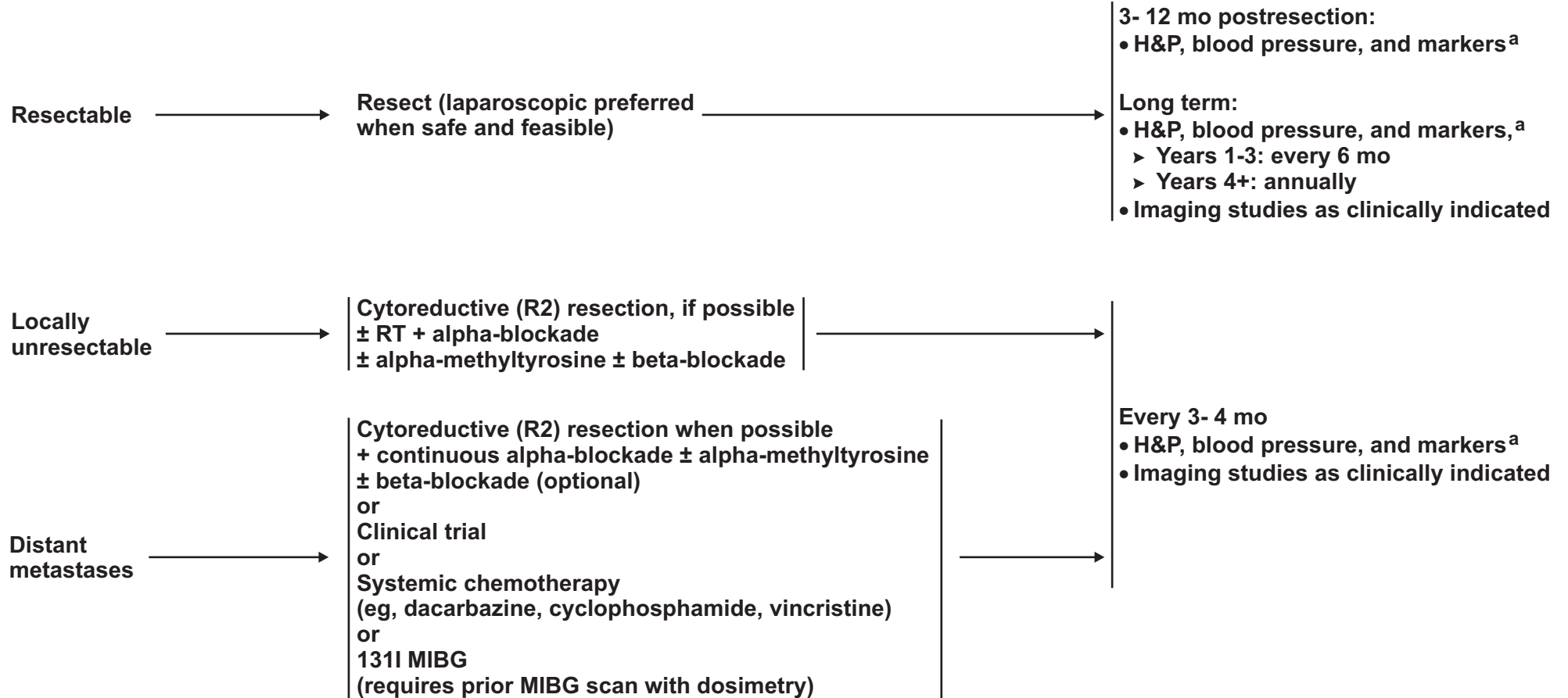
Note: All recommendations are category 2A unless otherwise indicated.

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



PRIMARY TREATMENT^e

SURVEILLANCE^f



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^eSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

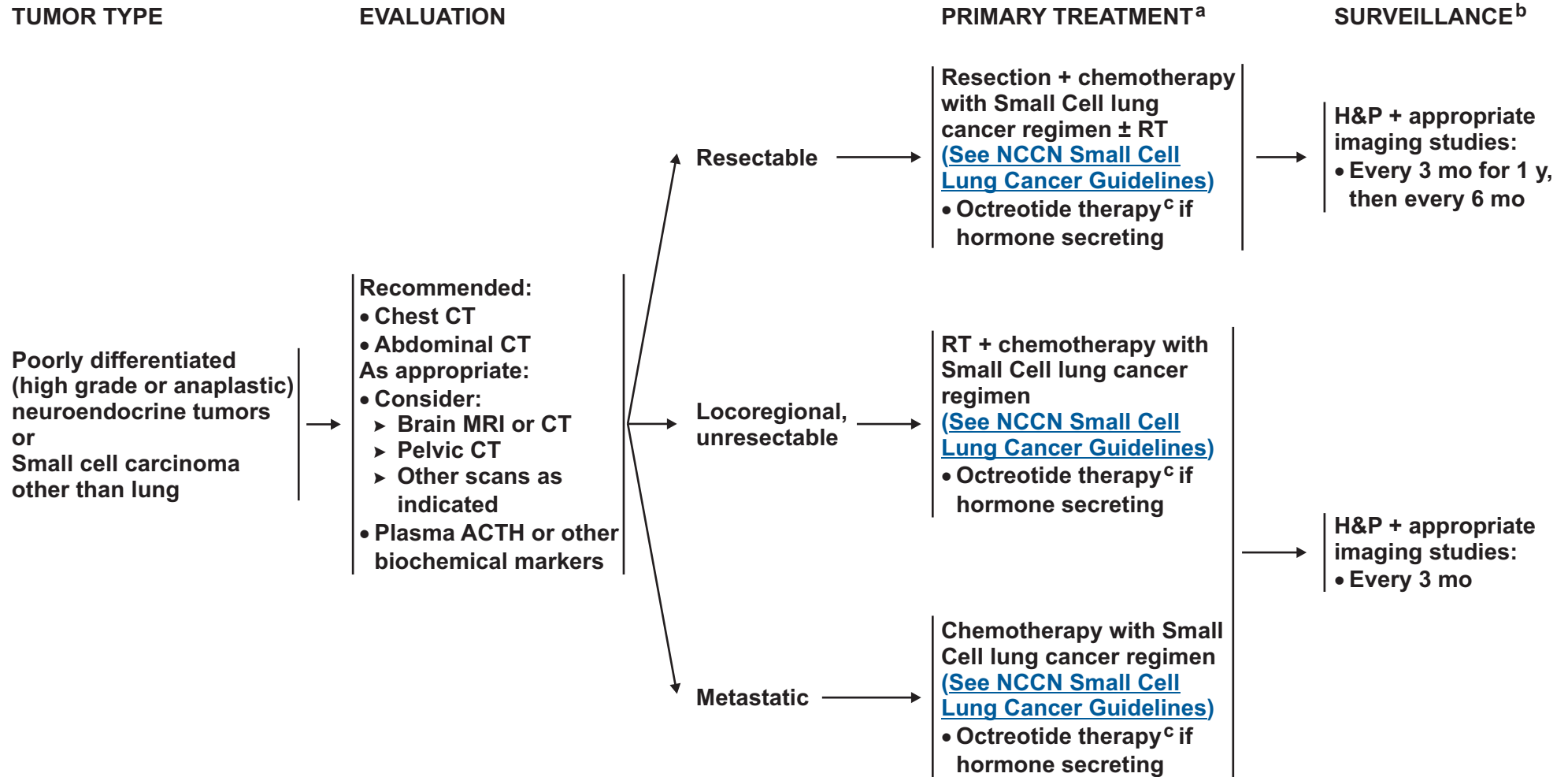
^fEarlier, if symptoms.

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



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Poorly Differentiated (High Grade or Anaplastic)/ Small Cell



^aSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^bEarlier, if symptoms.

^cOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

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



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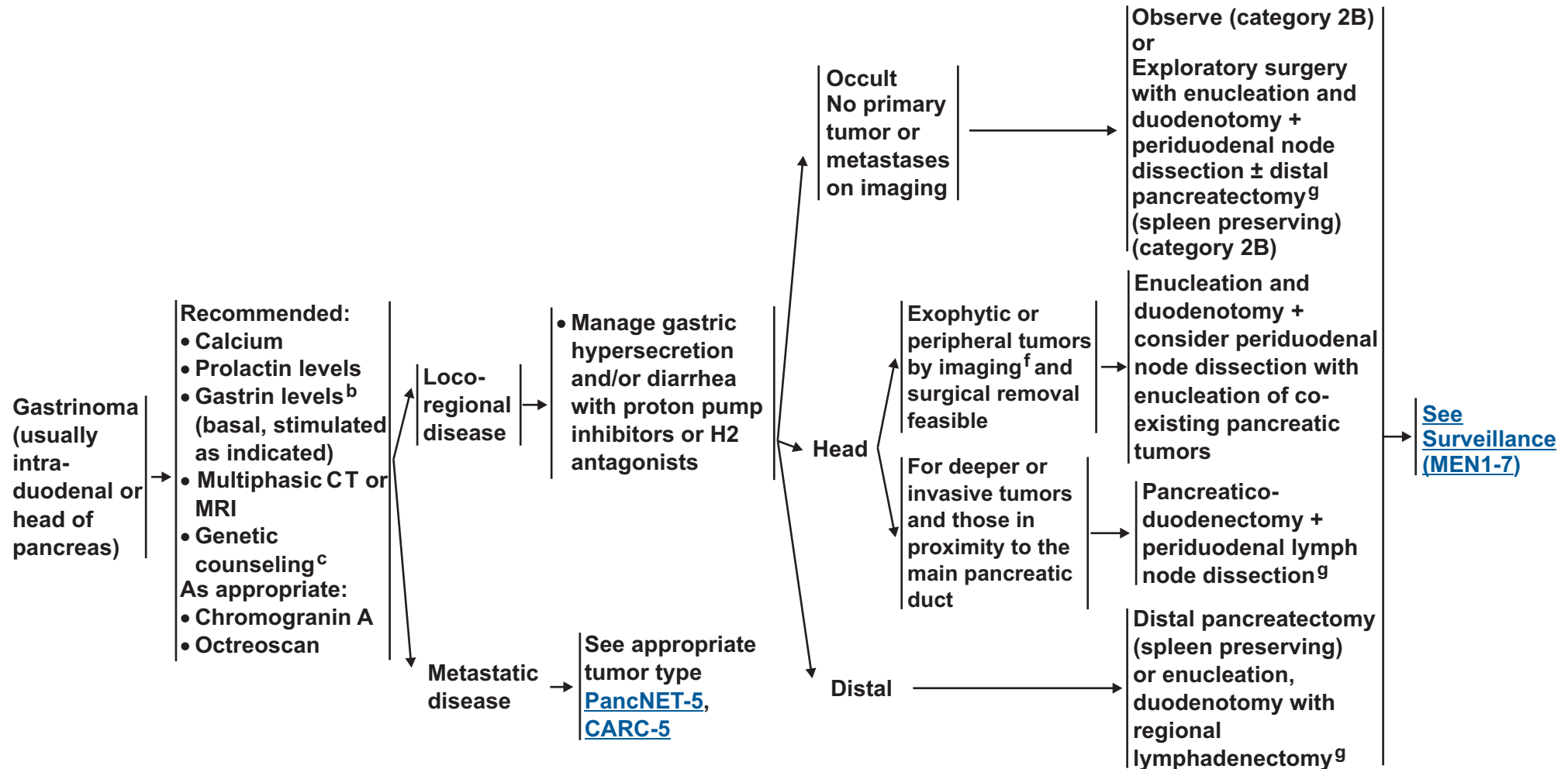
Multiple Endocrine Neoplasia, Type 1

**CLINICAL
DIAGNOSIS**

EVALUATION^a

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE^{d,e}

(If metastatic disease discovered, see appropriate tumor type, [PancNET-5](#), [CARC-5](#))



^a See [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^b Gastrin levels should be done fasting and off proton pump inhibitors.

^c Genetic counseling may include genetic testing when appropriate.

^d See [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^e Trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.

^f Not adjacent to the main pancreatic duct.

^g In patients undergoing abdominal surgery and octreotide planned, suggest prophylactic cholecystectomy.

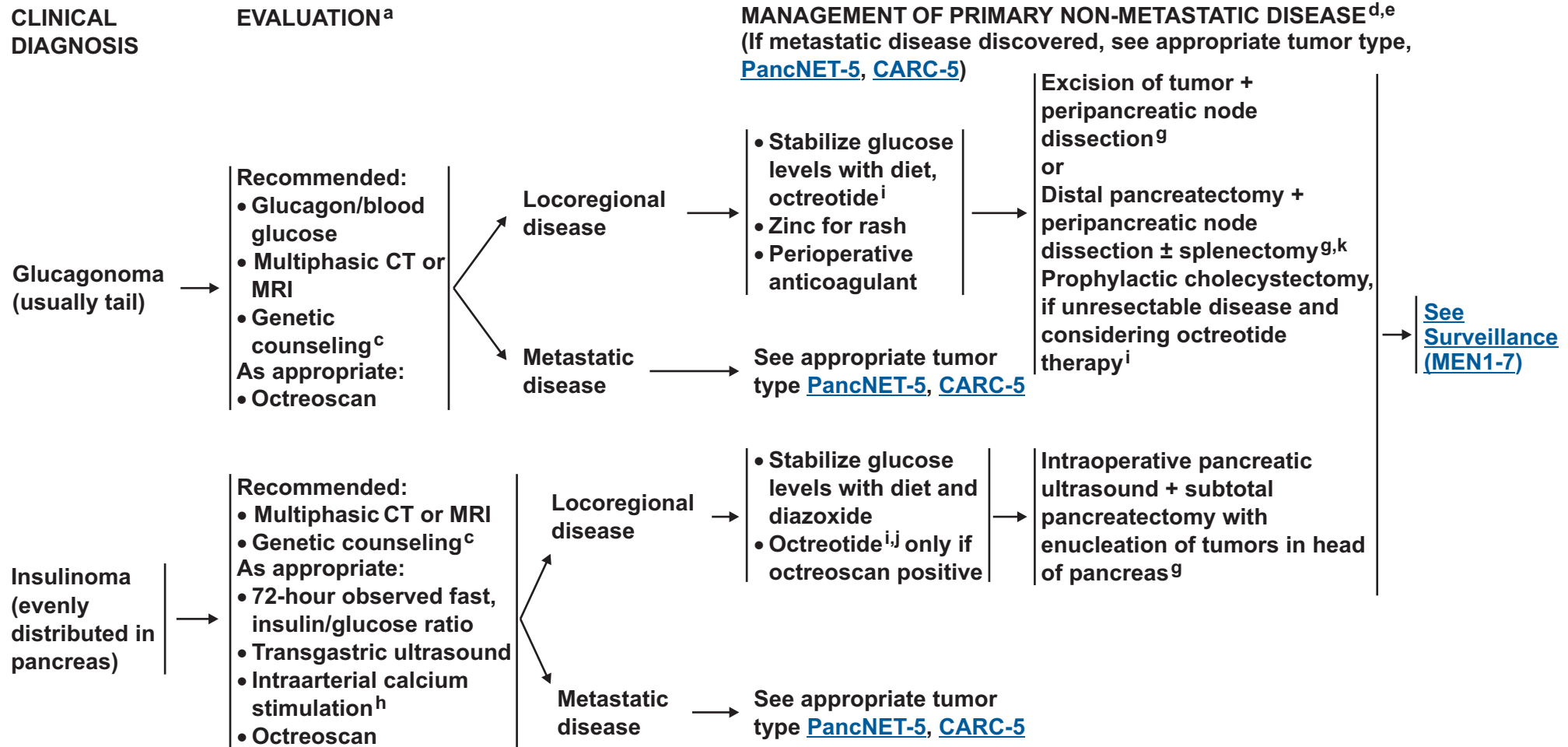
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Multiple Endocrine Neoplasia, Type 1



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^cGenetic counseling may include genetic testing when appropriate.

^dSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^eTrivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.

^gIn patients undergoing abdominal surgery and octreotide planned, suggest prophylactic cholecystectomy.

^hSee discussion (MS-7).

ⁱOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

^jMay worsen hypoglycemia in some patients (See discussion).

^kSplenectomy is probable, as tumors are usually malignant, relatively large, and situated in the tail of the pancreas.

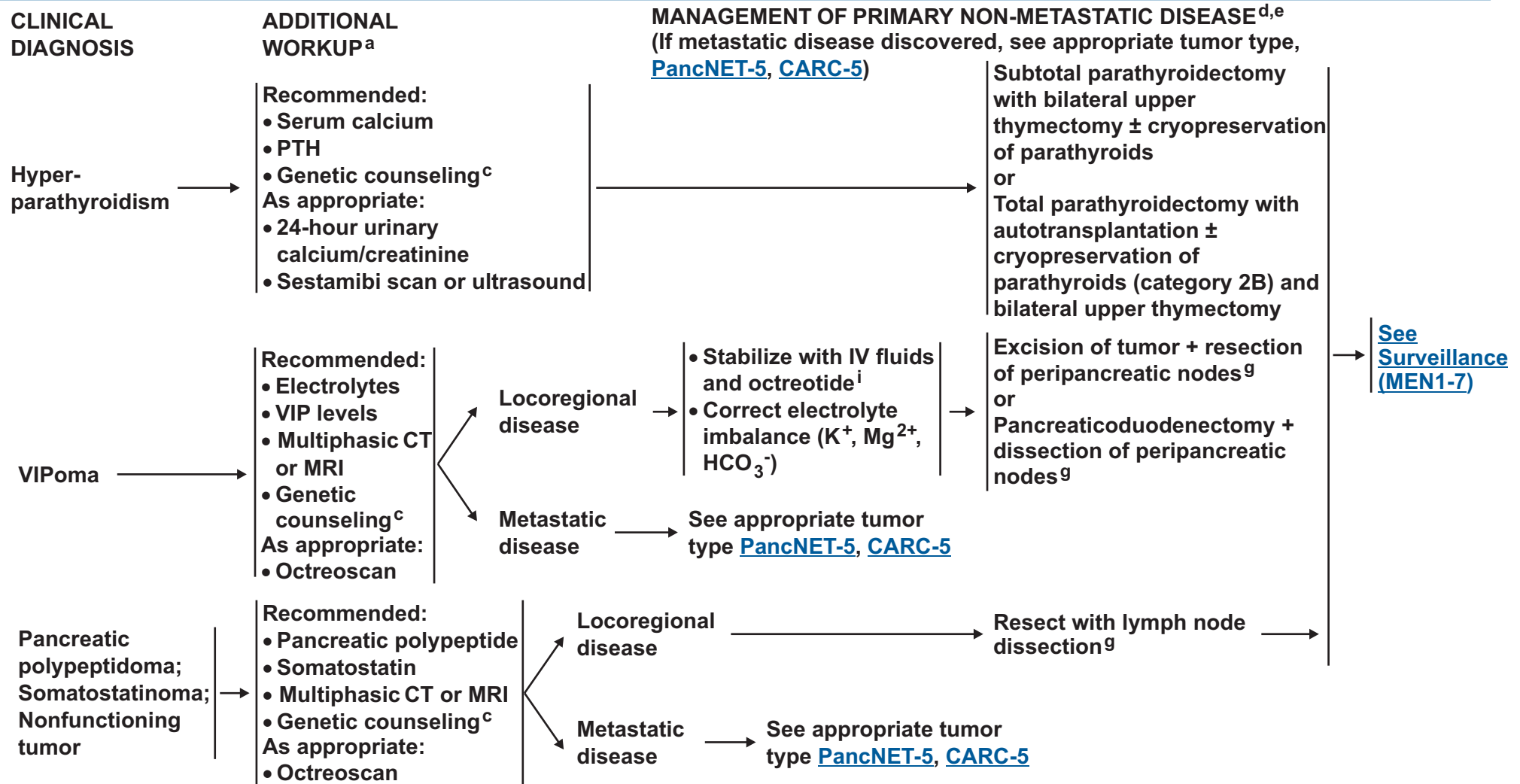
Note: All recommendations are category 2A unless otherwise indicated.

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



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Multiple Endocrine Neoplasia, Type 1



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^cGenetic counseling may include genetic testing when appropriate.

^dSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^eTrivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.

⁹In patients undergoing abdominal surgery and octreotide planned, suggest prophylactic cholecystectomy.

ⁱOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

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

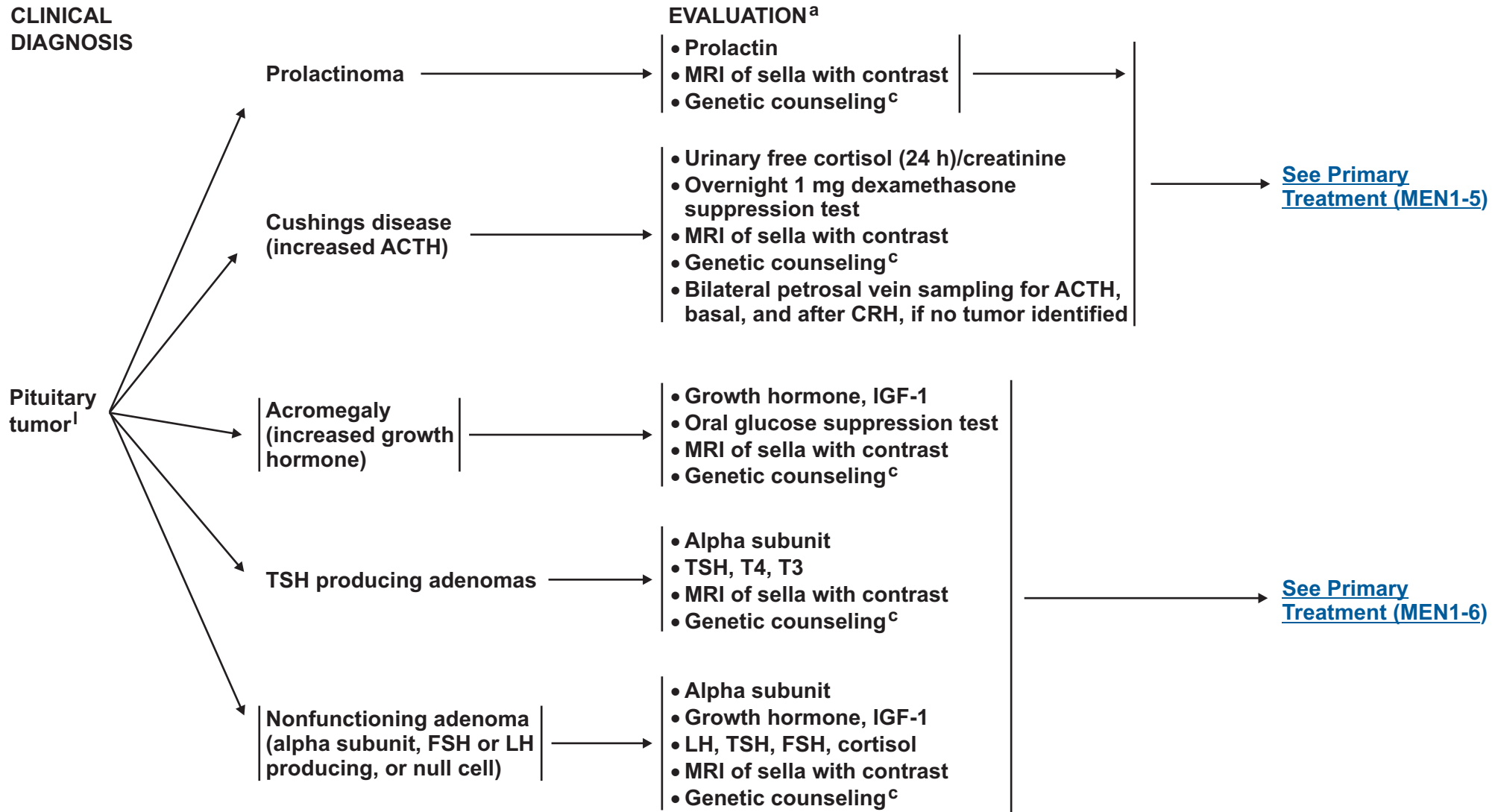
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



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Multiple Endocrine Neoplasia, Type 1

CLINICAL DIAGNOSIS



^aSee [Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\)](#).

^cGenetic counseling may include genetic testing when appropriate.

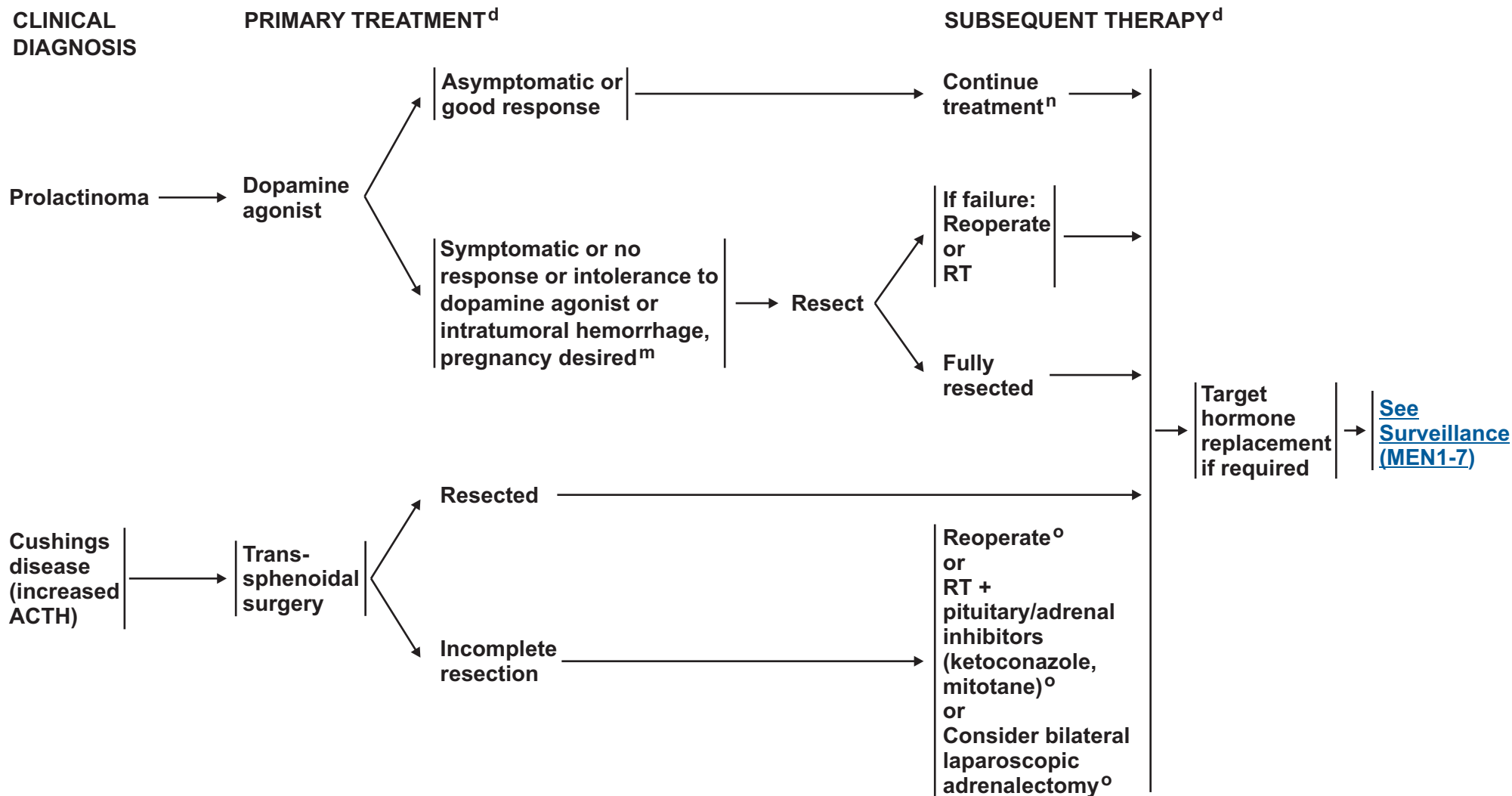
¹If tumor >1 cm, assess visual fields and screen for hypopituitarism including TSH, T4, ACTH stimulation test.

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



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Multiple Endocrine Neoplasia, Type 1



^dSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

^mContinue dopamine agonist or transsphenoidal resection of the tumor.

ⁿConsider discontinuation of treatment, with clinical and hormonal monitoring, if tumor regression and hormone levels normal.

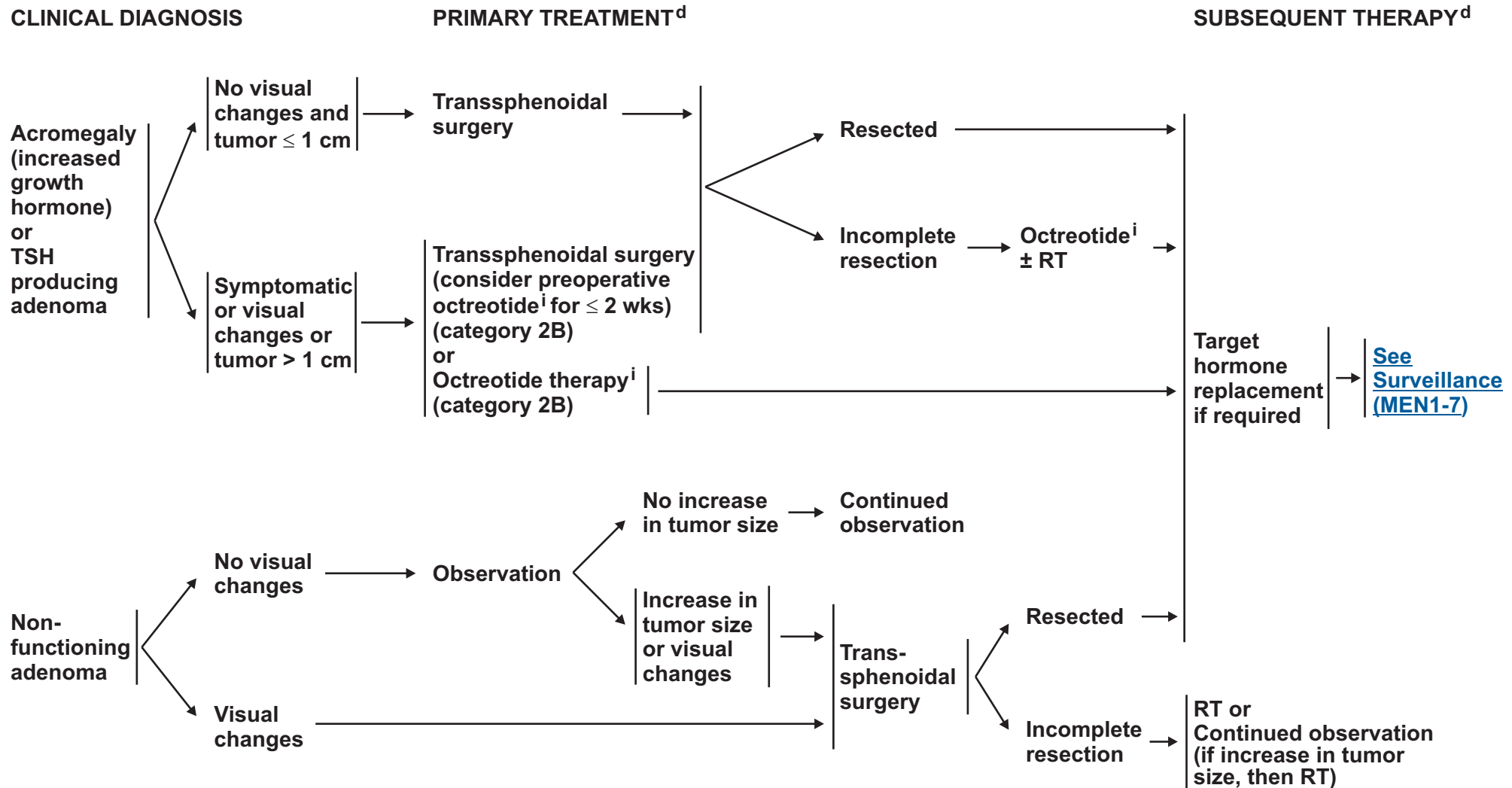
^oMany of the treatments can be considered sequentially.

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines™ Version 1.2011

Multiple Endocrine Neoplasia, Type 1



^dSee [Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\)](#).

ⁱOctreotide 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. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

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



SURVEILLANCE^P

- Multiple endocrine neoplasia, type 1:**
- Hyperparathyroidism
 - Gastrinoma
 - Glucagonoma
 - Insulinoma
 - VIPoma
 - Pancreatic polypeptidoma
 - Somatostatinoma
 - Nonfunctioning tumor
 - Pituitary tumor
 - Adrenal gland tumor
 - Thymus and bronchial carcinoid
 - Lipomas, skin angiomas



3-6 mo postresection:

- Multiphasic CT or MRI
- H&P and markers, calcium as appropriate

Long term:

- H&P and markers, calcium as appropriate
 - Years 1-3: every 6 mo
 - Years 4+: annually
- Imaging studies as appropriate

^PEarlier, if symptoms.

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

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

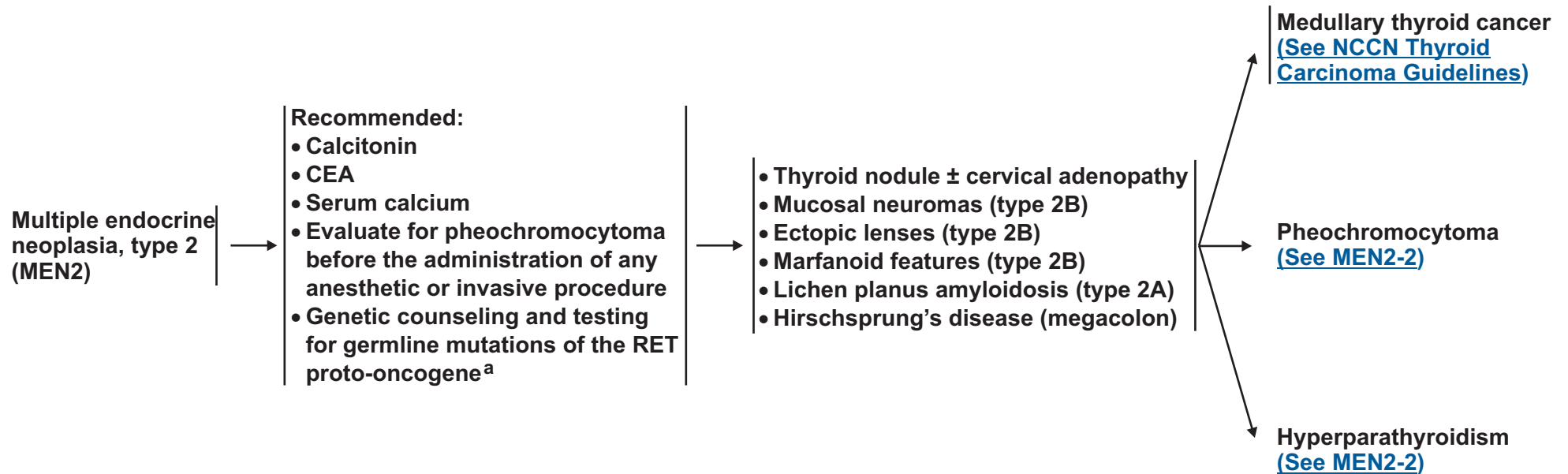


NCCN Guidelines™ Version 1.2011

Multiple Endocrine Neoplasia, Type 2

WORKUP

PHYSICAL EXAM



^aRecommendations for prophylactic thyroidectomy based on individual RET mutations are detailed in the [NCCN Thyroid Carcinoma Guidelines](#)-Medullary Thyroid Cancer.

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



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Multiple Endocrine Neoplasia, Type 2

CLINICAL DIAGNOSIS

EVALUATION^b

PRIMARY TREATMENT^c

SURVEILLANCE^d

Pheochromocytoma →

- Recommended:**
- Plasma-free metanephrine and normetanephrine or urine metanephrine
 - MRI or multiphasic CT
- As appropriate:**
- MIBG scan/Octreoscan



Adrenalectomy (involved side only, laparoscopic procedure preferred as appropriate)
[\(See PHEO-1\)](#)



- 3-6 mo postresection:**
- H&P, blood pressure, and markers^b
- Long term:**
- H&P, blood pressure, and markers^b
 - ▶ Years 1-3: every 6 mo
 - ▶ Years 4+: annually
 - Imaging studies as appropriate
 - Family screening including genetic counseling and testing
 - [See NCCN Thyroid Carcinoma Guidelines-Medullary Thyroid Carcinoma and Pheochromocytoma Guidelines \(PHEO-1\)](#)

Hyperparathyroidism →

- Recommended:**
- Parathyroid hormone
 - 24-hour urinary calcium/creatinine
 - 25-hydroxy vitamin D
- As appropriate:**
- Sestamibi scan
 - Neck ultrasound



**Four-gland identification:
Selective parathyroid resection**

^b[See Stains and Laboratory Studies Potentially Indicated in the Workup of Neuroendocrine Tumors \(NE-A\).](#)

^c[See Surgical Principles for Management of Neuroendocrine Tumors \(NE-B\).](#)

^dEarlier, if symptoms.

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



**IMMUNOHISTOCHEMICAL AND LABORATORY STUDIES POTENTIALLY
INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS¹**

<u>IMMUNOHISTOCHEMICAL STUDIES</u>	<u>GENERAL LABORATORY STUDIES</u>	<u>HORMONE-RELATED STUDIES (blood markers)</u>
<ul style="list-style-type: none"> • Basic for diagnosis <ul style="list-style-type: none"> ▶ Chromogranin A (category 3) ▶ Synaptophysin ▶ Cytokeratin ▶ Ki67 (MIB-1) and/or mitotic rate • Tumor-specific confirmation <ul style="list-style-type: none"> ▶ Gastrin ▶ Somatostatin ▶ Insulin ▶ VIP ▶ ACTH ▶ Glucagon ▶ Prolactin ▶ Calcitonin ▶ Pancreatic polypeptide ▶ Alpha subunits ▶ TSH ▶ PTH ▶ Proinsulin ▶ LH/FSH ▶ Growth hormone 	<ul style="list-style-type: none"> • Chemistries <ul style="list-style-type: none"> ▶ Calcium ▶ Phosphorus ▶ Electrolytes ▶ Magnesium ▶ Chloride/phosphorus ratio 	<ul style="list-style-type: none"> • Carcinoid <ul style="list-style-type: none"> ▶ 5-HIAA (24 h urine) ▶ Chromogranin A • Gastrinoma <ul style="list-style-type: none"> ▶ Gastrin • Insulinoma <ul style="list-style-type: none"> ▶ Proinsulin ▶ Insulin/glucose ratio ▶ C-peptide • VIPoma <ul style="list-style-type: none"> ▶ VIP • Glucagonoma <ul style="list-style-type: none"> ▶ Glucagon ▶ Blood glucose ▶ CBC • Other pancreas <ul style="list-style-type: none"> ▶ Chromogranin A ▶ Somatostatin ▶ Pancreatic polypeptide ▶ Calcitonin ▶ Parathyroid hormone related peptide • Pheochromocytoma/ paraganglioma <ul style="list-style-type: none"> ▶ Metanephrines (plasma and urine) ▶ Catecholamines (urine) ▶ Dopamine (urine) (optional) • Pituitary <ul style="list-style-type: none"> ▶ Growth hormone/IGF-1 ▶ Prolactin ▶ LH/FSH ▶ TSH ▶ Alpha subunits ▶ ACTH • Ectopic hormones <ul style="list-style-type: none"> ▶ ACTH ▶ GRH ▶ GHRH

¹For most of the blood studies, an 8 hour fast is generally recommended in addition to certain dietary adjustments depending on the test ordered. Ordering physicians should be aware that some medications can also affect the results but medications do not necessarily need to be discontinued if they are medically necessary. Below are examples:

Urine 5-HIAA: Patients should not eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, plantain, kiwi, dates, grapefruit, honeydew, or walnuts for a 48-hour period prior to start of urine collection. Additionally patients should avoid coffee, alcohol, and smoking for this time period.

Serotonin: Medications that may effect serotonin concentrations include lithium, monoamine oxidase (MAO) inhibitors, methyl dopa, morphine, and reserpine.

Chromogranin A: Impaired renal or hepatic function or treatment with proton pump inhibitors may result in artifactual elevations.

Gastrin: ≥ 8 hour fast.

VIP: 8 hour fast.

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SURGICAL PRINCIPLES FOR MANAGEMENT OF NEUROENDOCRINE TUMORS

- **Patients with localized neuroendocrine tumors including functional adenoma or carcinoma should be considered for definitive resection.**
- **For incidentally identified lesions that are suspected of being neuroendocrine tumors, experienced surgical judgment must be used regarding the operative approach (open exploration versus laparoscopic). In general, laparoscopic resection is preferable for patients suspected to have small, benign, functional adrenal tumors. An open exploration is recommended for tumors that have a high risk of being malignant.**
- **Resection includes total removal of the tumor with negative margins. For patients with locally advanced tumors, concomitant resection of adjacent organs such as kidney, liver, spleen, pancreas, stomach, colon, or vena cava when required to completely remove the directly invaded adjacent structure.**
- **Resection of recurrent tumor or previously unresectable tumor that has regressed should be considered for selected patients with excellent performance status and locoregional recurrence or isolated distant metastases when complete resection can be achieved.**
- **Some patients, including those with symptomatic recurrence from local effects or hormone hypersecretion, can be 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 unresectable tumor and/or distant metastases.**
- **Liver directed therapies (including liver resection, ablation or intrarterial therapies) for hepatic metastases from pancreatic neuroendocrine tumors following pancreaticoduodenectomy are associated with increased risk of perihepatic sepsis and liver abscess.**
- **Octreotide therapy should be administered immediately prior to resection of primary or metastatic functional (carcinoid) neuroendocrine tumors, if not already receiving such therapy.**
- **All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C).**

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

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



Staging

American Joint Committee on Cancer (AJCC)

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

Stomach

TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastases (M)

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

Duodenum/Ampulla/Jejunum/Ileum

TNM

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- T1** Tumor invades lamina propria or submucosa and size 1 cm or less* (small intestinal tumors); tumor 1 cm or less (ampullary tumors)
- T2** Tumor invades muscularis propria or size > 1 cm (small intestinal tumors); tumor > 1 cm (ampullary tumors)
- T3** Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into non-peritonealized tissues
- T4** Tumor invades visceral peritoneum (serosa) or invades other organs
- For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)

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

Distant Metastases (M)

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

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

[Continued on next page](#)

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Staging

American Joint Committee on Cancer (AJCC)

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

Colon or Rectum	
TNM	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 2 cm or less
T1a	Tumor size less than 1 cm in greatest dimension
T1b	Tumor size 1–2 cm in greatest dimension
T2	Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor invades peritoneum or other organs For any T, add (m) for multiple tumors
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastases (M)	
M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

[Continued on next page](#)

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Staging

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

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

Pancreatic	
TNM	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastases (M)	
M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

* This also includes the "PanInIII" classification.

[Continued on next page](#)

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Staging

American Joint Committee on Cancer (AJCC)

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

Appendiceal Carcinoid

TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastases (M)

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

ANATOMIC STAGE/PROGNOSTIC GROUPS

Carcinoid

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

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

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

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

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

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

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

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database estimated that the incidence of neuroendocrine tumors in the United States was 5.25 cases per 100,000 people in the year 2004.¹ Recent analyses have suggested that the diagnosed incidence of neuroendocrine tumors is increasing, and that the

prevalence of individuals with neuroendocrine tumors in the United States may exceed 100,000.¹

The majority of neuroendocrine tumors appear to be sporadic; risk factors for sporadic neuroendocrine tumors are poorly understood. Neuroendocrine tumors may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia types 1 and 2. Multiple endocrine neoplasia type 1 (MEN 1), associated with mutations in the *menin* gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands.² Multiple endocrine neoplasia type 2 (MEN 2), associated with mutations in the *RET* proto-oncogene, is characterized by the development of medullary thyroid cancer, pheochromocytoma (often bilateral), and hyperparathyroidism.³ Neuroendocrine tumors have also been associated with Von-Hippel Lindau disease, tuberous sclerosis complex, and neurofibromatosis.⁴

Neuroendocrine tumors are generally subclassified by site of origin and by histologic characteristics. Pancreatic neuroendocrine tumors commonly arise in the tail of the pancreas; carcinoid tumors most commonly arise in the lungs and bronchi, small intestine, appendix, or rectum. Neuroendocrine tumors are classified histologically based on tumor grade and differentiation. Three broad histologic categories are generally recognized: well-differentiated (low-grade) neuroendocrine tumors; moderately-differentiated (intermediate-grade) neuroendocrine tumors; and poorly-differentiated (high-grade) neuroendocrine tumors.

Patients with neuroendocrine tumors may or may not have symptoms attributable to hormonal hypersecretion. Such symptoms include intermittent flushing and diarrhea in patients with carcinoid syndrome,⁵ hypertension in patients with pheochromocytoma,⁶ and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic neuroendocrine tumors.⁷ Patients with



symptoms are considered to have “functional” tumors, and those without symptoms are considered to have “nonfunctional” tumors.

The 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), as well as medical, radiation, and surgical oncologists. These NCCN Neuroendocrine Tumor guidelines discuss the diagnosis and management of both sporadic and hereditary neuroendocrine tumors. Medical practitioners should note that unusual patient scenarios (presenting in less than 5% of patients) are not specifically discussed in these NCCN guidelines.

Sporadic Neuroendocrine Tumors

Carcinoid Tumors

Approximately one-third of carcinoid tumors arise in the lungs or thymus and two-thirds arise in the gastrointestinal tract. Sites of origin within the gastrointestinal tract include the stomach, small intestine, appendix, and rectum.¹ The prognosis for patients with carcinoid tumors varies according to the stage at diagnosis and primary site of the tumor. Recent analyses of the Surveillance Epidemiology and End Results (SEER) database demonstrated that 5-year-survival rates range from 82-97%, 63-87%, 21-74%, and 5.5-43%, for stages I through IV, respectively, for carcinoids of the rectum, colon, stomach, and small bowel.⁸⁻¹¹

Carcinoid tumors may secrete various hormones and vasoactive peptides. Bronchial carcinoids have been associated with ACTH production, and are a common cause of Cushing’s syndrome.¹² Carcinoid tumors arising in the small intestine or appendix are more

commonly associated with carcinoid syndrome, related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation causing episodic flushing and diarrhea.¹³ Additionally, about 10-30% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation or pulmonary stenosis.¹³

The metabolic products released by intestinal carcinoid tumors are rapidly destroyed by liver enzymes in the portal circulation, thus the classical syndrome, occurring in approximately 8% of patients with carcinoid tumors,¹⁴ is not usually observed unless metastases or rarely retroperitoneal disease have occurred, in which case hepatic metastases release metabolic products directly into the systemic circulation via the hepatic veins.

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

Evaluation of Carcinoid Tumors

Patients who present with carcinoid tumors should be evaluated with imaging studies to assess disease burden and possible primary location. Commonly used techniques include computed tomography (CT) and magnetic resonance imaging (MRI). Carcinoid tumors are highly vascular and can appear isodense with liver on CT scan, depending on contrast phase. Multi-phase CT scans should therefore be used for evaluation of liver metastasis. The majority of carcinoid tumors express high-affinity receptors for somatostatin^{13, 15}; radiolabeled somatostatin receptor scintigraphy, performed using the radiolabeled somatostatin analogue [¹¹¹In-DTPA] octreotide (OctreoScan), may also be used in the initial evaluation of carcinoid



tumor patients. Patients with positive octreotide scans are more likely to respond to treatment with somatostatin analogs.

Management of Locoregional Disease

The management of locoregional carcinoid tumors depends on tumor size and primary site, as well as the general condition of the patient. Specific recommendations for management of carcinoid tumor subtypes are described below.

Gastric carcinoid tumors

Three types of gastric carcinoid tumors are generally recognized: type 1 gastric carcinoids (associated with chronic atrophic gastritis), type 2 gastric carcinoids (associated with Zollinger-Ellison syndrome, and type 3 gastric carcinoids (sporadic).¹⁶ Type 1 and type 2 gastric carcinoids are both associated with hypergastrinemia.¹⁶ For hypergastrinemic patients whose tumors are 2 cm or smaller and either solitary or multiple, options include (1) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa; (2) observation; or (3) octreotide for patients with Zollinger-Ellison syndrome (category 2B recommendation). For hypergastrinemic patients with tumors larger than 2 cm either solitary or multiple, endoscopic resection (if possible) or surgical resection is indicated. Hypergastrinemic patients with low gastric pH, should be considered for gastrinoma. Patients with locoregional gastric carcinoid disease and normal gastrin levels are usually treated with radical resection of the tumor and removal of the perigastric lymph nodes.

Thymic carcinoid tumors

Localized and locoregional carcinoid tumors in the thymus are treated with surgical resection. Following incomplete resection of locoregional disease, radiation therapy (RT) alone or with chemotherapy is recommended (category 3 for addition of chemotherapy). Capecitabine

or 5-fluorouracil at radiosensitizing doses may be considered. Cisplatin or carboplatin with etoposide may be appropriate for patients with moderately differentiated or atypical tumors.

Bronchopulmonary carcinoid tumors

For localized or locoregional bronchopulmonary tumors, refer to the Lung Neuroendocrine Tumors algorithm, which is part of the NCCN Small Cell Lung Cancer Guidelines.

Carcinoid tumors of the duodenum, small intestine, and colon

For lesions arising in the duodenum, endoscopic resection is recommended for locoregional disease. Transduodenal local excision with or without lymph node sampling and pancreaticoduodenectomy are other options for primary treatment of non-metastatic duodenal carcinoid tumors.

For patients presenting with tumors in the jejunum, ileum, or colon, surgical resection of the bowel with regional lymphadenectomy is recommended. The surgical procedure should include careful examination of the entire bowel, because multiple synchronous lesions may be present. If future treatment with octreotide is anticipated, a prophylactic cholecystectomy should be considered given the association between long-term treatment with somatostatin analogs and the development of gallstones.¹⁷

Appendiceal carcinoid tumors

Most appendiceal carcinoid tumors are identified incidentally, during appendectomy performed for appendicitis. For appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient.¹⁸ Patients with an incomplete resection or with tumors greater than 2 cm are at risk for locoregional or distant metastases. Such patients should be staged with abdominal/pelvic CT or MRI scans. If no



distant disease is identified, they should undergo a right hemicolectomy.

Carcinoid tumors of the rectum

The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumors, examination under anesthesia (EUA) prior to the procedure should be considered for tumors 1-2 cm in size. Tumors larger than 2 cm, tumors with invasion of the muscularis propria, or tumors associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection (APR).¹⁹

Surveillance

Most patients with carcinoid tumors of the jejunum/ileum/colon, duodenum, appendix, rectum, and thymus as well as type 3 gastric carcinoid lesions with normal gastrin levels should be re-evaluated 3 to 12 months after resection (earlier if the patient is symptomatic) and every 6 to 12 months thereafter. For patients with type 1 or type 2 gastric carcinoids, surveillance with EGD every 6-12 months for the first three years and annually thereafter is recommended, with imaging studies performed as clinically indicated. Surveillance for other types of carcinoid tumors should include complete patient history and physical examination (H&P), and imaging studies such as CT (abdominal and/or pelvic triple-phase) and MRI.

Chromogranin A may be used as a tumor marker (category 3); while not diagnostic, elevated levels have been associated with recurrence.²⁰ Chromogranin A levels can be elevated in a number of concurrent medical conditions, including renal or hepatic insufficiency, and are also commonly elevated in the setting of concurrent proton pump inhibitors. Several Panelists therefore caution that rising chromogranin A levels in

an asymptomatic patient with a tumor that appears stable by imaging does not necessarily indicate that a patient should be initiated on a new therapy.

5-HIAA in a 24-hour urine sample may also be considered as a biochemical marker for monitoring in some cases. While monitoring patients following treatment for a carcinoid tumor, decreasing levels of 5-HIAA indicates a response to treatment, while increasing or excessive concentration indicates that the treatment has not been successful. A patient with symptoms may still have a carcinoid tumor even if the concentration of 5-HIAA is normal. Diet and a variety of drugs can affect the 5-HIAA test. Therefore, patients should be advised not to eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts, plantain, kiwi, dates, grapefruit, honeydew, or walnuts for a 48-hour period prior to start of urine collection. Additionally patients should avoid coffee, alcohol, and smoking for this time period. Medications that can increase 5-HIAA include acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (an ingredient found in some cough medicines), and phenobarbital.

Nuclear medicine scanning (PET scan or OctreoScan) is not routinely recommended for surveillance following definitive resection, but may be indicated to assess disease location and disease burden in cases of suspected recurrence.

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



indicated. Follow up recommendations also differ to some extent for patients with gastric carcinoid tumors. Hypergastrinemic (type 1 or type 2) patients with small gastric carcinoid tumors who did not require endoscopic resection or treatment should be evaluated with H&P every 6 to 12 months. Imaging studies or surveillance may be performed on these patients as clinically indicated. Follow-up endoscopies are recommended for patients with type 1 and type 2 gastric carcinoid tumors. Surveillance every 6 to 12 months for the first 3 years and annually thereafter is appropriate if no evidence of recurrence or progression is seen. If clinically indicated, imaging studies should also be performed. Antrectomy to remove the source of gastrin production can be considered in patients with type 1 gastric carcinoids if new lesions or increasing tumor burden is observed.

Management of Locoregional Unresectable Disease and/or Metastatic Carcinoid Tumors

Baseline imaging recommendations for patients suspected to have distant metastatic disease include multi-phase technique CT or MRI.^{21, 22} Baseline levels of chromogranin A (category 3) or 5-HIAA may also be considered to monitor subsequent progression (discussed in the section above). OctreoScan can also be considered both to assess sites of metastases and to assess somatostatin receptor status if treatment with octreotide is being considered. The most common sites of metastases from carcinoids include regional/mesenteric lymph nodes, liver, bones, and lung.

In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection. In such patients, resection of the primary tumor and metastases should be performed. Resection of the primary site in the setting of unresectable metastases is generally not indicated if the primary site remains asymptomatic and is relatively stable. However, it is not uncommon for patients with small bowel

primary tumors to experience symptoms of intermittent abdominal pain from episodic bowel obstruction or bowel ischemia related to the primary tumor and surrounding fibrosis. Palliative small bowel resection is recommended in such patients.

Patients who have metastatic carcinoid tumors and carcinoid syndrome should be treated with octreotide.¹⁷ Doses of short-acting octreotide include 150-250 mcg administered subcutaneously (SC) 3 times daily (TID). The long-acting release (LAR) formulation of octreotide is used for the chronic (preventive) management of patients with the carcinoid syndrome; doses of LAR octreotide include 20-30 mg intramuscularly (IM) every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.²³⁻²⁵ A cardiology consultation and echocardiogram to assess whether the patient has carcinoid heart disease should also be considered in patients with carcinoid syndrome with signs and symptoms of heart disease or with planned major surgery.¹⁷ Cardiac heart disease is frequent in patients with the carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation.^{26, 27}

In asymptomatic patients with a low tumor burden, the NCCN panel recommends either (1) observation with imaging and marker studies every 3 to 6 months until the disease becomes symptomatic or progressive; (2) enrollment in a clinical trial; or (3) octreotide therapy.

There is no clear consensus on the timing of octreotide initiation in asymptomatic patients with carcinoid tumors. The recommendation to consider octreotide in such patients is based on the interim results of a placebo controlled phase III trial (PROMID), which showed that median time to tumor progression in the octreotide LAR group versus the



placebo group was 14.3 and 6 months, respectively ($P = 0.000072$). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group. The study found that functionally active and inactive tumors responded similarly.²⁸

While initiation of octreotide can be considered in patients with no symptoms and low tumor burden, it may also be appropriate to defer initiation of octreotide in such patients until there is evidence of tumor progression. In patients who have clinically significant tumor burden, on the other hand, initiation of octreotide is recommended. Initiation of octreotide is also recommended if there is evidence of disease progression.

Patients with clinically significant progression of metastatic carcinoid tumors can pursue several options. In general, such patients should be started on treatment with octreotide if they are not already receiving octreotide treatment. In addition to octreotide, cytoreductive surgery may be considered if near complete resection can be achieved (category 2B); treatment with everolimus can also be considered (category 3 recommendation; see discussion below). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization,^{29, 30} radioembolization [category 2B],³⁰⁻³⁵ or ablative therapies such as radiofrequency ablation (RFA), cryotherapy, microwave^{36, 37}) are recommended. If no other options are feasible, then systemic therapy (category 3) with cytotoxic agents such as interferon,^{24, 38, 39} temozolomide, dacarbazine, 5-fluorouracil, and capecitabine can be considered. Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a definitive progression-free or overall survival benefit.

A number of investigational therapies have shown preliminary evidence of activity in patients with advanced carcinoid tumors. These include VEGF pathway inhibitors (bevacizumab, sunitinib, and sorafenib),⁴⁰⁻⁴² as well as inhibitors of mammalian target of rapamycin (mTOR).^{20, 34, 43, 44} Everolimus is an inhibitor of mTOR that has been the subject of recent trials. It was well tolerated and showed promising anti-tumor effects in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial.⁴⁴ In a randomized phase III trial, patients with advanced carcinoid tumors were randomized to receive octreotide LAR with or without everolimus.⁴⁵ Based on local investigator assessment of response, patients receiving octreotide plus everolimus had a median progression-free survival duration of 12 months, as compared to 8.6 months for patients receiving octreotide alone ($P = 0.018$). Based on centrally evaluated radiologic response, however, the difference in progression-free survival did not meet the pre-defined threshold for statistical significance. The panel lists consideration of everolimus for carcinoid tumors following progression as a category 3 recommendation.

Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced carcinoid tumors.⁴⁶⁻⁴⁹ This approach remains investigational, and randomized trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in advanced carcinoid are anticipated.

Islet Cell Tumors (Pancreatic Endocrine Tumors)

According to a population-based study, malignant pancreatic endocrine tumors account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence.⁵⁰ Although the peak incidence of occurrence is between ages 40 and 69 years, a significant number of patients diagnosed with islet cell tumors are under



the age of 35.^{50, 51} An estimated 40% or more of pancreatic endocrine tumors are nonfunctional (and up to 90% of these are malignant); the remainder manifest with clinically evident hormonal symptoms.⁷ The characteristics of functional endocrine tumors of the pancreas are summarized in Table 1.⁵¹ Of these functioning tumors, up to 70% are insulinomas. Approximately 15% are glucagonomas, and gastrinomas and somatostatinomas account for another 10%; most (80% to 90%) of these are malignant with higher risk for the development of metastases.⁵¹ The remaining rare functioning islet cell tumors include VIPoma and pancreatic polypeptidoma (PPoma). Islet cell tumors occurring in patients with MEN 1 or MEN 2 are typically multiple and require different treatment strategies than those used for patients with sporadic pancreatic endocrine tumors, which are usually solitary (see below). Gastrinoma is the most common pancreatic islet cell tumor in patients with MEN 1 followed by insulinomas.⁵²

Evaluation of Islet Cell Tumors (Pancreatic Endocrine Tumors)

For nonfunctioning islet cell tumors, the recommended evaluation includes CT or MRI scan. OctreoScan, serum chromogranin A (category 3), and pancreatic polypeptides may be tested as clinically appropriate. Chromogranin A levels are elevated in 60% to 100% of patients with either functioning or nonfunctioning pancreatic endocrine tumors. The sensitivities and specificities of Chromogranin A for the detection of neuroendocrine tumors range between 70% and 100%.^{53, 54} Care should be taken in measuring Chromogranin A and interpreting the results, as spuriously elevated levels of Chromogranin A have been reported in patients using proton pump inhibitors, in patients with renal or liver failure, in patients with hypertension, and in those with chronic gastritis. The family history of the patient must be considered to rule out MEN-1 syndromes.

Gastrinomas

Gastrinoma is often suspected in patients with severe gastroduodenal ulcer symptoms such as dyspepsia, sometimes accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of gastrin levels (basal and stimulated).⁵⁵ Diagnosis of gastrinoma can be confounded by the concurrent use of proton pump inhibitors, which will elevate serum gastrin levels. Importantly, the vast majority of patients who are found to have an elevated level of serum gastrin do not have a gastrinoma but have achlorhydria or are receiving proton pump inhibitors or antacids. Gastrin levels (basal or stimulated) must be measured after the patient is off proton pump inhibitor therapy for at least 1 week. In addition, imaging studies (CT/MRI scan) often aid not only in localizing the tumor but also in confirming the diagnosis. Other tests such as an OctreoScan and chromogranin A levels (category 3) may be carried out as appropriate.

Insulinomas

Insulinomas are generally small tumors that are best localized by transgastric ultrasound. Although 90% of insulinomas pursue an indolent course and can be cured surgically, it is important to document large tumors with possible liver metastases by CT/MRI scans because it may change surgical strategy. The diagnosis of insulinoma may be established by determination of insulin/glucose ratio. An insulin level greater than 3 mIU/mL (usually greater than 6 mIU/mL) when blood glucose is less than 40 to 45 mg/dL, with an insulin-to-glucose ratio of 0.3 or greater reflecting the inappropriate secretion of insulin at the time of hypoglycemia, document these tumors.⁵⁶⁻⁵⁸ Patients with insulinoma also have elevated levels of C-peptide.⁵⁶

Endoscopic ultrasound has been shown to localize about 82% of pancreatic endocrine tumors.⁵⁹ Insulinomas can also be localized by injecting calcium into selective pancreatic arteries and measuring the



insulin levels in the right (usually) or left hepatic vein (Imamura-Doppman procedure).⁶⁰ Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative. Insulinomas are less consistently octreotide-avid than other pancreatic neuroendocrine tumors, and OctreoScan may consequently be less useful as an imaging technique in insulinomas than in other tumor subtypes. Additionally, octreotide should be used with caution in patients with insulinoma, as it may precipitate or worsen hypoglycemia (see Preoperative management, below).

Glucagonomas and VIPomas

For glucagonomas with diabetes, characteristic skin rash, and diarrhea, the panel recommends a blood test for glucagon/blood glucose, multiple contrast enhanced CT/MRI, and OctreoScan as appropriate. For VIPomas with characteristic watery diarrhea, testing for vasoactive intestinal polypeptide (VIP) and electrolytes is recommended. A CT or MRI scan and an OctreoScan (particularly for VIPoma) may be useful for identifying large tumors or metastatic disease and are recommended routinely for suspected VIPoma.

Primary Treatment of Islet Cell Tumors (Pancreatic Endocrine Tumors)

Preoperative management

Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. For gastrinomas, gastrin hypersecretion may be treated with histamine H₂-receptor antagonists or with proton pump inhibitors. Octreotide can also be considered in most pancreatic neuroendocrine tumor subtypes. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Octreotide should be used with caution in patients with insulinoma

because it can also suppress counter-regulatory hormones such as growth hormone, glucagon, and catecholamines. In this situation, octreotide can precipitously worsen hypoglycemia and in some cases can result in fatal complications.⁶¹

Stabilization of glucose levels with IV fluids and/or octreotide may be useful for patients with glucagonoma or VIPoma (if OctreoScan positive).¹⁷ Zinc supplementation is helpful in glucagonoma patients with severe skin rash; potassium, magnesium, and bicarbonate can be administered to VIPoma patients to correct electrolyte imbalance. Because of the severe weight loss common with patients with glucagonoma, total parenteral nutrition (TPN) may also be considered for these patients. All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group c).

Surgical management

Laparoscopy should be considered for nonfunctioning tumors to successfully locate and stage the tumors. Depending on the size, location, and type of tumor, recommended options for nonfunctioning pancreatic tumors include either (1) laparoscopic resection; (2) pancreaticoduodenectomy (ie, Whipple procedure); (3) subtotal pancreatectomy; or (4) distal pancreatectomy. For small nonfunctioning tumors, the risks and benefits of surgical resection should be carefully weighed. For rare functioning tumors such as somatostatinoma, ACTHoma, PTH-rP-secreting tumors, and PPoma, the treatment recommendations are similar to that of nonfunctioning tumors.

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 (1)



observation or (2) exploratory surgery with enucleation of tumors if identified at operation and duodenotomy with removal of periduodenal nodes. Gastrinomas in the head of the pancreas, that are exophytic or peripheral tumors as determined by imaging and are not immediately adjacent to the pancreatic duct, should be enucleated. Removal of the periduodenal nodes may be considered. Gastrinomas that are deeper or invasive and those with proximity to the main pancreatic duct should be managed by pancreaticoduodenectomy with periduodenal node dissection. Gastrinomas in the distal pancreas are treated with either distal pancreatectomy with or without splenectomy or with tumor enucleation.

The primary treatment for locoregional insulinomas, because they are primarily benign, is enucleation. This procedure can be done laparoscopically for localized solitary tumor within the body and tail of the pancreas. Sporadic tumors are usually solitary whereas familial tumors are multiple. If enucleation is not possible due to invasion or the location of the tumor within the pancreas, then the following options may be considered (1) segmental resection of the pancreas; (2) pancreaticoduodenectomy; or (3) distal pancreatectomy with preservation of the spleen.

Most glucagonomas are malignant and calcified and located in the tail of the pancreas, with regional node involvement. Therefore, the recommended treatment includes either (1) excision of the tumor (usually in the pancreas tail) with peripancreatic nodal dissection; or more commonly (2) distal pancreatectomy with resection of the peripancreatic lymph nodes and splenectomy. For larger tumors or those not located in the pancreatic tail, pancreaticoduodenectomy may be required. For glucagonomas, perioperative coagulation can be considered because of the increased risk of pulmonary emboli.

As with nonfunctioning tumors, recommended options for VIPoma depend on the size, location, and invasion of the tumor and include either (1) excision of the tumor or distal pancreatectomy with resection of peripancreatic lymph nodes or spleen; or (2) pancreaticoduodenectomy with dissection of peripancreatic nodes for tumors in the head of the pancreas.

Surveillance

Patients with pancreatic endocrine tumors should undergo follow-up 3 to 12 months after resection, or earlier if the patient presents with symptoms, and every 6 to 12 months thereafter with an H&P, appropriate tumor markers, and imaging studies such as CT/MRI. OctreoScan and PET scan are not recommended for routine surveillance. Surgical resection is recommended for resectable locoregional recurrence.

Management of Locoregional Unresectable Disease and/or Metastatic Islet Cell Tumors

Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases. In patients with limited hepatic disease, surgical excision of both the primary tumor and liver metastases should be considered when possible and can be performed in a staged or synchronous fashion. When performing staged pancreaticoduodenectomy and liver resection, hepatectomy should be considered prior to pancreatic resection in order to reduce the risk of perihepatic sepsis due to the contaminated biliary tree.⁶² For patients with unresectable liver metastases, options include hepatic regional therapies such as arterial embolization, radioembolization (category 2B),³¹⁻³⁵ chemoembolization,⁶³ and local ablative therapy (RFA, cryotherapy, microwave).^{36, 37} To date, there are no randomized clinical trials assessing the effectiveness of these therapies, and prospective data for these interventions are limited.



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

For symptomatic patients, those who initially present with clinically significant tumor burden, or those with clinically significant disease progression, several different options can be considered. These include treatment with biologically targeted agents (everolimus or sunitinib), treatment with cytotoxic chemotherapy, or treatment with somatostatin analogs (category 2B). The panel also lists cytoreductive surgery as a category 2B recommendation for these patients.

Biologically targeted therapies

The biologically targeted agents everolimus and sunitinib have recently been confirmed to have anti-tumor activity and to improve progression-free survival in patients with advanced pancreatic neuroendocrine tumors. Everolimus, administered orally at a dose of 10 mg once daily, was evaluated in a multi-center study (RADIANT-3) enrolling 410 patients with advanced, progressive pancreatic neuroendocrine tumors.⁶⁴ In this study, the median progression-free survival duration for patients randomized to everolimus was 11.0 months, as compared to 4.6 months for patients receiving placebo, ($P < 0.001$). Sunitinib, administered orally at a dose of 37.5 mg once daily, was compared to placebo in a multi-center, randomized study of patients with advanced, progressive metastatic pancreatic neuroendocrine tumors.⁶⁵ The study was designed to enroll 340 patients, but was discontinued after enrollment of 171 patients, prior to the pre-defined efficacy analysis. At the time of study discontinuation, patients who received sunitinib had a median progression-free survival duration of 11.4 months, compared to

5.5 months for patients receiving placebo ($P < 0.001$). The objective response rate seen with sunitinib was 9.3%.⁶⁵

Somatostatin analogs

Patients with symptoms of hormone secretion should, in most cases receive treatment with octreotide and/or other medication to manage their symptoms as previously described. Patients without hormone-related symptoms who have a positive OctreoScan can be considered for treatment with octreotide (category 2B), although no randomized studies to date have demonstrated an anti-tumor effect of octreotide in pancreatic neuroendocrine tumors.

Cytotoxic chemotherapy

Cytotoxic chemotherapy is another option for patients with unresectable or metastatic 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.⁶⁶ A more recent retrospective review from the MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin. More recently, oral temozolomide-based therapy has become increasingly used in patients with advanced pancreatic neuroendocrine tumors. Temozolomide has been administered using different schedules and either alone or in combination with other agents. Reported response rates with these regimens range from 8-70%.⁶⁷⁻⁷¹ Other agents with reported antitumor activity include dacarbazine (DTIC), fluorouracil, and capecitabine.⁷¹⁻⁷³



Neuroendocrine Unknown Primary Tumors

According to a SEER database analysis a primary tumor site could not be found in as many as 4,752 (13%) out of 35,618 neuroendocrine tumors.¹

Evaluation of Neuroendocrine Unknown Primary Tumors

The initial evaluation of a patient with neuroendocrine tumors of unknown primary includes patient's family history, clinical manifestations, laboratory studies, imaging studies, and/or immunohistochemical studies. The family history is particularly relevant as it may identify affected relatives and patients who are at increased risk for multiple endocrine tumors such as in patients with MEN 1 or MEN 2.

Potential primary sites may be investigated with imaging studies, such as CT or MRI. Ultrasound or endoscopic ultrasound evaluation of the pancreas is useful for patients with possible insulinomas or other neuroendocrine tumors of the pancreas. Many neuroendocrine tumors express specific receptors for amines or peptides (eg, somatostatin receptors); and OctreoScan may also be helpful in localizing certain neuroendocrine tumors.⁷⁴ In addition, radionucleotide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan can be occasionally useful in finding a primary tumor, but is less sensitive in well differentiated neuroendocrine tumors and should only be considered in cases of poorly differentiated tumors.

If the primary tumor site is found by imaging studies, the tumors are managed as per the treatment algorithms for individual sites. If a primary tumor is not identified, additional workup includes core needle or fine needle aspiration biopsy. Alternatively, biopsy resection can be

performed based on location of lesions, as clinically appropriate. Functional adrenal neoplasms and suspected carcinoid tumor syndrome needs to be ruled out prior to biopsy or invasive procedures. Also prior to biopsy or manipulation, alpha blockage is required for suspected pheochromocytoma or paraganglioma and octreotide premedication is required in suspected functioning carcinoid tumor.

Evaluation of the cytology or pathology specimen includes use of basic stains for the diagnosis of a neuroendocrine tumor (chromogranin A, synaptophysin, cytokeratin) and of tumor-specific stains to confirm the diagnosis. Laboratory studies are recommended depending on the tumor type suspected. Serum chromogranin levels are usually elevated in patients with neuroendocrine tumors. The grade of differentiation (well, moderately, or poorly differentiated) is also useful for profiling these tumors and predicting prognosis and should be included in the evaluation.⁷⁵

Primary Treatment of Neuroendocrine Unknown Primary Tumors

The endpoint of the evaluation is the pathologic categorization of neuroendocrine tumors of unknown primary into two categories: (1) poorly differentiated or (2) well and moderately differentiated. Poorly differentiated neuroendocrine tumors should be treated as described below (see Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors). Well and moderately differentiated tumors should be treated similarly to typical carcinoids tumors, as described above.

Adrenal Gland Tumors

Adrenocortical carcinomas (ACCs) are rare (incidence 1 to 2 per million).⁷⁵⁻⁷⁷ There is a bimodal age distribution with peak incidences in early childhood and in the fourth to fifth decades of life. The female to male ratio is approximately 1.5 to 1.^{78,79} The majority of cases are sporadic, however ACCs have been observed in association with



several hereditary syndromes including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and multiple endocrine neoplasia type 1 (MEN 1).^{2, 80-83} The underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated; however it appears that inactivating somatic mutations of the *p53* tumor suppressor gene (chromosome 17p13^{84, 85}), as well as alterations at the 11p15 locus (site of the *IGF-2* gene^{86, 87}) occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.^{76, 88-90} Signs and symptoms associated with hypersecretion of cortisol, called Cushing's syndrome, include weight gain, weakness (primarily in proximal muscles), hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae, buffalo hump, supraclavicular fat pad enlargement, hyperglycemia, and hypokalemia. Aldosterone-secreting tumors may present with hypertension, weakness, and hypokalemia. Androgen-secreting tumors in women may induce hirsutism, deepening of the voice, and oligo/amenorrhea.⁸⁸ 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.^{88, 91}

Evaluation of Adrenal Gland Tumors

Evaluation of patients with adrenal gland tumors should include evaluation for evidence of functional characteristics, as well as evaluation of tumor morphology.

Functional evaluation

When hyperaldosteronism is suspected, plasma aldosterone and renin activity should be assessed, as should electrolyte levels. When patients present with symptoms of Cushing's syndrome, the following tests can be considered: serum ACTH and cortisol; 24-hour urinary free cortisol;

dexamethasone suppression test (1 mg of dexamethasone at bedtime followed by a fasting serum cortisol at 8 AM)⁸⁸; evaluation of sex steroids serum dehydroepiandrosterone sulfate (DHEA-S) and 17-keto and 17,21-dihydroxy steroids.⁸⁸ A pheochromocytoma should always be excluded with fractional plasma free metanephrine and a 24-hour urine fractionated metanephrine for confirmation. Levels of plasma free metanephrines greater than 2-fold increased above normal are suggestive of pheochromocytoma. Concurrent medications should be reviewed before metanephrine testing for those that interfere with plasma metanephrines evaluation, which include acetaminophen and certain beta- and alpha-adrenoreceptor blocking drugs.

Morphologic evaluation

On CT scans with intravenous contrast, ACCs often appear heterogenous and poorly circumscribed. There may be adjacent lymph nodes or liver metastases. 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.⁹² 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 more than 60%, the tumor is likely benign.⁹³ Chemical-shift MRI is highly sensitive and specific for differentiation of benign from malignant adrenal tumors, because most benign tumors contain fat, whereas most malignant tumors do not. MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.^{94, 95} Whether CT or MRI scans are performed, they should follow an adrenal protocol to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics.

**Primary Treatment of Adrenal Gland Tumors**

In patients with a history of current or prior malignancy with risk of adrenal metastasis, an image-guided needle biopsy is recommended after a functioning adrenal neoplasm (in particular pheochromocytoma) is ruled out. If the tumor is determined to be a metastasis from another site, treatment should be according to the appropriate NCCN disease-specific treatment guideline.

Hyperaldosteronism

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 30.⁹⁶ Hyperaldosteronism is rarely malignant, but malignancy should be suspected if the tumor has an irregular morphology, is lipid poor, does not wash-out on contrast-enhanced CT, is greater than 3 cm in size, or is secreting more than one hormone. When malignant hyperaldosteronism is suspected an open adrenalectomy is recommended, as these malignant tumors are prone to rupture.^{97, 98}

Benign hyperaldosteronism is much more common and can be caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia. Adrenal vein sampling for aldosterone is considered the standard for distinguishing these two causes of benign hyperaldosteronism. CT imaging is not always reliable. Cortisol measurement in the catheterization samples is only used to confirm proper catheter placement in this situation. Laparoscopic adrenalectomy is recommended for adenoma, while bilateral adrenal hyperplasia can be managed medically with spironolactone or eplerenone for hypertension and hypokalemia.

Cushing's syndrome

Elevated levels of cortisol are indicative of Cushing's syndrome. Patients who experience symptoms secondary to adrenocortical steroid secretion may require treatment for palliation of symptoms such as hypertension, hyperglycemia, hypokalemia, and muscle atrophy. Cushing's syndrome can be caused by a benign adrenal tumor (adrenal adenoma) or a malignant adrenal tumor, neither of which produce ACTH. Malignancy should be suspected if the tumor is greater than 5 cm or is inhomogeneous with irregular margins and/or local invasion. CT or MRI of the head, neck, chest, abdomen, and pelvis is required to evaluate for other disease and local invasion. For localized disease, the tumor and adjacent lymph nodes should be resected by open adrenalectomy in the case of malignancy. Laparoscopic resection is not recommended for malignant disease because of the tendency of these tumors to rupture.^{97, 98} For disseminated disease, please see Treatment of Metastatic or Unresectable Adrenal Carcinoma, below.

Benign adrenal adenomas are removed by laparoscopic adrenalectomy, when feasible. Post-operative corticosteroid supplementation is required until recovery of the hypothalamus-pituitary-adrenal (HPA) axis. ACTH-independent Cushing's syndrome can also rarely be caused by bilateral multinodal hyperplasia, which can be managed medically with adrenostatic agents including ketoconazole, metyrapone, aminoglutethimide, and mitotane for hypercortisolism. Ketoconazole is most commonly used (at doses of 400-1200 mg per day) due to its easy availability and relatively tolerable toxicity profile. Bilateral adrenalectomy is recommended when medical management of severe Cushing's syndrome fails.

Elevated levels of ACTH indicate that excessive cortisol secretion is not coming from the adrenal gland. Pituitary tumors, which are usually benign, and ectopic tumors in the lung, thyroid, pancreas, or bowel are



probable sources. If an ectopic tumor is found, it should be removed if possible. Otherwise, a bilateral laparoscopic adrenalectomy is recommended.

Non-functioning tumors

Adrenal tumors that do not secrete hormones are often discovered incidentally during scans for unrelated reasons and are thus sometimes called incidentalomas. Most non-functioning tumors are benign and can be left untreated. If no change in size is noted on repeat imaging, no further follow-up is required. Adrenalectomy can be considered with growth of the mass. Masses demonstrating radiographic features of myelolipoma are considered benign. In addition, tumors less than 4 cm that are homogenous with smooth margins and that appear lipid-rich by CT or MRI criteria are also usually benign. Larger tumors (4-6 cm) with similar features can also be left untreated, but repeat imaging is recommended sooner (3 to 6 months versus 6 to 12 months). If such larger tumors continue to grow, malignancy should be suspected and adrenalectomy is recommended. This procedure can be performed laparoscopically, with a planned conversion to an open procedure if evidence of local invasion is observed during surgery.

Malignancy should be strongly suspected for non-functioning tumors larger than 4 cm that are lipid-poor by CT or MRI with rapid washout >60% at 15 minutes or with irregular margins or that are internally heterogenous. CT or MRI imaging of the head, neck, chest, abdomen, and pelvis is recommended to evaluate for other disease and local invasion when the primary tumor is >6 cm. Open adrenalectomy is recommended for larger tumors. Smaller tumors (4-6 cm) that are suspected to be malignant can be approached laparoscopically with planned conversion to an open procedure with evidence of local invasion.

Adjuvant Therapy of Nonmetastatic Adrenal Carcinoma

Surgical resection of the tumor with removal of the adjacent lymph nodes is recommended in patients with localized adrenal carcinoma and may require removal of adjacent structures such as the liver, kidney, pancreas, spleen, and/or diaphragm for complete resection. Open adrenalectomy is preferred due to increased risk for local recurrence and peritoneal spread when done laparoscopically. No adjuvant therapy is recommended for low-grade tumors. For patients with high grade adrenal carcinoma suspected of having gross residual disease due to invasion and incomplete resection, the NCCN panel recommends consideration of adjuvant mitotane therapy and/or radiation therapy to the adrenal tumor bed. Both high- and low-grade tumors should be followed-up by imaging and biomarkers (for functioning tumors) every 3 to 6 months.

Due to the rarity of ACCs, there are no published randomized, prospective trials of adjuvant therapy. The majority of retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticolytic agent.⁹⁹⁻¹⁰¹ The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany.¹⁰² In the Italian cohort, nearly half of the patients received adjuvant mitotane (47/102 patients) at doses ranging from 1 to 5 grams daily, whereas none of the 75 German patients received adjuvant mitotane. The median duration of treatment was 29 months. In follow-up, disease-free survival and overall survival were significantly longer in those treated with mitotane versus the controls, suggesting that adjuvant mitotane may be an effective post-operative strategy. The optimal doses and duration of treatment have not yet been standardized, but blood levels of mitotane should be monitored and kept at about 14 mg/ml. Higher doses may be difficult for patients to tolerate, while lower doses may be less effective.¹⁰³ Due to the



adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed in order to prevent adrenal insufficiency.

Treatment of Metastatic or Unresectable Adrenal Carcinoma

Treatment strategies for metastatic adrenal carcinomas include resection with or without adjuvant chemotherapy (see below) for low grade tumors. According to the NCCN panel, for metastatic adrenal carcinomas that are low grade and especially for functional tumors, resection may be considered if greater than 90% of the tumor and metastases can be removed. Otherwise the option is systemic therapy preferably in a clinical trial.

Treatment strategies for metastatic high-grade adrenal carcinomas include palliative chemotherapy or radiation; external beam radiation therapy may be of benefit to the metastatic sites or to adrenal tumor bed.

Chemotherapy for Advanced Adrenal Carcinoma

Choices for systemic therapy for locally advanced or metastatic disease are (1) mitotane monotherapy; (2) cisplatin or carboplatin with etoposide, with or without doxorubicin, and with or without mitotane; and (3) streptozocin with or without mitotane. Mitotane monotherapy has been studied in the setting of locally advanced or metastatic disease.¹⁰⁴⁻¹⁰⁶ Partial response rates are thought to be around 10-30% at most.¹⁰³

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 gm daily) with cisplatin, etoposide, and doxorubicin in 72 patients with unresectable adrenal carcinoma, yielding an overall response rate of 49% (by WHO criteria)

and a complete hormonal response in 16 of 42 patients with functioning tumors.¹⁰⁷ Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%.¹⁰⁸ 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 following surgery; 1 (8%) had stable disease for 3 months, and the other 8 (67%) showed no response. Analysis of results from an international randomized trial comparing treatment of metastatic adrenocortical carcinoma with etoposide, doxorubicin, cisplatin, and mitotane to treatment with streptozocin and mitotane (FIRM-ACT) is underway.¹⁰⁹ The toxicity of concurrent chemotherapy plus mitotane should be considered in treatment decision making.

Because of the poor results of systemic chemotherapy in adrenal carcinomas, there has been some interest in looking at novel therapies such as targeted therapies using IGF-1 inhibitors. A randomized, double-blind, placebo-controlled, phase III trial comparing an inhibitor of IGF-1R administered as a single agent in patients with locally advanced or metastatic adrenocortical carcinoma is currently underway.¹¹⁰

Pheochromocytoma/Paragangliomas

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla, and they occur in 0.1% to 1% of hypertensive patients. Pheochromocytomas release catecholamines, resulting in hypertension, arrhythmia, and/or hyperglycemia. Although 90% of patients with pheochromocytomas have sporadic disease, pheochromocytomas occur in about 50% of patients with MEN 2A, MEN 2B, and other familial diseases (such as neurofibromatosis, von Hippel-Lindau syndrome, Osler-Weber-Rendu syndrome). The peak incidence of occurrence for pheochromocytomas is between the third



and fifth decade of life, but they generally occur at a younger age and are more likely to be bilateral in patients with familial disease. About 10% of pheochromocytomas are malignant; 90% arise in the adrenal medulla. The remaining 10% are ectopic/extra-adrenal pheochromocytomas that arise from para-aortic sympathetic ganglia and are called paragangliomas. Paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% versus 10%). About 40% of paragangliomas are functional, secreting norepinephrine and normetanephrine.

Evaluation of Pheochromocytoma/Paragangliomas

If pheochromocytoma is suspected, plasma free metanephrine with a normetanephrine test or 24-hour urine level for metanephrine establishes the diagnosis in most patients. Imaging studies, including chest/abdominal CT scan or MRI, are recommended. An MIBG (metaiodobenzylguanidine) scan is highly effective in localizing pheochromocytomas (including extra-adrenal tumors) and is recommended, especially when the tumor is not identified by either MRI or CT scan.¹¹¹ An OctreoScan is optional and is used if multiple tumors are suspected or CT results are negative. A bone scan should be performed if clinically indicated. Genetic counseling is recommended and may include genetic testing when appropriate.

Primary Treatment of Pheochromocytoma/Paraganglioma

Surgical resection is the mainstay of treatment for both benign and malignant pheochromocytomas and paragangliomas. Surgery or stress can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Before surgery, the patient should receive a pre-operative treatment with alpha-adrenergic blockade (such as phenoxybenzamine,¹¹² a non-selective alpha blocker), forced hydration, and sodium loading for at least 7 days. Additional adrenergic blockage of alpha₁ receptors with

prazosin, terazosin, or doxazosin can also be performed,¹¹³ when long term therapy is required for metastatic pheochromocytoma. The tyrosine hydroxylase inhibitor alpha-methyltyrosine can also be administered prior to surgery to help prevent hypertensive crisis. Beta-adrenergic blockade may be used after initiation of alpha-adrenergic blockade and 10 days before surgery to prevent or treat tachyarrhythmias after correction of hypovolemia. Choices include non-cardioselective beta blockers, such as propranolol, nadolol, or labetalol, or cardioselective beta blockers, such as atenolol and metoprolol. The calcium channel blocker nicardipine may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The panel acknowledges that other effective agents can be used for alpha and beta blockage. The panel also points out that rapid-acting intravenous alpha-adrenergic antagonists (eg, phentolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room to control blood pressure.

A laparoscopic approach, when safe and feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas.¹¹⁴ If possible, cytoreductive resection is also recommended for the treatment of isolated distant metastases. Cytoreductive resection is also recommended for locally unresectable disease, if possible, with or without RT. Symptoms can be controlled using alpha blockade with or without alpha-methyltyrosine, and with or without beta blockade for locally unresectable or distant metastases. In addition, other options for distant metastases include: (1) clinical trial; (2) systemic chemotherapy with cyclophosphamide, vincristine, and dacarbazine¹¹⁵; or (3) consideration of iodine-131-MIBG therapy after confirming dosimetrically that tumors take up MIBG.^{116, 117}

**Surveillance**

Surveillance intervals are similar to those for other neuroendocrine tumors. H&P should be performed and blood pressure and tumor markers should be measured 3 to 12 months after resection, then every 6 months for the first 3 years, and annually thereafter. Patients with persistent disease need more frequent examination at intervals of every 3 to 4 months. In addition, imaging studies should be done as clinically indicated. Of course, timing for these surveillance events and procedures can be earlier if symptoms dictate.

Poorly Differentiated Neuroendocrine Tumors or Small Cell Tumors

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

Evaluation of Poorly Differentiated (High Grade or Anaplastic) / Small Cell Tumors

CT scans of the chest and abdomen are recommended to locate potential primary sites. Brain MRI or CT and pelvic CT scans with other imaging studies (as clinically indicated) should also be considered to determine the site and extent of the disease. Plasma ACTH or other biochemical markers are recommended, as indicated.

Primary Treatment of Poorly Differentiated (High Grade or Anaplastic) / Small Cell Tumors

For resectable anaplastic/small cell tumors, surgical resection and chemotherapy with a small cell lung cancer regimen (see NCCN Small Cell Lung Cancer Guidelines) with or without radiotherapy are advised. For unresectable locoregional disease, radiotherapy in combination with chemotherapy (again, with a small cell lung cancer regimen) is recommended. If metastatic tumors are present, chemotherapy alone (with a small cell lung cancer regimen) is recommended. Octreotide therapy is recommended for hormone-secreting tumors (resectable, locoregional unresectable, or metastatic).

Surveillance

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

Multiple Endocrine Neoplasia (MEN)

The MEN syndromes are caused by tumors that affect endocrine organs. There are two main types of MEN: MEN 1 and MEN 2. MEN 1 is an autosomal dominant inherited syndrome mainly affecting the parathyroid glands (causing hyperparathyroidism), pituitary gland, and endocrine pancreas; MEN 1 may also be associated with carcinoid tumors of the lung and thymus, adrenal tumors, multiple lipomas, and cutaneous angiomas. MEN 2 is also an autosomal dominant inherited syndrome and is associated with medullary thyroid cancer (MTC; 98%); pheochromocytoma (50%), often bilateral; and hyperparathyroidism (25%).

Once the diagnosis of either MEN 1 or MEN 2 syndromes is made, genetic counseling is recommended, which may include genetic testing



when appropriate. Familial MTC occurs in patients with MEN 2 syndromes as well as in those with isolated MTC. Both MEN 1 and MEN 2 syndromes as well as familial MTC are inherited as autosomal dominant diseases. MEN 1 is associated with the germline mutation or inactivation of a tumor suppressor gene *MEN1* (chromosomal locus 11q13 encoding the menin protein),¹¹⁸ whereas MEN 2 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.¹¹⁹ Table 2 summarizes the tumors in patients with multiple endocrine neoplasias. Of interest, somatic mutation of the *MEN1* gene is the most common known genetic alteration in sporadic parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids.² Somatic *RET* mutations are also found in sporadic MTC.¹²⁰ All patients with MTC should be tested for germline mutation as about 10% of patients with presumed sporadic MTC have a germline mutation of the *RET* oncogene.

MEN 1

MEN 1 (or Wermer syndrome), as previously mentioned, involves mainly the parathyroid glands, pituitary gland, and pancreas, but it may also be associated with carcinoid tumors (eg, thymus, bronchial), adrenal tumors, and multiple lipomas and skin angiomas. Over 98% of patients with this syndrome either have or will develop primary hyperparathyroidism, and about 50% develop symptoms from functioning benign or malignant neoplasms of the pancreas.² About 35% of patients have functioning tumors of the pituitary, and an additional 20% of patients also have or develop nonfunctioning islet cell tumors.¹²¹ Examples of functional syndromes include hypercalcemia related to multiple abnormal parathyroid glands; galactorrhea or amenorrhea associated with a prolactinoma; Zollinger-Ellison syndrome associated with gastrinoma and hypersecretion of gastrin; and

Cushing's syndrome or acromegaly related to a pituitary tumor or solitary or bilateral adrenal tumors. Ectopic Cushing's syndrome may be caused by a pancreatic islet cell tumor, a thymic carcinoid, a bronchial carcinoid, or MTC. Cushing's syndrome may also rarely be due to a solitary small cell tumor of the lung. In addition, although rare, patients may develop symptoms as a result of excesses of several hormones from one or more glands, 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 MEN 1 and hypoglycemia related to insulinoma have multiple islet cell neoplasms. Patients with MEN 1 and Zollinger-Ellison syndrome also frequently have more than one islet cell tumor. Of these tumors, 70% are gastrin-secreting carcinoids in the duodenum and/or periduodenal lymph nodes. Nonfunctioning pancreatic islet cell tumors are usually larger when clinically detected and are more likely to be malignant. Overall, about 10% of insulinomas and up to 90% of gastrinomas are malignant.^{51, 122} Malignant islet cell tumors of the pancreas and carcinoid tumors of the thymus are the most common causes of death associated with MEN 1. The clinical characteristics of pancreatic endocrine tumors are summarized in Table 1.

Evaluation of MEN1 Syndromes

The guidelines list a series of possible tests to further define sites of involvement for patients known to have or suspected of having MEN 1. The recommended tests include: (1) laboratory tests evaluating hormone, glucose, and/or calcium levels, (2) imaging tests needed to localize the site of the tumor or hyperplasia, and (3) genetic counseling for patients suspected of having MEN 1 syndrome, which may include genetic testing to identify one of the characteristic predisposing



germline mutations. OctreoScan is also frequently recommended depending on the tumor type suspected. A thorough family history should be obtained from the patient, and family members should be considered for further testing for hypercalcemia, elevated chromogranin A levels, and *MEN1* gene status. Specific additional recommendations based on tumor type are detailed below.

Pancreatic tumors in MEN 1

Approximately 75% of patients with MEN 1 and islet cell tumors have functioning tumors. The various characteristics of endocrine tumors of the pancreas (gastrinoma, glucagonoma, insulinoma, VIPoma, somatostatinoma, PPoma) are summarized in Table 1. The workup for pancreatic islet cell tumors in the context of MEN 1 is similar to that for sporadic islet cell tumors. For details on the evaluation for pancreatic tumors, see the section on Islet Cell Tumors (Pancreatic Endocrine Tumors), above.

Parathyroid tumors in MEN 1

Primary hyperparathyroidism with parathyroid tumors is the most common component of MEN 1. Parathyroid hormone (PTH) testing and measuring serum calcium levels are recommended if hyperparathyroidism is suspected. The presence of elevated or high-normal levels of serum calcium and elevated levels of PTH confirm a diagnosis of hyperparathyroidism in a patient without hypocalciuria.

Additional tests that may be considered include 24-hour urinary calcium and creatinine tests to rule out benign familial hypocalciuric hypercalcemia. Imaging of the parathyroid glands using sestamibi scan or ultrasound is optional but may aid in identifying ectopically situated parathyroids. The technetium 99m sestamibi (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, but these scans are only about 35% accurate in patients with familial hyperparathyroidism. Neither scan can distinguish between adenomatous and hyperplastic parathyroid glands. Because most patients with familial hyperparathyroidism have multiple abnormal parathyroid glands, preoperative localization studies are less accurate and abnormal parathyroid glands are best identified during surgery.^{123, 124}

Pituitary tumors in MEN 1

Various laboratory tests are available for evaluating suspected pituitary tumors. These tests include an overnight dexamethasone suppression test, a 24-hour urinary free cortisol test for patients with Cushing's syndrome, and bilateral petrosal vein sampling for basal and corticotropin releasing hormone (CRH)-stimulated adrenocorticotrophic hormone (ACTH) in patients with suspected pituitary Cushing's syndrome. The latter procedure can distinguish between a possible ACTH-secreting pituitary tumor and an ectopic source of ACTH if no tumor is identified. Patients with ectopic Cushing's syndrome have markedly elevated ACTH levels and usually a more dramatic onset and progressive clinical course. Those with Cushing's disease (pituitary adenoma) have moderately increased ACTH levels. In contrast, those with Cushing's syndrome due to benign or malignant adrenal tumors have suppressed levels of ACTH. For patients with a possible prolactinoma, determination of the serum prolactin level may aid in the diagnosis. Growth hormone levels, such as insulin-like growth factor-1 (IGF-1), and an oral glucose suppression test are necessary to diagnose acromegaly. When pituitary tumors are suspected because of hyperthyroidism, then alpha subunit, thyroid-stimulating hormone (TSH), T3, and T4 levels need to be analyzed. Moreover, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol also aid in the recognition of nonfunctioning tumors together with IGF 1. In



addition, an MRI of the sella with contrast is recommended to evaluate whether a pituitary adenoma is present, and, as mentioned previously, genetic counseling of the patient and family that may include genetic testing is recommended if MEN 1 is suspected.

Primary Treatment of MEN 1 Syndromes

Primary therapy of locoregional disease in MEN1 patients focuses on treatment of the specific hormonal syndrome and/or treatment of the underlying hyperplasia or tumor. In most instances, surgical excision by an experienced neurosurgeon is the initial treatment of choice for functioning tumors, whereas asymptomatic tumors (such as pituitary tumors) may be treated medically or with observation if no local mass effects are present. All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus influenza b, and meningococcus group C), preoperatively. Furthermore, in patients undergoing abdominal surgery in whom octreotide treatment is planned, prophylactic cholecystectomy can be considered, because cholelithiasis is a common side effect of octreotide.¹⁷ Metastatic disease is treated according to the appropriate tumor type the same way in MEN1 patients as in patients with neuroendocrine tumors arising sporadically.

Primary treatment of pancreatic tumors in MEN1

Initial treatment of pancreatic islet cell tumors associated with MEN 1, similar to sporadic islet cell tumors, focuses on surgical excision, preceded by medical management (if necessary). However, in contrast to patients with sporadic disease where tumor is usually solitary, islet cell tumors associated with MEN 1 are frequently multiple; thus, surgery may be more extensive. For example, removal of a single functioning adenoma, although a reasonable approach for sporadic tumors, usually misses additional (possibly malignant) tumors in the setting of MEN1. Furthermore, the largest tumor may also not be the functioning tumor.

Therefore, surgical treatment of insulinoma, in the setting of MEN 1, typically consists of a subtotal pancreatectomy with enucleation of tumors in the head of the pancreas, as identified with intraoperative ultrasound.¹²⁵ Glucose levels can be managed preoperatively with diet and diazoxide. Octreotide should be used with caution in insulinoma because it can also suppress counter-regulatory hormones such as growth hormone, glucagon, and catecholamines. In this situation, octreotide can precipitously worsen hypoglycemia.⁶¹

For gastrinomas, any symptoms of gastrin hypersecretion may be treated with histamine H₂-receptor antagonists or with proton pump inhibitors before surgical intervention. In patients with MEN 1, 70% of gastrinomas are associated with extrapancreatic tumors in the duodenum; thus, treatment generally includes tumor enucleation and duodenotomy with excision of small tumors with periduodenal lymph node dissection. If the tumor is occult and primary tumor is not found, the panel recommends 2 options: (1) observation (category 2B); (2) duodenotomy and tumor enucleation with periduodenal node dissection with or without spleen-preserving distal pancreatectomy (category 2B). For gastrinomas that are exophytic or are peripheral tumors as determined by imaging and not immediately adjacent to the pancreatic duct, enucleation should be done with duodenotomy. Removal of the periduodenal nodes may be considered along with enucleation of coexisting pancreatic tumors.

Gastrinomas that are deeper or invasive or with proximity to the main pancreatic duct should be managed by pancreaticoduodenectomy with periduodenal node dissection. Gastrinomas in the distal pancreas are treated with either distal pancreatectomy with spleen preservation or tumor enucleation and duodenotomy with regional lymphadenectomy.



Glucagonomas are typically situated in the tail of the pancreas and are usually malignant. Recommended options for resectable disease include (1) tumor excision with peripancreatic node dissection; or (2) distal pancreatectomy and peripancreatic lymph node dissection. Splenectomy is almost always performed, because the tumors are usually malignant, relatively large, and situated in the tail of the pancreas. For unresectable disease in which octreotide therapy is being considered, prophylactic cholecystectomy is recommended, due to the frequency of cholelithiasis in patients receiving somatostatin analogs.¹⁷ Preoperative medical management of glucagonomas includes stabilization of glucose levels with diet or octreotide, zinc for rash, and consideration of a perioperative anticoagulant.

For patients with VIPoma, the panel recommends either the excision of the tumor with resection of peripancreatic lymph nodes or pancreaticoduodenectomy with dissection of peripancreatic lymph nodes, depending on the position of the tumor. Patients should be stabilized preoperatively with IV fluids and octreotide, and electrolyte imbalances should be corrected. For PPoma, somatostatinoma, and other nonfunctional tumors of the pancreas, the panel recommends resection with lymph node dissection.

Primary treatment of parathyroid tumors in MEN 1

Treatment options for parathyroid hyperplasia in patients with MEN 1 include subtotal parathyroidectomy with removal of the bilateral upper thymus (which is a common site of ectopic parathyroid glands and thymic carcinoid tumors) with or without cryopreservation of parathyroid tissue. Total parathyroidectomy with autotransplantation of parathyroid tissue with or without bilateral removal of the upper thymus, and with or without cryopreservation of parathyroids (category 2B), is another recommended option.^{126, 127} 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. In contrast to sporadic hyperparathyroidism, patients with familial hyperparathyroidism (including MEN 1), isolated familial hyperparathyroidism, or hyperparathyroidism associated with jaw tumor syndrome are more likely to develop recurrent disease. The latter patients are also more likely to have or develop parathyroid carcinoma. Follow-up includes determining blood calcium levels every 6 months for 3 years and yearly thereafter.

Primary treatment of pituitary tumors in MEN 1

The recommended treatment for pituitary tumors associated with MEN 1 depends on which hormone is present in excess and on whether the tumor causes localized symptoms. For example, the primary treatment recommended for pituitary prolactinoma is a dopamine agonist (eg, bromocriptine, pergolide).¹²⁸ For a patient with a symptomatic pituitary prolactinoma (as evidenced by visual changes or increasing pituitary size), with no response or intolerance to dopamine agonist, or with disease of sudden onset (indicating intratumoral hemorrhage), surgery may be necessary. If mass effects are present or pregnancy is desired, transsphenoidal resection is recommended. If complete resection is not achieved, recommendations include re-excision and postoperative radiotherapy. Target-organ hormone replacement therapy is recommended if required following surgery or following a good response to dopamine agonist.

For pituitary Cushing's syndrome indicated by an increased ACTH level, the primary treatment recommended by the panel is transsphenoidal surgery. Repeat surgery or radiotherapy with pituitary/adrenal inhibitors (eg, ketoconazole, mitotane) is recommended for incomplete resection or for persistent disease;



bilateral laparoscopic adrenalectomy may also be considered. Many of these treatments can be considered sequentially.

For pituitary acromegaly indicated by increased levels of growth hormone or goiter with or without hyperthyroidism due to a TSH-producing adenoma, transsphenoidal surgery without octreotide treatment is recommended for tumors 1 cm or smaller without associated visual changes. However, for tumors larger than 1 cm or those associated with visual changes or symptoms, preoperative treatment with octreotide for 2 weeks or less (category 2B) or octreotide therapy in lieu of surgery (category 2B) may be considered. Patients with nonfunctioning adenomas without visual changes may be observed. However, transsphenoidal surgical resection is indicated for patients with enlarging tumors or visual changes, which suggest progression. For all incompletely resected tumors, RT or continued observation is recommended.

Surveillance

All patients with MEN 1 should be followed with an H&P, tumor markers, and calcium levels as appropriate and with imaging studies such as CT/MRI 3 to 6 months following resection. The follow-up tests should be repeated every 6 months for the first 3 years after surgery and annually thereafter. All close family members of patients with MEN 1 should be genetically counseled, and genetic testing should be considered.

MEN 2

MEN 2 can be further subdivided into MEN 2A (Sipple's syndrome) and MEN 2B based on the spectrum of accompanying endocrine tumors and disorders, as noted in Table 2. MTC is seen in nearly 100% of patients with MEN 2A and MEN 2B and is often the first manifestation of the syndrome. Patients with MEN 2A, in addition to MTC, may have

or develop pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%). Most patients with MEN 2B have mucosal neuromas, intestinal ganglioneuromas, or ectopic lenses as well as a Marfanoid habitus in addition to MTC; 50% of these patients have pheochromocytoma, but almost none have hyperparathyroidism (less than 1%).

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 MEN 2 normally arises in the first to third decades of life, but sporadic MTC is typically diagnosed in the fourth to fifth decades of life. All types of familial MTC are typically multifocal and preceded by C-cell hyperplasia; however, sporadic MTC is usually unifocal. Familial MTC arising in the absence of other endocrine malignancies or disorders is least aggressive; whereas MTC associated with MEN 2B is the most aggressive. MEN 2A, MEN 2B, and familial MTC are all autosomal dominant inherited diseases and are associated with germline mutations of the proto-oncogene, *RET*.^{3, 129}

The initial symptoms associated with MEN 2A and MEN 2B 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. In addition, nearly all MEN 2B patients have Marfanoid habitus, mucosal neuromas, poor dentition, and/or intestinal ganglioneuromas. Some patients also have ectopic lenses in the eye or very flexible joints. MEN 2A is also associated with lichen planus amyloidosis and with Hirschsprung's disease.



For a full discussion of the management of MTC, consult the NCCN Thyroid Cancer Guidelines. The following discussion focuses on the presentation of MEN 2 and on the issues unique to MTC in this setting.

Evaluation of MEN 2A, MEN 2B, and Familial MTC

All patients with MTC should be screened by genetic testing for a mutation in the *RET* proto-oncogene. If the test is positive, the patient and family members should be referred to a genetic counselor for further 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 have more aggressive tumors or coexisting colon cancer. Localization tests selectively include ultrasound, CT, or MRI.

MEN 2 patients presenting with MTC should be evaluated for a coexisting pheochromocytoma (see next paragraph) before administration of anesthetic or before any invasive procedure. Because patients with pheochromocytoma have persistent vasoconstriction, these patients must be treated preoperatively – with alpha-adrenergic blockade (phenoxybenzamine) or with alpha methyltyrosine – to avoid a hypertensive crisis during surgery on the thyroid or adrenal glands. The intravascular volume is expanded preoperatively with increased oral salt and fluid intake. Forced hydration along with alpha blockade is necessary to prevent hypotension immediately after the tumor is removed. After institution of alpha blockade and hydration, beta-adrenergic blockade may be necessary to treat tachyarrhythmia.

Pheochromocytoma is diagnosed by the presence of elevated levels of blood plasma metanephrine/normetanephrine and/or elevated 24-hour urinary catecholamines and metabolites such as metanephrine. These

blood and urine tests are the most sensitive and specific tests for diagnosis of pheochromocytoma.^{130, 131} Urinary dopamine level tests are considered optional. Localization tests include CT or MRI with 0.5-cm sections through the adrenal area and with optional use of MIBG scan or OctreoScan. These radionucleotide scans may be useful if the CT/MRI scans are negative.

As mentioned previously, a total of about 25% of patients with MEN 2A either have or will develop hyperparathyroidism. A parathyroid workup is therefore recommended for MEN 2 patients; it consists of blood calcium levels, 25-hydroxy vitamin D levels, PTH determinations, and a 24-hour urine collection to assess both calcium and creatinine levels. A neck ultrasound or a sestamibi scan should be performed as appropriate in patients with primary hyperparathyroidism.

A physical exam is also recommended for MEN 2 patients to evaluate for the presence of thyroid nodules with or without cervical adenopathy, mucosal neuromas, ectopic lenses, megacolon, and lichen planus amyloidosis.

In patients with a positive *RET* oncogene test that are scheduled for a prophylactic thyroidectomy (see below), a preoperative neck ultrasound scan of the thyroid gland and cervical lymph nodes is essential to document intrathyroidal tumors and to possibly identify enlarged cervical lymph node metastases. If masses are not observed in the thyroid gland and if basal and stimulated calcitonin tests are negative in patients with *RET* mutation, prophylactic central node dissection is probably unnecessary.^{132, 133}

Primary Treatment of MEN2A, 2B and Familial MTC

The treatment of both MTC and pheochromocytoma associated with MEN 2 is similar to the management of their sporadic counterparts (see



Pheochromocytoma/Paraganglioma, above, and see the NCCN Thyroid Carcinoma Guidelines). The exception is for patients with familial disease who are much more likely to have bilateral thyroid carcinomas and bilateral pheochromocytomas. In patients with a positive *RET* oncogene test who are otherwise asymptomatic, prophylactic thyroidectomy is performed at diagnosis or during the first year of life in patients with MEN 2B and before the age of 6 for patients with MEN 2A and familial MTC.^{132, 133}

Patients with MEN 2 and familial MTC are more prone to postoperative hypoparathyroidism, because the thyroid gland is removed for treatment of C-cell hyperplasia or MTC. The consensus of the NCCN panel was for selective resection of abnormal parathyroid glands and for leaving normal parathyroid glands (marked with a clip or stitch in situ during thyroid surgery) in situ when possible, although some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC. Another situation for autotransplantation of the parathyroid gland is when the blood supply to a parathyroid gland is possibly compromised. For patients with sporadic hyperparathyroidism, MEN 2B, or familial MTC without MEN, the parathyroid gland should be transplanted to the sternocleidomastoid muscle as it will rarely become hyperplastic.

However, when a normal parathyroid gland cannot be preserved in patients with MEN 2A, it should 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.

Surveillance

For MEN 2 patients, a routine H&P including blood pressure and markers should be performed 3 to 6 months after resection, then every 6 months during the first 3 years, and annually thereafter. Imaging studies (ultrasound, CT, MRI) should be performed selectively, as clinically indicated. After surgery for MTC, repeat calcitonin and CEA tests should be performed at 3 to 6 months, and then annually if negative. As indicated elsewhere in these guidelines, surveillance timing is dictated by patient symptoms and laboratory testing. As previously mentioned, family members of all patients with MTC should be tested for a germline *RET* mutation and genetic counseling should be considered.



Table 1
Characteristics of Endocrine Tumors of the Pancreas

Tumor	Major Clinical Symptom	Predominant Hormone	Islet Cell Type	Malignant Potential	Other Clinical Features
Gastrinoma	Recurrent peptic ulcer disease	Gastrin	γ	Very high	Diarrhea/steatorrhea
Insulinoma	Hypoglycemia (fasting or nocturnal)	Insulin	β	Low	Catecholamine excess
Glucagonoma	Diabetes mellitus, Migratory necrolytic erythema	Glucagon	α	Very high	Panhypoaminoaciduria, Thromboembolism, Weight loss
VIPoma	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)	Vasoactive intestinal polypeptide (VIP)	δ	High	Metabolic acidosis, Hyperglycemia, Hypercalcemia, Flushing
Somatostatinoma	Diabetes mellitus Diarrhea/steatorrhea	Somatostatin	δ	Very high	Hypochlorhydria, Weight loss, Gall bladder disease
PPoma	Hepatomegaly, Abdominal pain	Pancreatic polypeptide (PP)	PP cells	Very high	Occasional watery diarrhea

Adapted with modifications from Skarin AT., Atlas of Diagnostic Oncology. Philadelphia, Elsevier Science, 2003. Copyright 2003, with permission from Elsevier.⁵¹



Table 2

Tumors in Patients with Multiple Endocrine Neoplasia

Organ	Neoplasm	Patients Affected (%)
MEN1		
Parathyroid	Hyperplasia	98
Pituitary	Adenoma	35
Pancreas	Islet cell	50
Multiple	Carcinoid	3
Adrenal	Cortical adenoma	Uncommon
	Cortical carcinoma	rare
Thyroid	Adenoma	Uncommon
	Papillary	Uncommon
Adipocyte	Lipoma	Uncommon
MEN2A		
Thyroid	Medullary carcinoma	98
Adrenal	Pheochromocytoma	50
Parathyroid	Hyperplasia	25
MEN2B		
Thyroid	Medullary carcinoma	98
Adrenal	Pheochromocytoma	50
Parathyroid	Hyperplasia	1
Neuroma	Mucosal neuroma	95
	Intestinal ganglioneuroma	



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