National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Neuroendocrine Tumors

V.2.2010

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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

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Print the Neuroendocrine Tumors Guideline

These 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 these 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 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. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010

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Summary of the Guidelines updates

The 2.2010 version of the Neuroendocrine Tumors guidelines represents the addition of the Discussion section correspondent to the changes in the algorithm.

Summary of changes in the 1.2010 version of the Neuroendocrine Tumors Guidelines from the 2.2009 version include:

Staging

- **The 2010 American Joint Committee on Cancer (AJCC) TNM Staging System for Neuroendocrine Tumors were added to the guidelines: gastric, small bowel, colonic, rectal, and ampulla of Vater carcinoid tumors [well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas]) on ST-1 and ST-2; pancreatic on ST-3; and appendiceal carcinoid on ST-4 .**

Carcinoid tumors

- **Surveillance of carcinoid tumors, the bullet regarding markers was separated and modified as, "consider 5-HIAA" and "consider chromogranin A *(category 3)*".**

CARC-2

- **Footnote, "Resect grossly involved lymph nodes in mesentery only if it can be accomplished without compromising extensive amounts of small bowel potentially resulting in short bowel syndrome" was removed.**

CARC-4

- **Thymus, locoregional disease, complete resection, "RT (category 2B) ± chemotherapy (category 3 for addition of chemotherapy)" was removed and directed to surveillance.**

CARC-5

- **Distant metastases,**
  - **Imaging: "Consider octreoscan" was added.**
  - **"Consider 5-HIAA" and "consider chromogranin A (category 3)" were added.**
  - **3rd bullet was modified, "Resect primary tumor if locally symptomatic or if complete resection *of all known disease* can be achieved".**
- **Footnote m, PROMID study reference was added.**
- **"Interferon (category 2B) was removed from unresectable, liver disease management options and added to footnote 's'.**

Islet Cell Tumors

- **Footnote c, "Consider MEN1 family history for all patients with pancreatic neuroendocrine tumors" was added to the islet cell tumors algorithm.**

ISLT-1

- **Gastrinoma, "occult, no primary tumor*or metastases on imaging*" was added for clarification.**
- **Gastrinoma of the pancreatic head, the size criterion (≤ 5 cm and > 5 cm) was removed and the management was separated by "*Exophytic or peripheral tumors by imaging and surgical removal feasible*" and "*For deeper or invasive tumors and those in proximity to the main pancreatic duct*" with corresponding footnote g, "Not adjacent to the main pancreatic duct."**
  - **"Exophytic or peripheral tumors by imaging and surgical removal feasible", the management was modified by adding, "Enucleation and duodenotomy + *consider* periduodenal node dissection."**
  - **"For deeper or invasive tumors and those in proximity to the main pancreatic duct" the recommended management is "Pancreatico-duodenectomy + periduodenal lymph node dissection"**

ISLT-4

- **Management of recurrent, unresectable, locoregional disease, "Consider RT for symptom control and consider clinical trial" were replaced by a link, "See Management of Locoregional Unresectable Disease and/or Distant Metastases (ISLT-5)".**

ISLT-5

- **"Locoregional unresectable disease" was added to the title.**
- **Asymptomatic, "extrahepatic" was removed from unresectable.**
- **Footnote p, "everolimus (category 2B)" and "sunitinib (category 2B)" were added as examples of agents used in metastatic islet cell tumors and "interferon" was removed from the footnote.**

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Summary of the Guidelines updates (continued)

Summary of changes in the 1.2010 version of the Neuroendocrine Tumors Guidelines from the 2.2009 version include:

Adrenal Gland Tumors

AGT-2

- Hyperaldosteronism, contralateral gland abnormal or patient age > 45 y, "consider" was added to "adrenal vein sampling for aldosterone and cortisol."

AGT-4

- Non-functioning tumor, 4-6 cm, "Lipid-poor adenoma by CT or MRI criteria" was modified by adding "*with rapid washout > 60% at 15 min*..."

AGT-5

- Adrenal carcinoma, footnote h, "Cross sectional imaging to stage disease" was added.
- "Resected" was removed from "localized disease" and "unresectable" was removed from "metastatic disease."
- Localized disease, "Resect tumor and adjacent lymph nodes" and "Open adrenalectomy recommended" with corresponding footnote i, "Increased risk for local recurrence when done laparoscopically" was added.

Pheochromocytoma

PHEO-1

- Footnote c, "Phenoxybenzamine: 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" is new to the page.

PHEO-2

- Distant metastases, "131I MIBG treatment" was modified as "131I MIGB *as compassionate use on clinical trial."*

Multiple Endocrine Neoplasia, Type 1

MEN1-1

- Gastrinoma of the pancreatic head, the size criterion (≤ 5 cm and > 5 cm) was removed and the management was separated by "*Exophytic or peripheral tumors by imaging and surgical removal feasible*" and "*For deeper or invasive tumors and those in proximity to the main pancreatic duct*" with corresponding footnote f, "Not adjacent to the main pancreatic duct."
  - "Exophytic or peripheral tumors by imaging and surgical removal feasible", the management was modified by adding, "Enucleation and duodenotomy + *consider* periduodenal node dissection *with enucleation of co-existing pancreatic tumors*."
  - "For deeper or invasive tumors and those in proximity to the main pancreatic duct" the recommended management is "Pancreatico-duodenectomy + periduodenal lymph node dissection"

NE-A

- "Immunohistochemical studies" replaced the title "stains".
- "Ki67 (MIB-1)" was added as an example of a study basic for diagnosis.
- "Neuron-specific enolase" was removed from "tumor specific confirmation".
- Footnote '1' was added to include examples of blood and urine test ordered which may require fasting and certain dietary adjustments. In addition physicians should be aware that some medications can also affect the results.

NE-B

- 2nd bullet was modified by adding "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."
- 4th bullet was modified by adding, "Resection of recurrent tumor *or unresectable tumor that has regressed* should be considered..."
- 7th bullet was modified by adding "Octreotide therapy should be administered immediately prior to resection of primary or metastatic *functional (carcinoid)* neuroendocrine tumors, *if not already receiving such therapy*."

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DIAGNOSIS AND CLINICAL PRESENTATIONS

Carcinoid tumors[a]
Clinical presentations:
- Small bowel, Colon (See CARC-1)
- Appendix (See CARC-1)
- Rectal (See CARC-2)
- Gastric (See CARC-3)
- Thymus, Bronchial (See CARC-4)
- Atypical lung carcinoid
- Recurrent or Metastatic disease (See CARC-5)

Islet cell tumors (Pancreatic endocrine tumor)[a]
Clinical presentations:
- Nonfunctioning pancreatic tumors (See ISLT-1)
- Gastrinoma (See ISLT-1)
- Insulinoma, Glucagonoma (See ISLT-2)
- VIPoma (See ISLT-3)
- Recurrent disease (See ISLT-4)
- Metastatic disease (See ISLT-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 disease
  - Acromegaly
  - TSH producing adenomas
  - Nonfunctioning adenoma
- Adrenal gland tumor (See AGT-1)
- Thymus, Bronchial Carcinoid (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 (MEN 2B)
- Mucosal neuromas (MEN2B)
- Lichen planus amyloidosis (MEN2A)

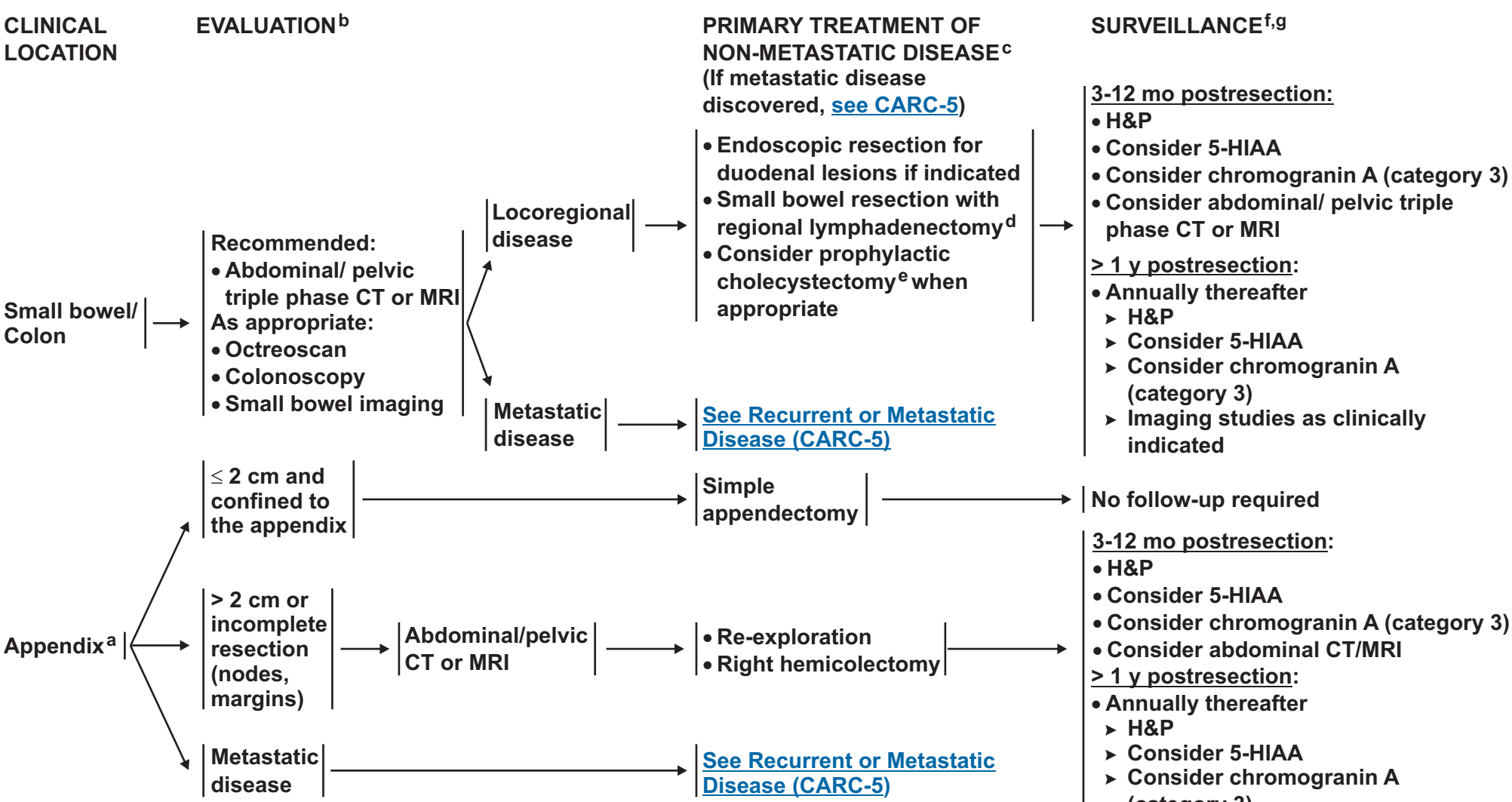
Merkel cell carcinoma (See Merkel Cell Carcinoma Guidelines)

[a]Guidelines pertain to well and moderately differentiated tumors. For poorly differentiated/high grade/anaplastic or small cell carcinomas, see ANAP-1.
[b]Includes adrenal cortical tumors and incidentaloma.

Note: All recommendations are category 2A unless otherwise indicated.
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[a] If histology is goblet cell or adenocarcinoid, manage as colon adenocarcinoma. See NCCN Colon Cancer Guidelines.

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

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

[d] Should include careful examination of the entire bowel as multiple synchronous lesions may be present.

[e] If possible future need for octreotide.

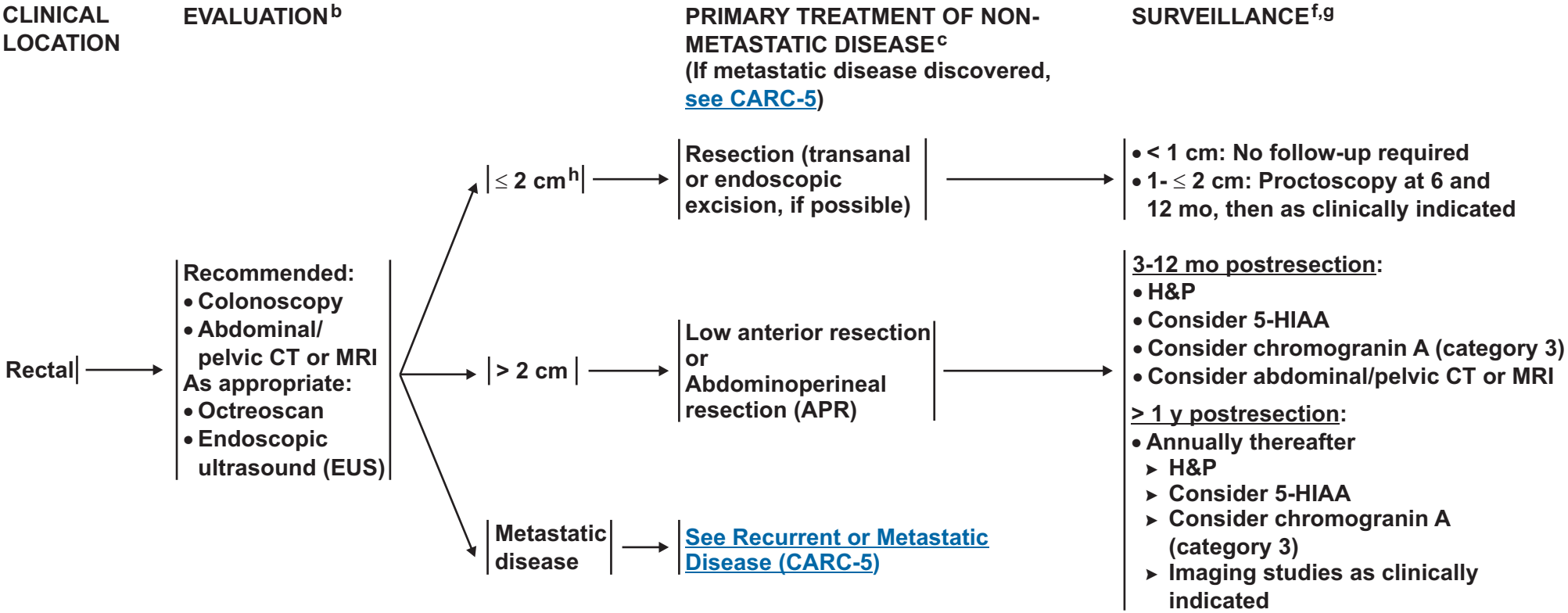
[f] Earlier, if symptoms.

[g] Octreoscan and PET scan not recommended for routine surveillance.

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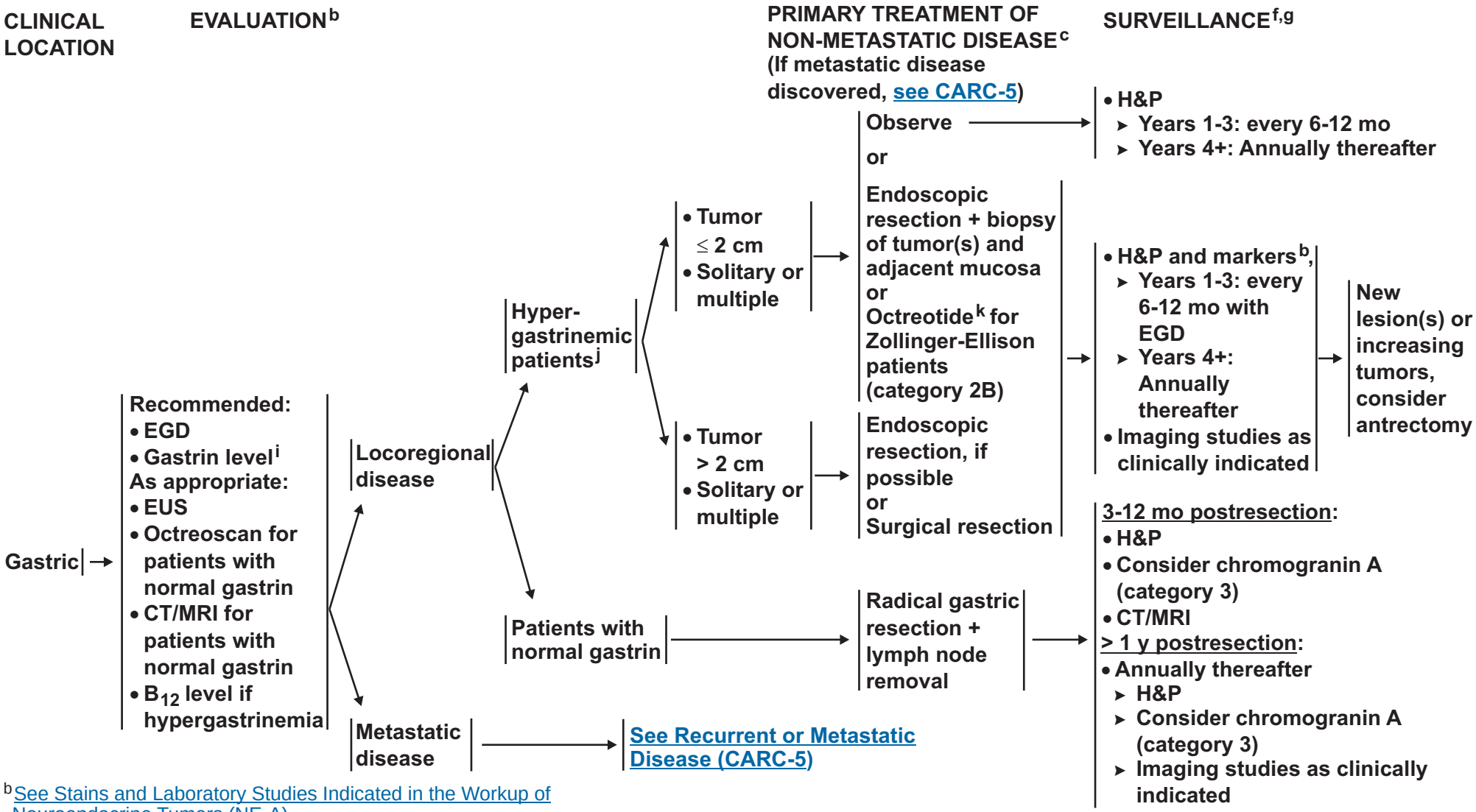


[b] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[f] Earlier, if symptoms.
[g] Octreoscan and PET scan not recommended for routine surveillance.
[h] For 1-2 cm tumors, consider examination under anesthesia (EUA) with radical resection if muscularis propia invasion or node positive.

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

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

[f] Earlier, if symptoms.

[g] Octreoscan and PET scan not recommended for routine surveillance.

[i] Gastrin levels needs to be completed while fasting and off protein pump inhibitors for 1 week.

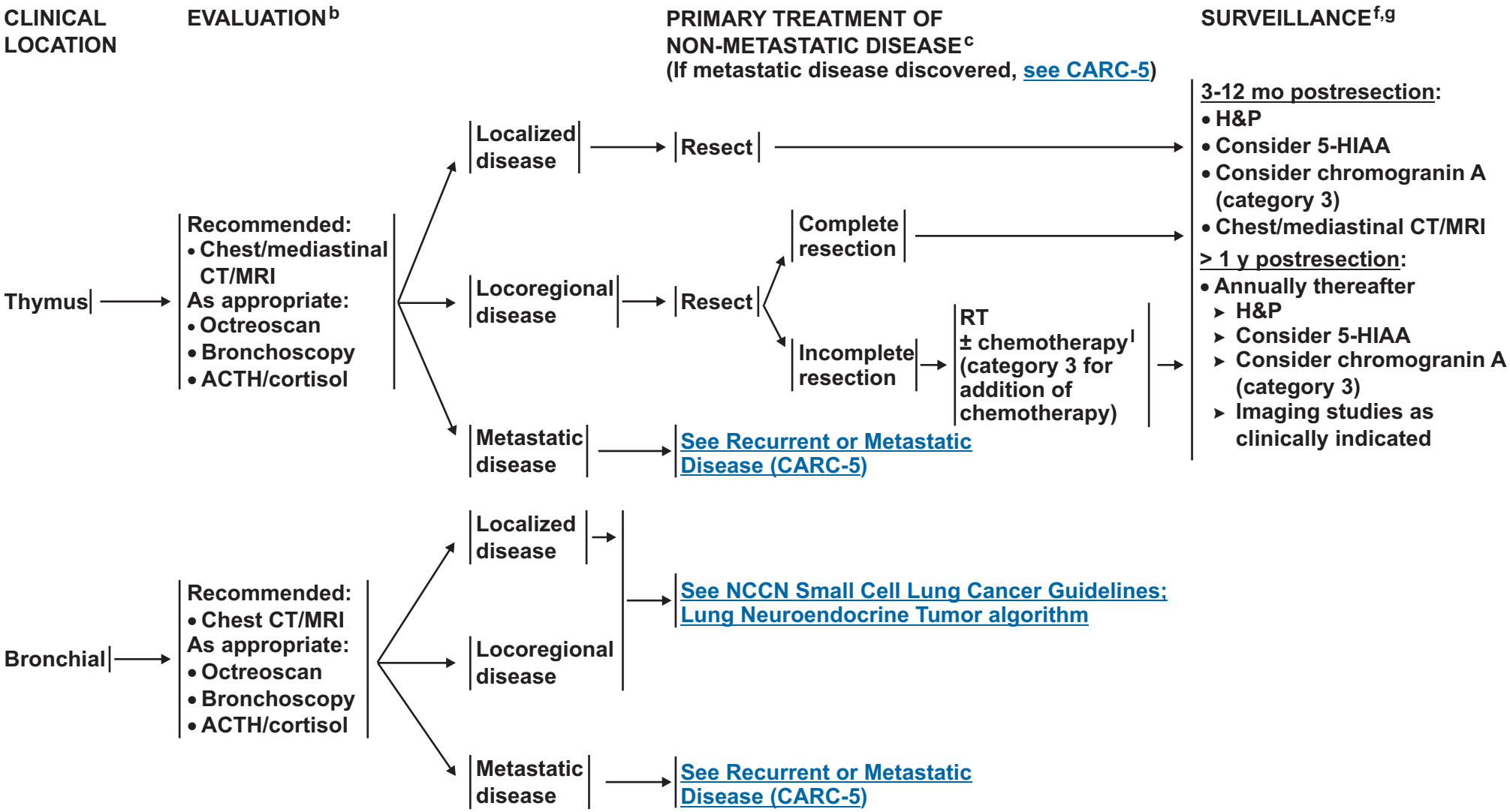
[j] If gastric pH is low, see gastrinoma on ISLT-1 or MEN1-1.

[k] 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.

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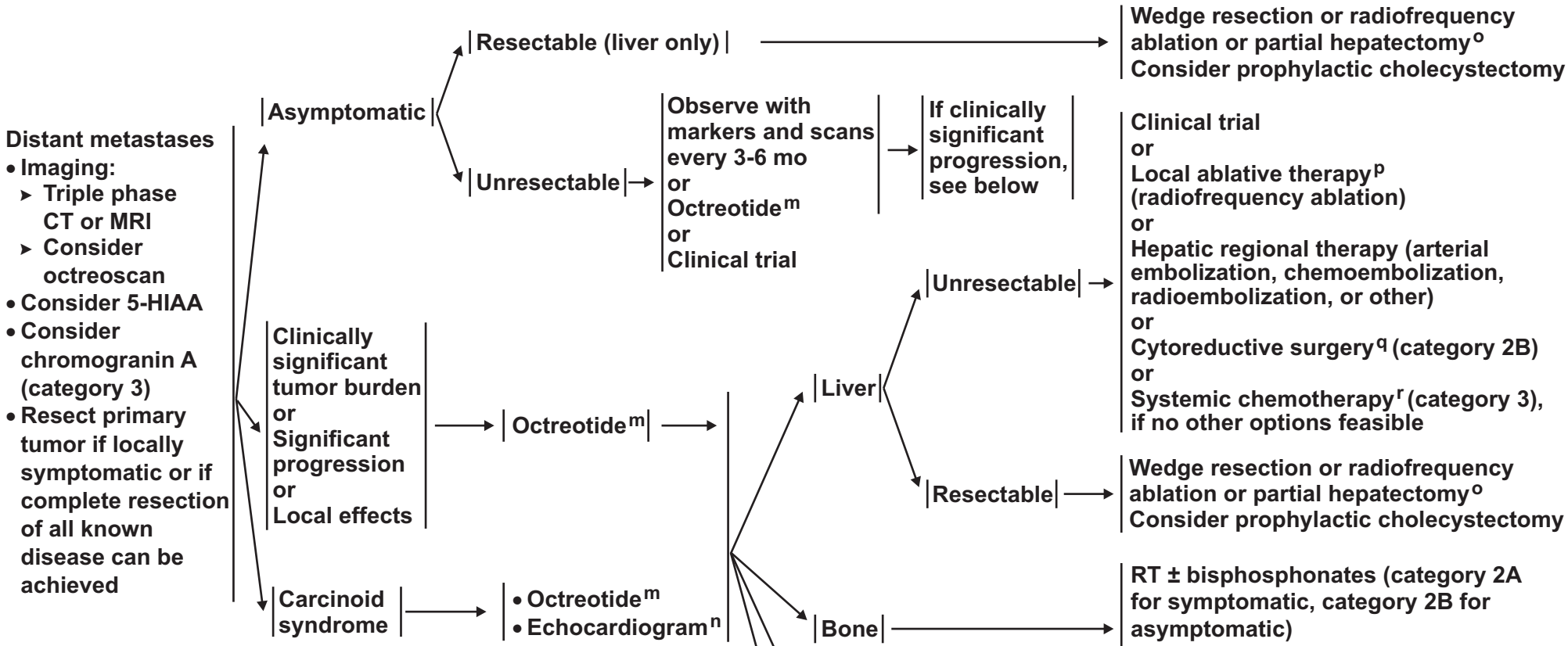
[b] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[f] Earlier, if symptoms.
[g] Octreoscan and PET scan not recommended for routine surveillance.
[l] Consider 5-fluorouracil or capecitabine 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 RECURRENT OR UNRESECTED DISEASE[c]



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

[m] 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. See PROMID study: J Clin Oncol. 2009;27:4656-4663.

[n] If signs and symptoms of heart disease or planning major surgery.

[o] Including removal of intestinal primary.

[p] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

[q] Only if near complete resection can be achieved.

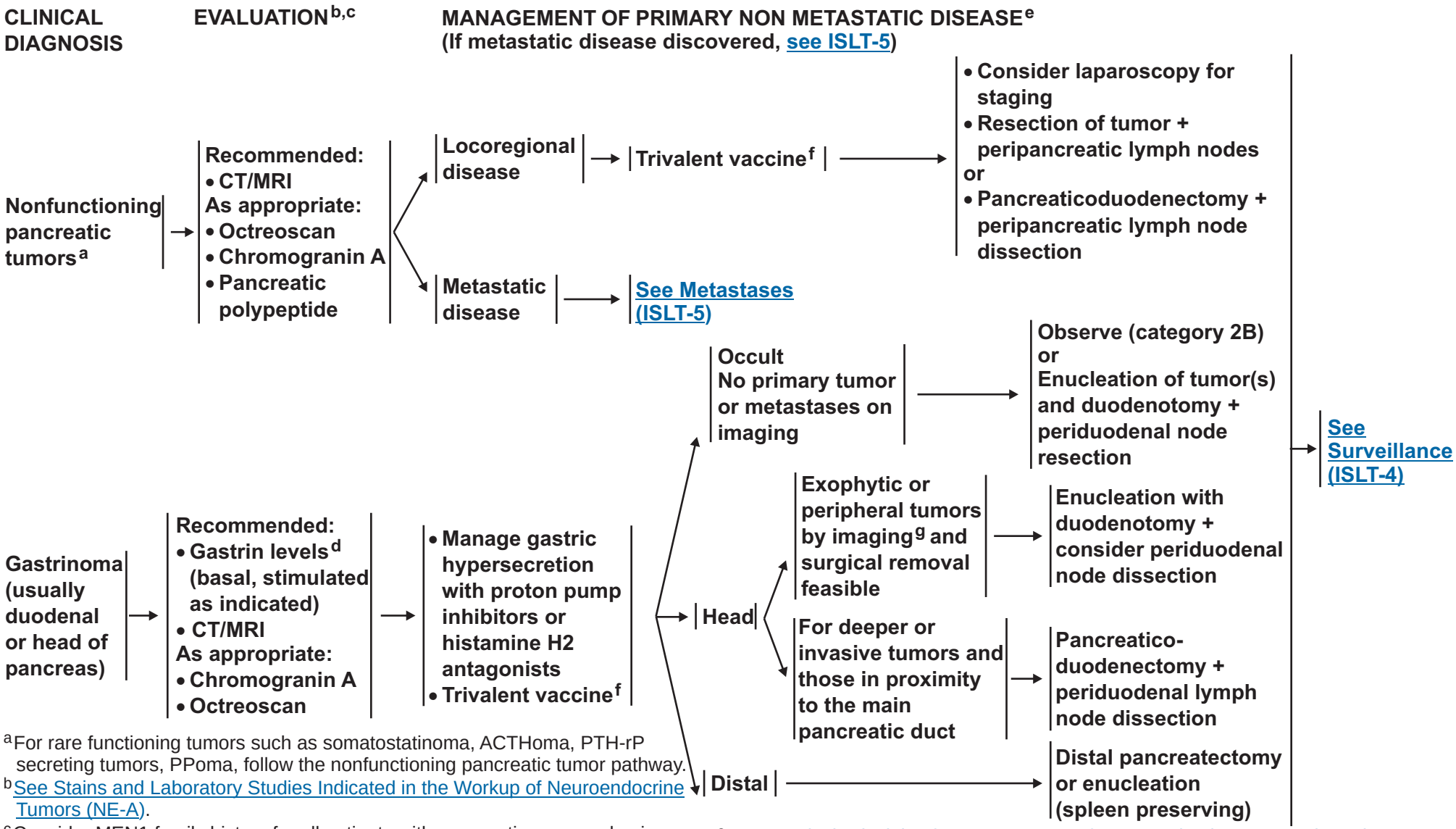
[r] Anticancer agents such as, capecitabine, dacarbazine, 5-fluorouracil, interferon, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a progression-free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

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Neuroendocrine Tumors
Islet Cell Tumors
(Pancreatic Endocrine Tumors)

Guidelines Index
Neuroendocrine TOC
Staging, Discussion, References



[a] For rare functioning tumors such as somatostatinoma, ACTHoma, PTH-rP secreting tumors, PPoma, follow the nonfunctioning pancreatic tumor pathway.

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

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

[d] Gastrin levels needs to be completed while fasting and off protein pump inhibitors for 1 week.

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

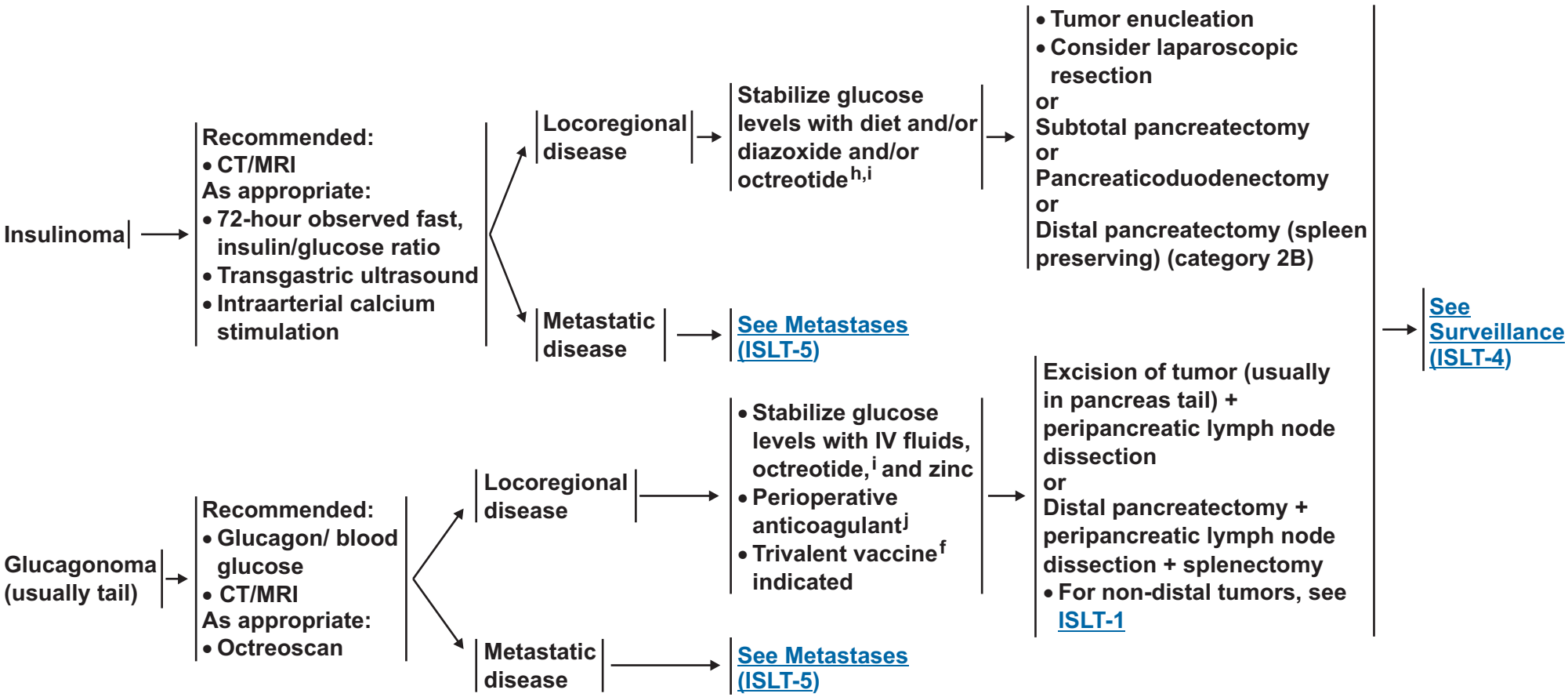
[f] Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.

[g] Not adjacent to the main pancreatic duct.

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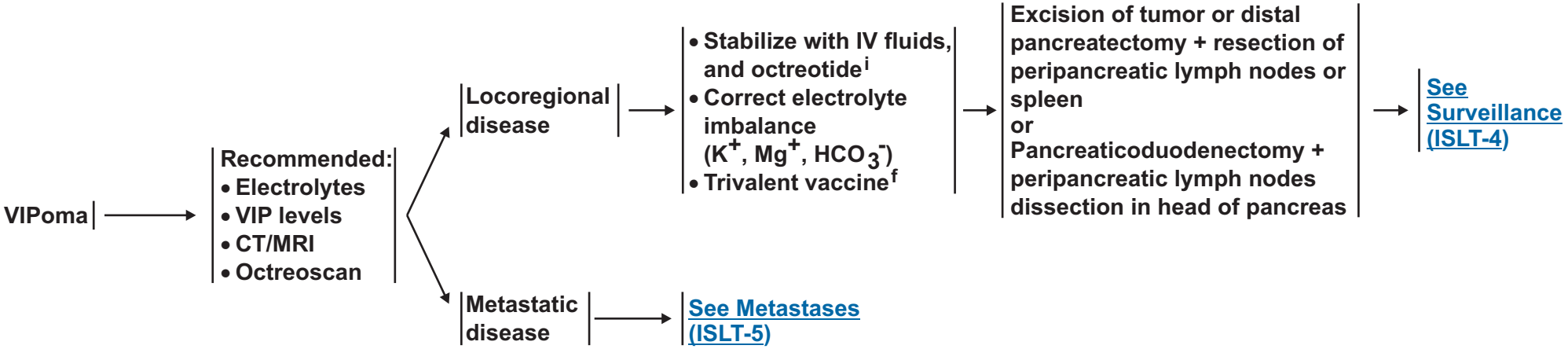


[b] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[c] Consider MEN1 family history for all patients with pancreatic neuroendocrine tumors.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[f] Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.
[h] May worsen hypoglycemia in some patients (see discussion) and maybe useful if octreoscan positive.
[i] 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.
[j] Consider venacaval filter for patients at risk for deep vein thrombosis.

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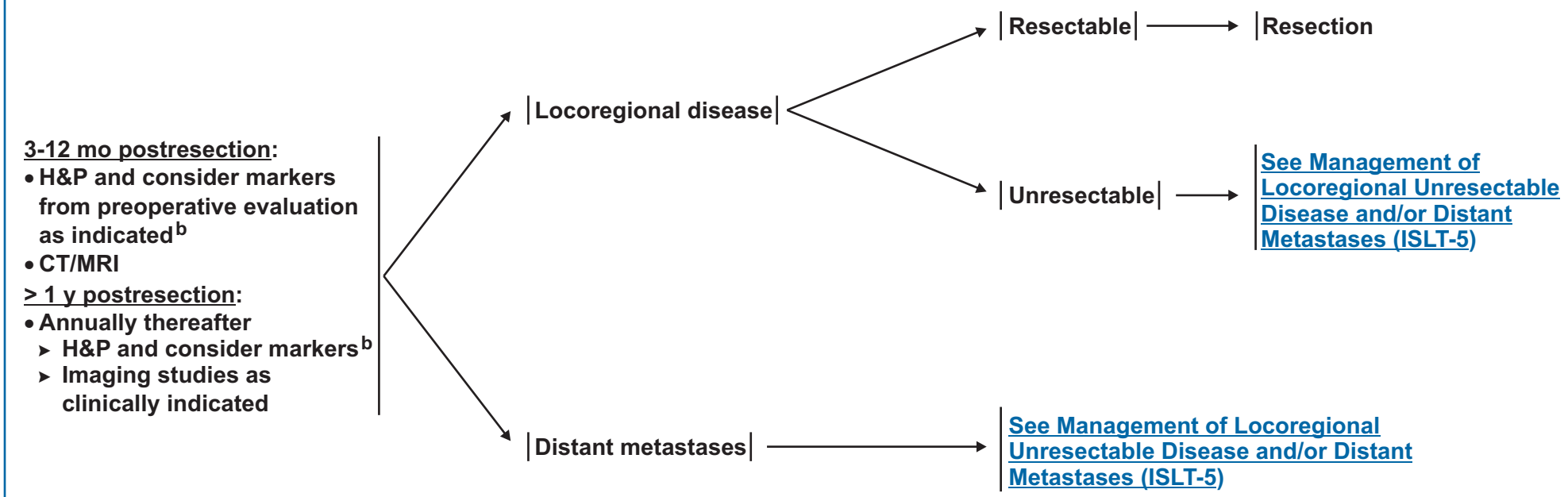
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[f] Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C), if considering surgery with possible splenectomy.
[i] Octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency 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.

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SURVEILLANCE[k,l] **RECURRENT DISEASE** **MANAGEMENT OF RECURRENT DISEASE**[e]



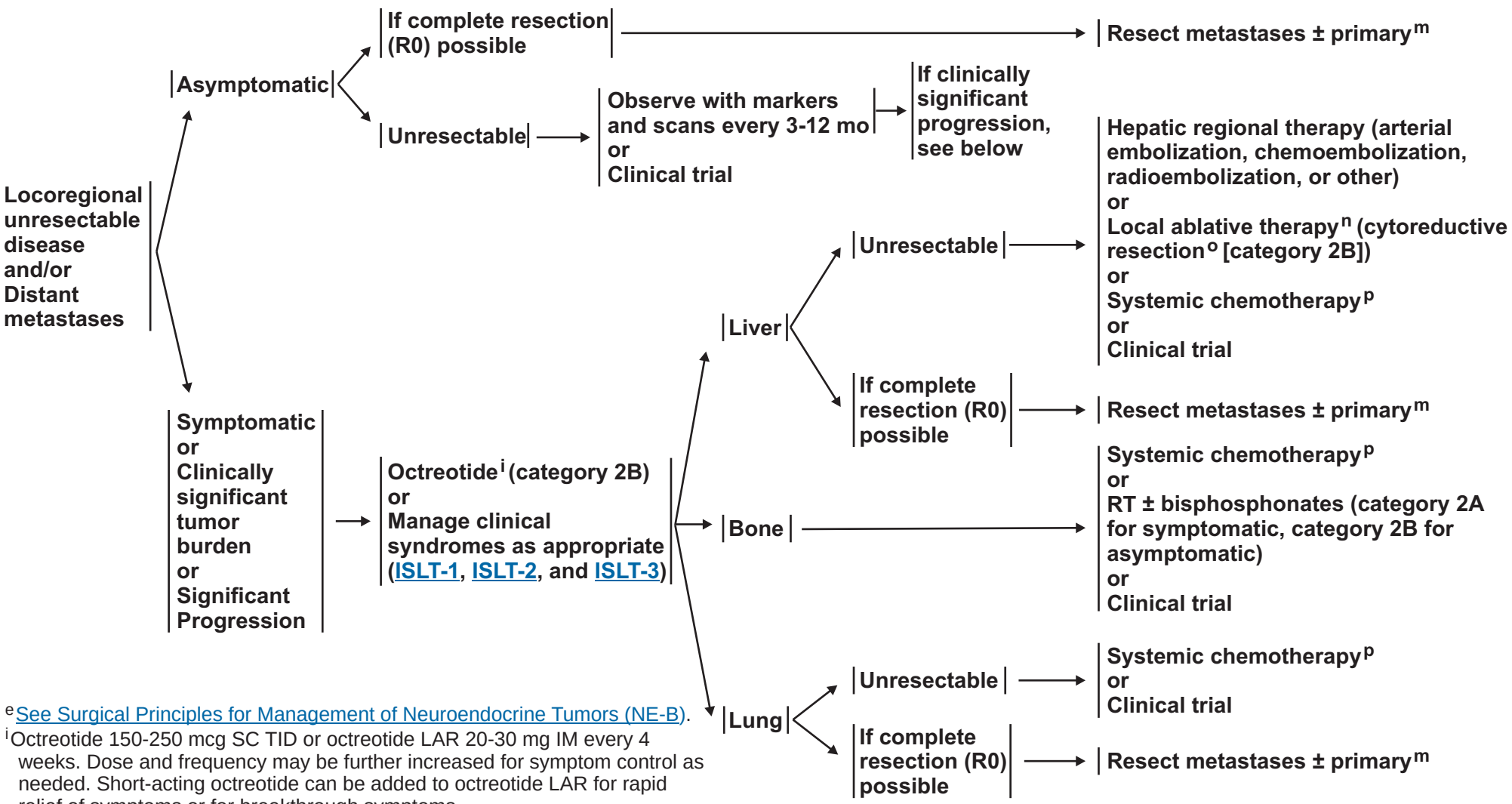
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[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[k] Earlier, if symptoms.
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MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[e]



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

[i] 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.

[m] Synchronous or staged resection if clinically possible.

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

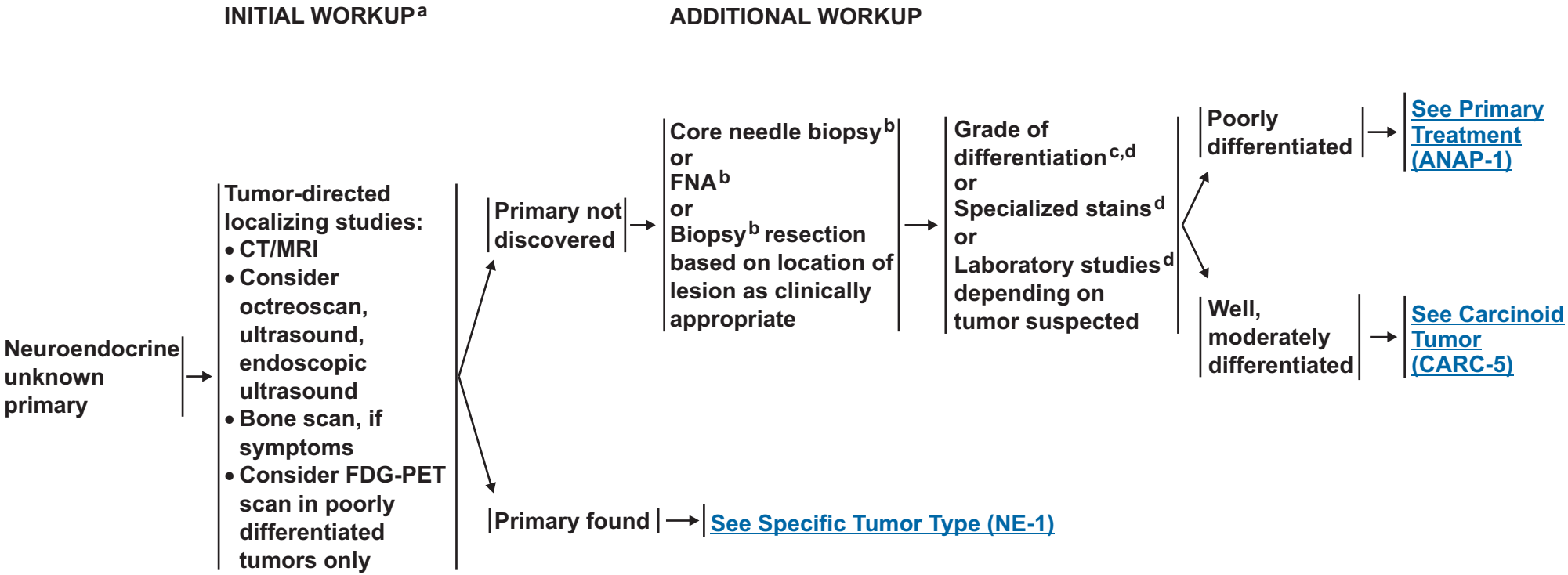
[o] Only if near complete resection can be achieved.

[p] The following agents have been used: everolimus (category 2B), sunitinib (category 2B), capecitabine, dacarbazine, doxorubicin, 5-FU, streptozocin, and temozolomide.

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Neuroendocrine Unknown Primary



[a] Sequence may vary.

[b] Rule 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.

[c] Well, 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 Indicated in the Workup of Neuroendocrine Tumors (NE-A).

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Adrenal Gland Tumors

CLINICAL PRESENTATION

EVALUATION[a]

CLINICAL DIAGNOSIS

Adrenal tumor on imaging

- **History of prior or current malignancy with risk of adrenal metastasis** → See Additional Evaluation (AGT-2)

Functional evaluation

- **Pheochromocytoma**
  - Fractional plasma metanephrines
  - Urine metanephrines
- **Cushings syndrome**
  - Serum ACTH, cortisol, DHEA
  - 24 h urine for free cortisol
  - Overnight 1 mg dexamethasone suppression test with 8 am plasma cortisol
  - Consider 17-keto and 17,21- dihydroxy steroids
- **Hyperaldosteronism**
  - Plasma aldosterone, renin activity
  - Electrolytes

Morphologic evaluation

- Adrenal protocol CT[b] scan or MRI[c] to determine contrast washout (CT), lipid content (MRI), size, heterogeneity, and margin characteristics

→ **Hyperaldosteronism, tumor < 3 cm, smooth** → See Primary Treatment (AGT-2)

→ **Hyperaldosteronism (rare), tumor > 3 cm, or irregular/ inhomogeneous morphology or secreting of more than one hormone** → See Primary Treatment (AGT-2)

→ **ACTH independent Cushings syndrome** → See Primary Treatment (AGT-3)

→ **ACTH-dependent Cushings syndrome** → See Primary Treatment (AGT-3)

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

→ **Pheochromocytoma**
- **Elevated (> 2 times normal) plasma metanephrines or confirmed elevation of urine metanephrines**

→ See Pheochromocytoma guidelines (PHEO-1)

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

[b] If unenhanced is < +10, then the tumor is probably benign. If unenhanced > +10, 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(3):629-633.)

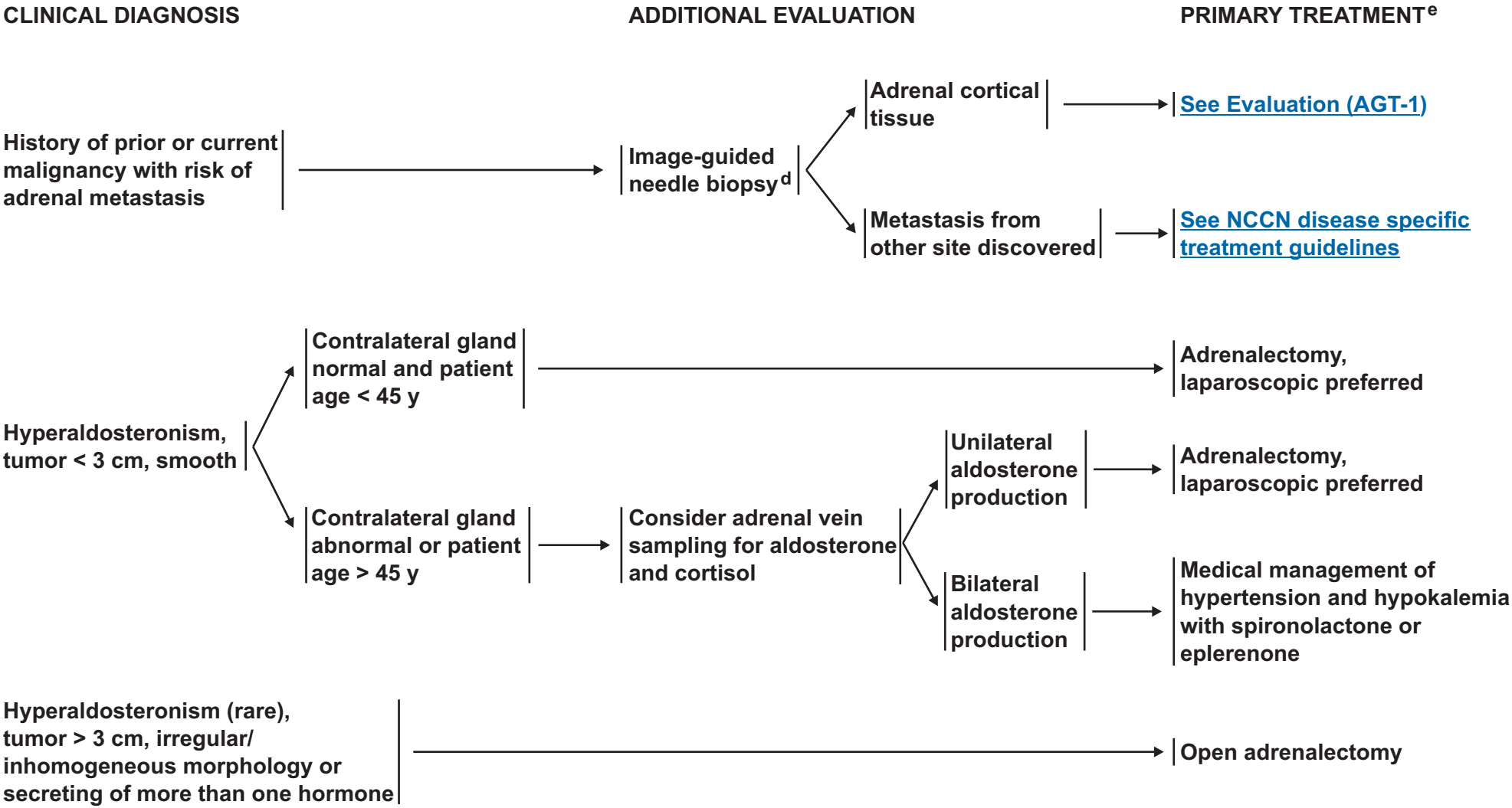
[c] Chemical shift imaging.

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Adrenal Gland Tumors



[d] Rule out functioning adrenal neoplasm before biopsy.
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).

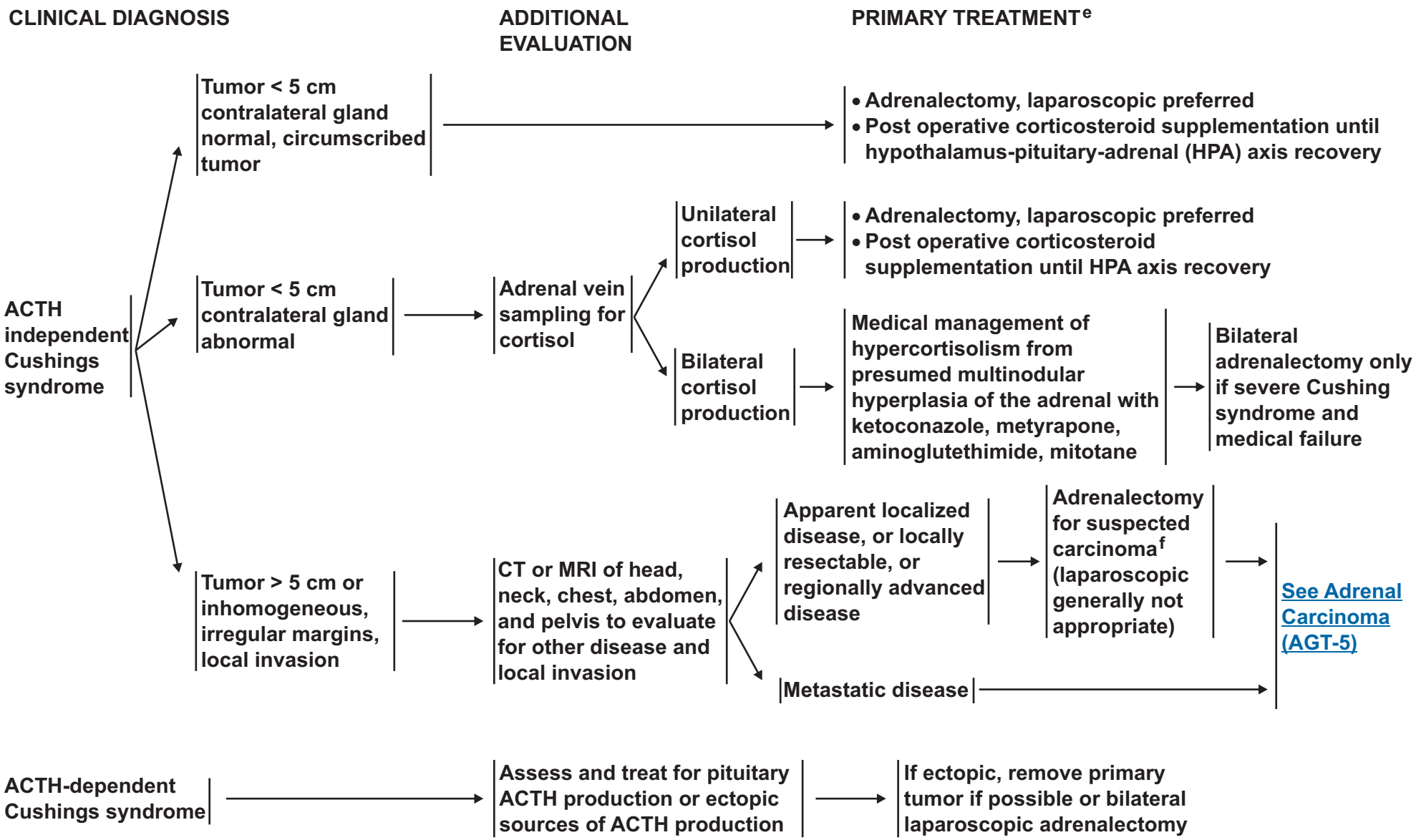
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Adrenal Gland Tumors

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

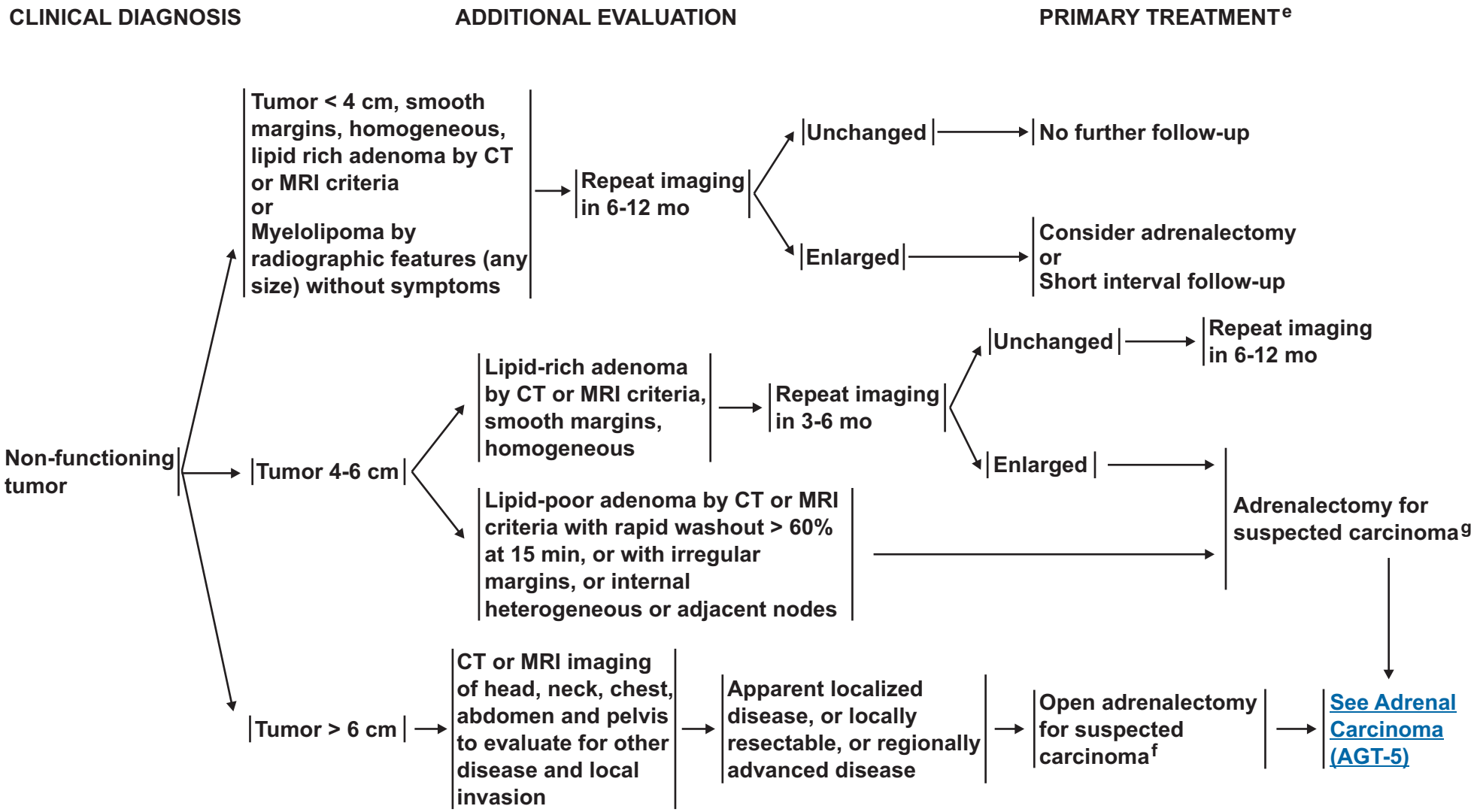
[f] May require removal of adjacent structures (liver, kidney, pancreas, spleen, diaphragm) for complete resection.

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Adrenal Gland Tumors

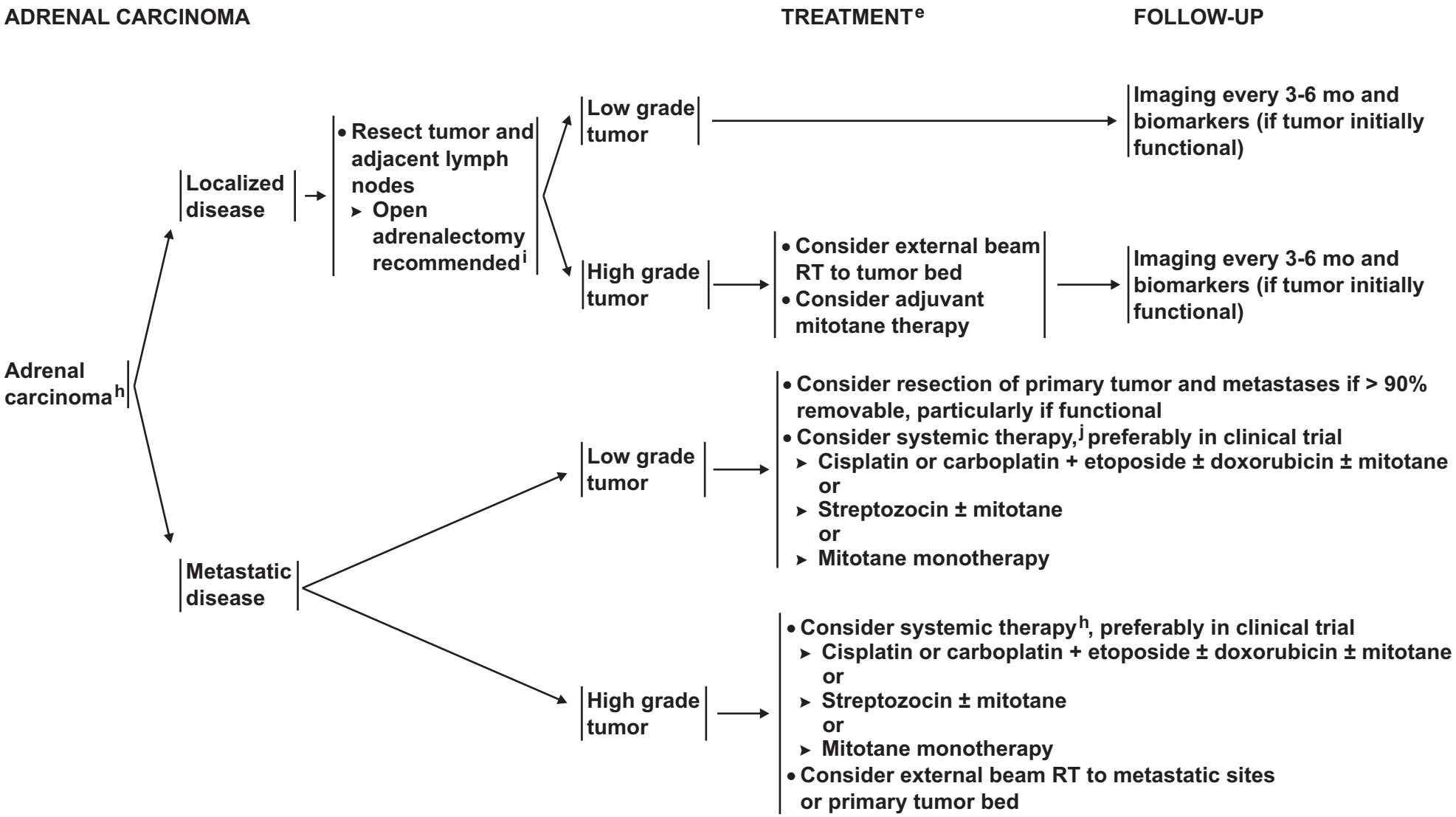


[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[f] May require removal of adjacent structures (liver, kidney, pancreas, spleen, diaphragm) for complete resection.
[g] If size resectable by laparoscopy, may explore laparoscopically with planned conversion for evidence of local invasion.

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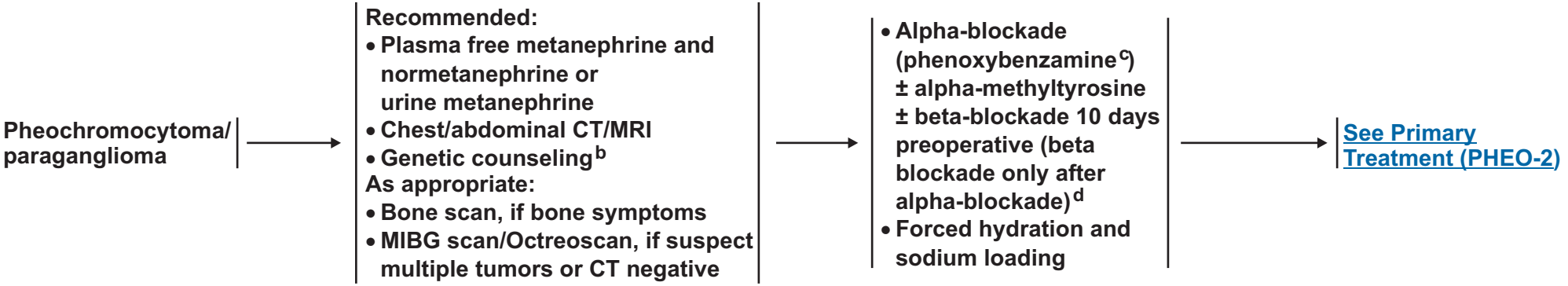


[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[h] Cross sectional imaging to stage disease.
[i] Increased risk for local recurrence when done laparoscopically.
[j] IGF-1 inhibitor may be useful. Consider a clinical trial.

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

[b] Genetic counseling may include genetic testing when appropriate.

[c] Phenoxybenzamine: 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.

[d] Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonist such as phentolamine and rapid-acting intravenous beta-blockers, such as 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 beta-blockers, such as propranolol, nadolol, or labetalol; cardioselective agents, such as atenolol and metoprolol can be used after initiation of alpha blockade.

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Pheochromocytoma

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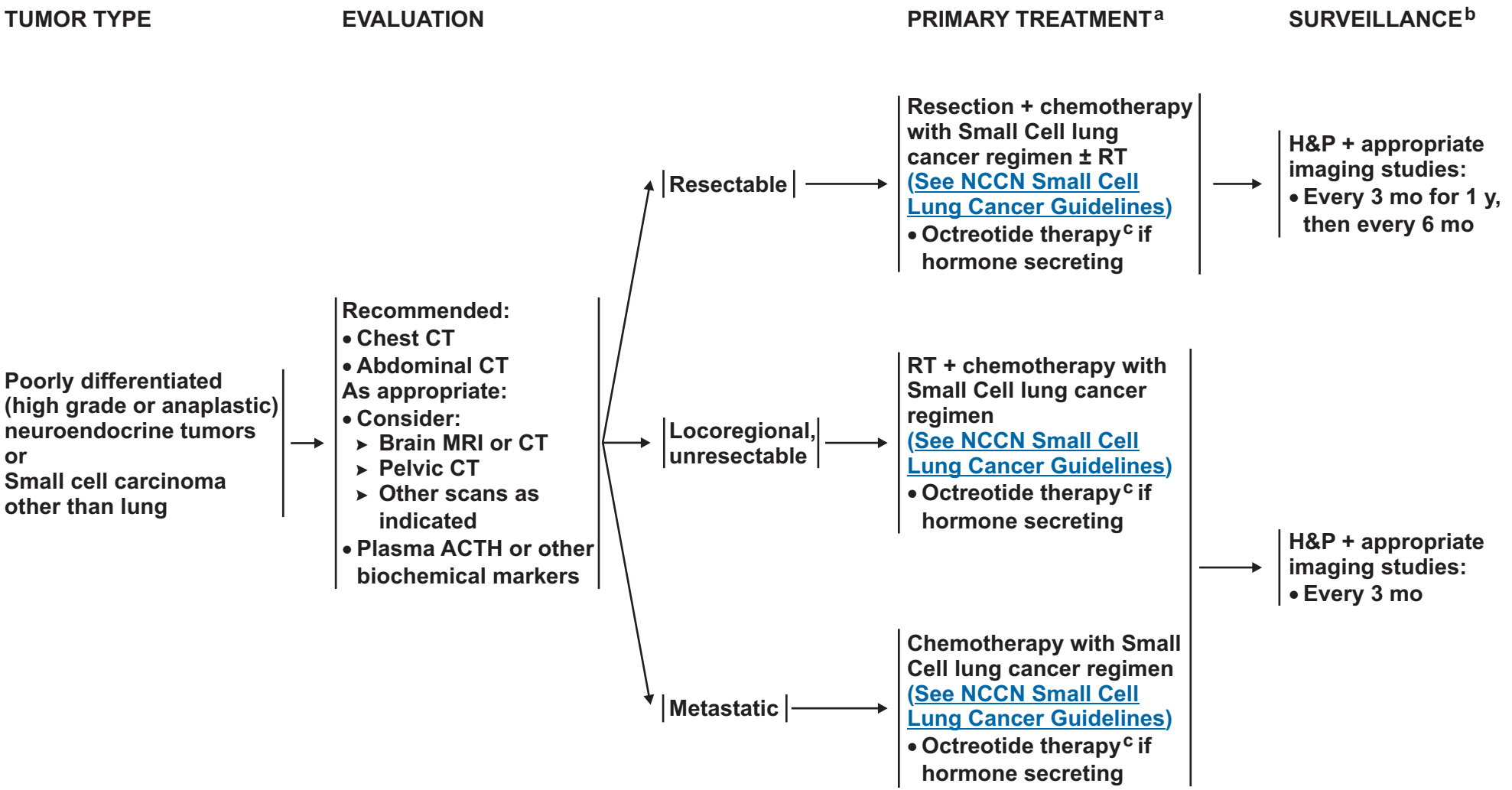
	PRIMARY TREATMENT[e]	SURVEILLANCE[g]
Resectable	Resect (laparoscopic preferred when safe and feasible)	3- 12 mo postresection: • H&P, blood pressure, and markers[a] Long term: • H&P, blood pressure, and markers,[a] ➤ Years 1-3: every 6 mo ➤ Years 4+: annually • Imaging studies as clinically indicated
Locally unresectable	Cytoreductive (R2) resection, if possible ± RT + alpha-blockade ± alpha-methyltyrosine ± beta-blockade	Every 3- 4 mo • H&P, blood pressure, and markers[a] • Imaging studies as clinically indicated
Distant metastases	Cytoreductive (R2) resection when possible + continuous alpha-blockade ± alpha-methyltyrosine ± beta-blockade (optional) or Clinical trial or Systemic chemotherapy (eg, dacarbazine, cyclophosphamide, vincristine) or 131I MIBG as compassionate use on clinical trial[f] (requires prior MIBG scan with dosimetry)	

[a] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[f] For additional information, see www.fda.gov.
[g] Earlier, if symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
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[a] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).

[b] Earlier, if symptoms.

[c] 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.

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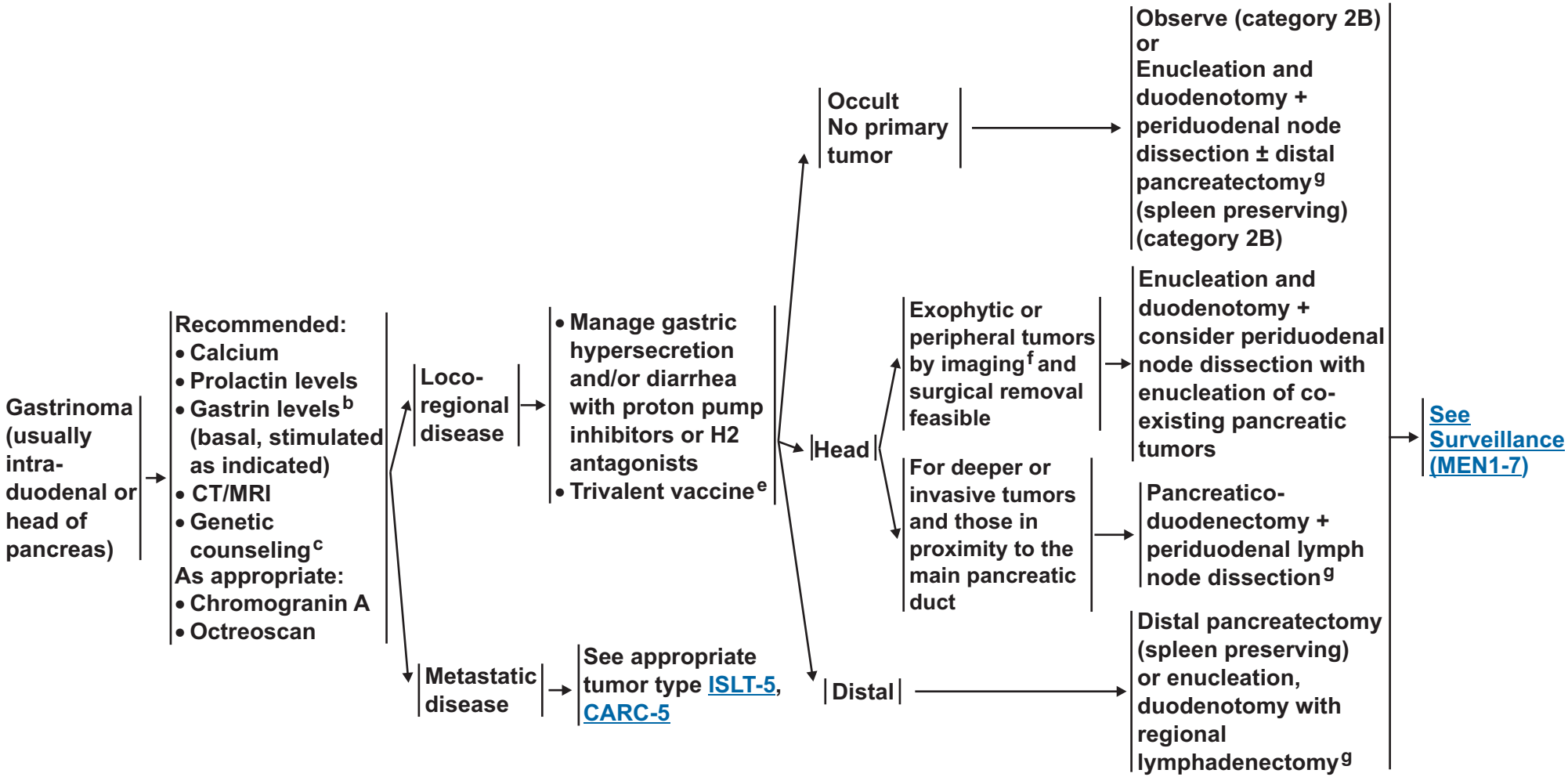
Multiple Endocrine Neoplasia, Type 1

PARATHYROID, PITUITARY, PANCREATIC, CARCINOID, MULTIPLE LIPOMAS, ANGIOMAS

CLINICAL DIAGNOSIS

EVALUATION[a]

MANAGEMENT OF PRIMARY NON METASTATIC DISEASE[d]
(If metastatic disease discovered, see appropriate tumor type, ISLT-5, CARC-5)



[a] See Stains and Laboratory Studies 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.

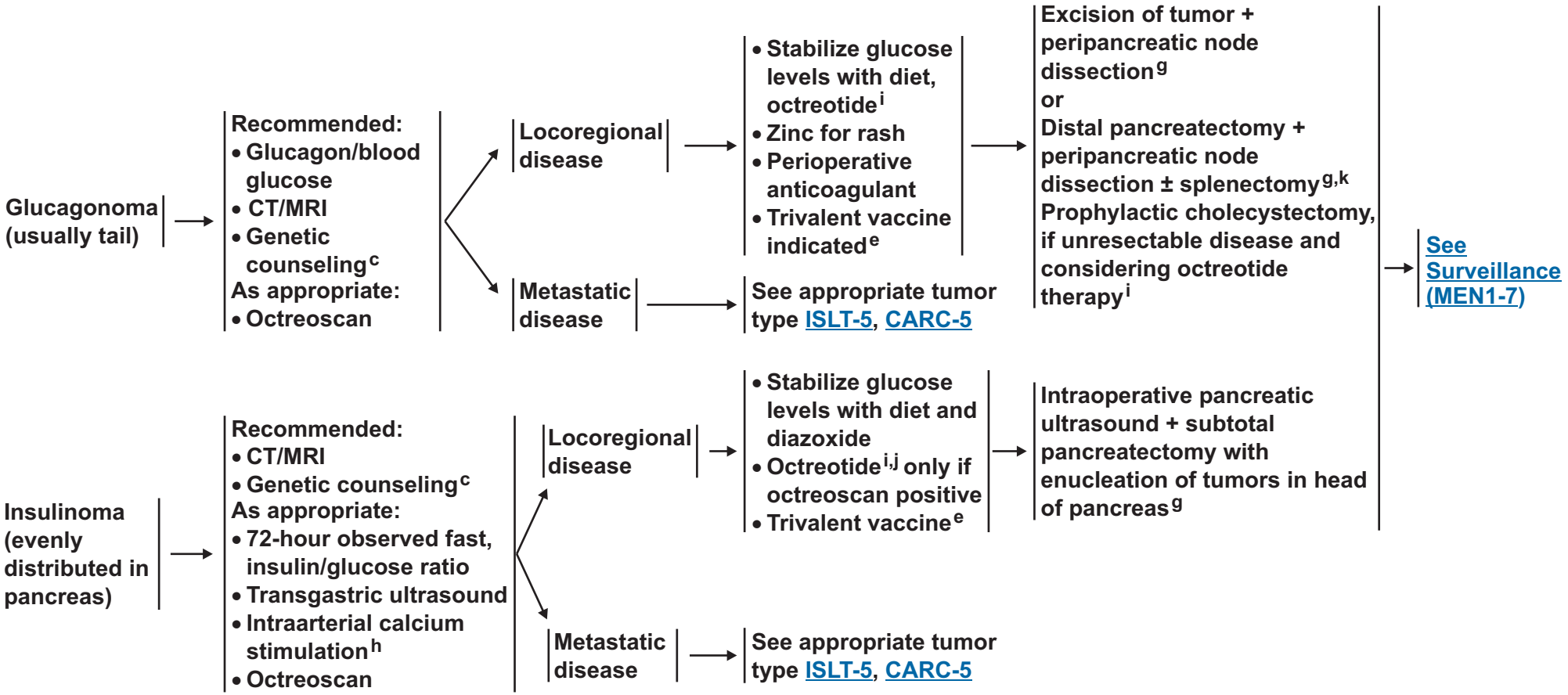
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Multiple Endocrine Neoplasia, Type 1

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

[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.

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

[h] See discussion (MS-6).

[i] 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.

[j] May worsen hypoglycemia in some patients (See discussion).

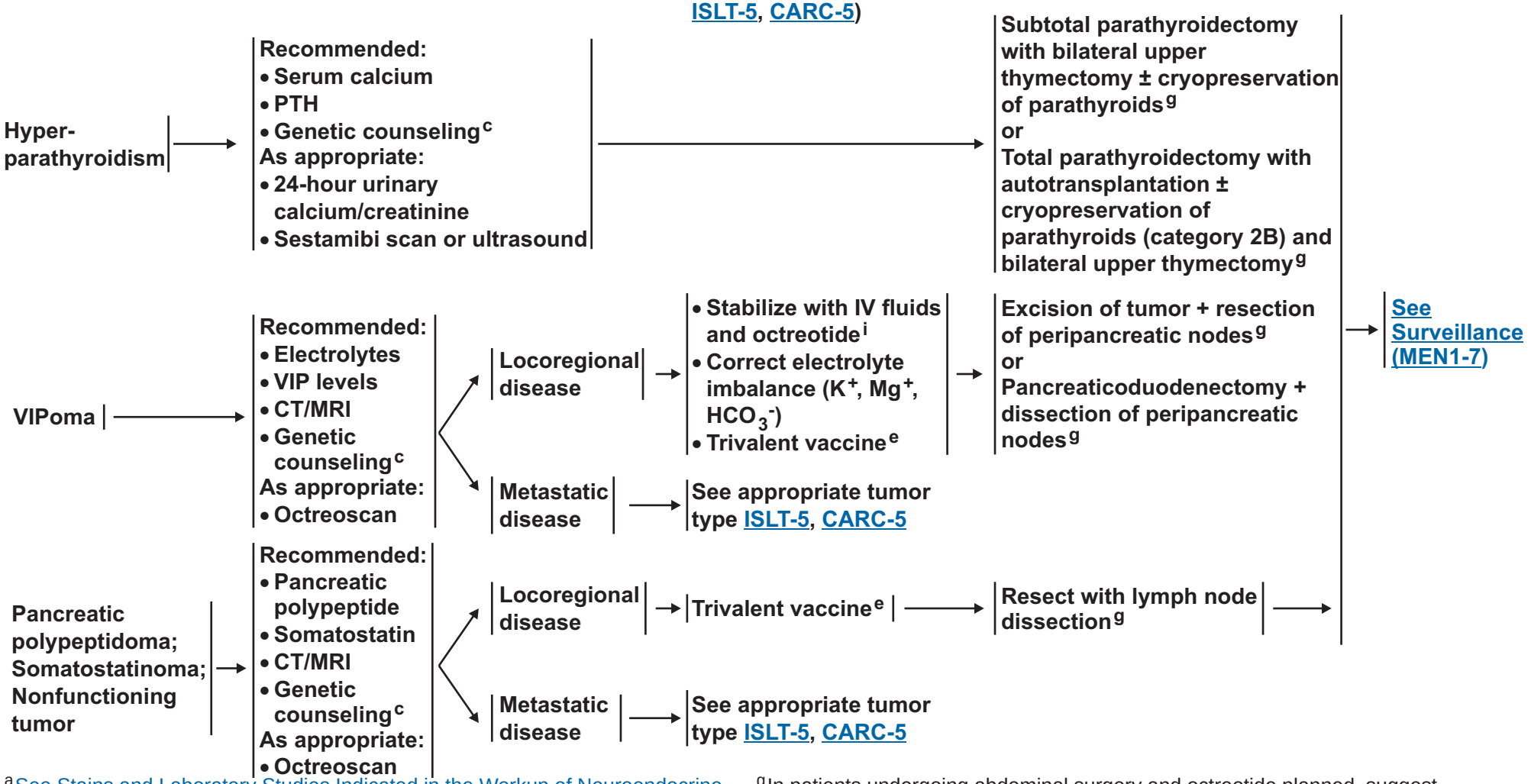
[k] Splenectomy is probable, as tumors are usually malignant, relatively large, and situated in the tail of the pancreas.

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Multiple Endocrine Neoplasia, Type 1



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

[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.

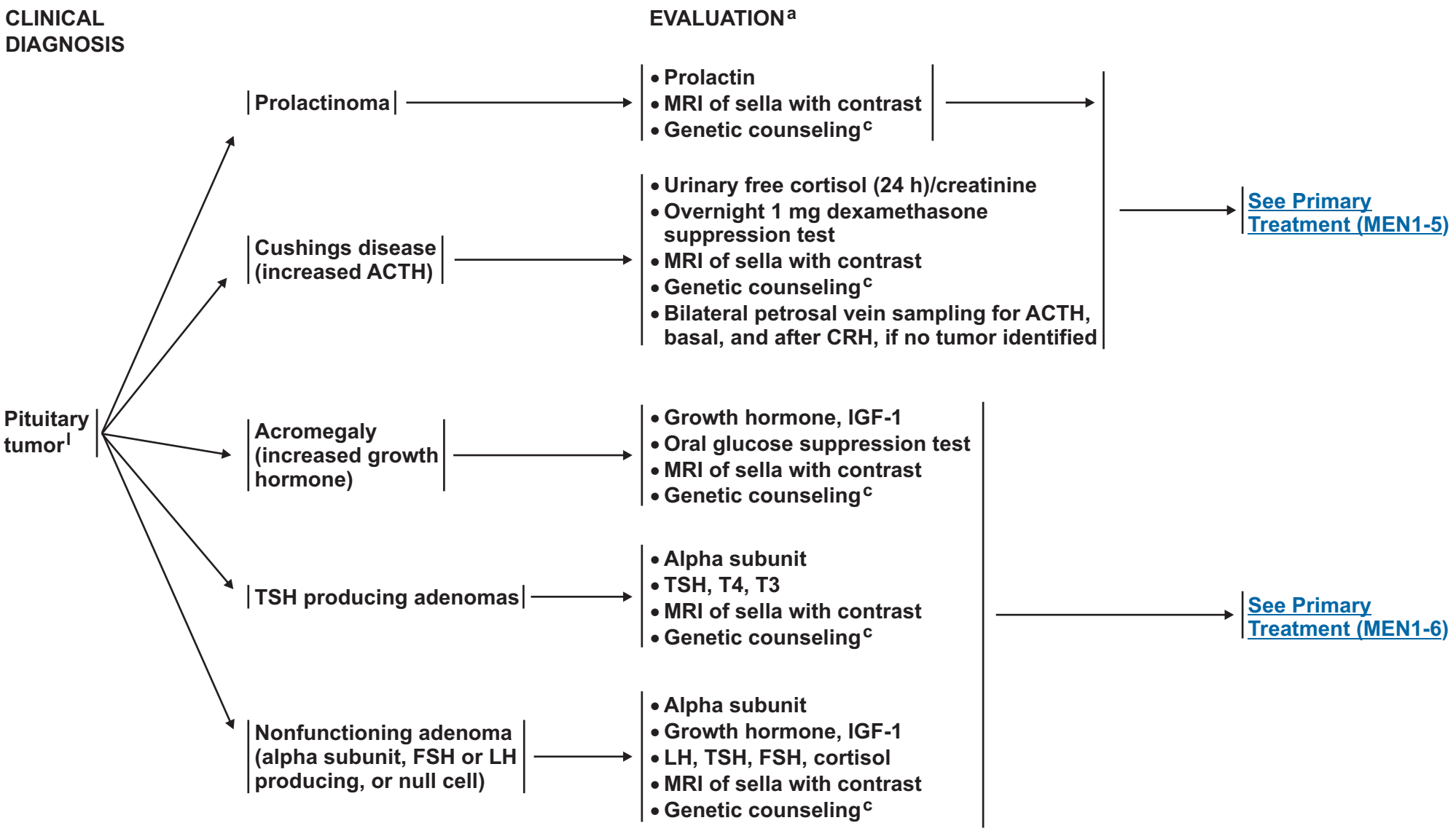
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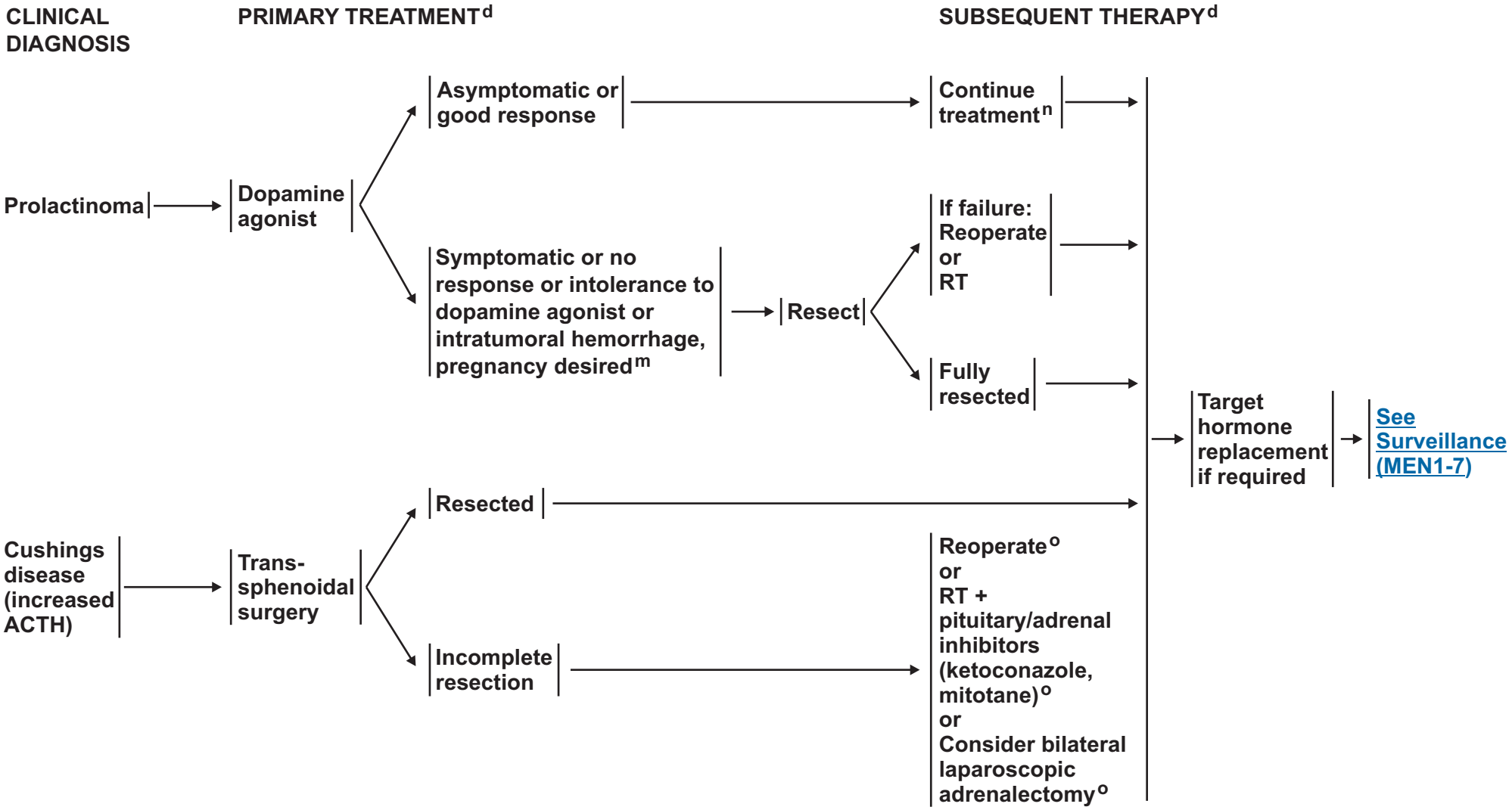
[a] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[c] Genetic counseling may include genetic testing when appropriate.
[l] If tumor >1 cm, assess visual fields and screen for hypopituitarism including TSH, T4, ACTH stimulation test.

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Multiple Endocrine Neoplasia, Type 1

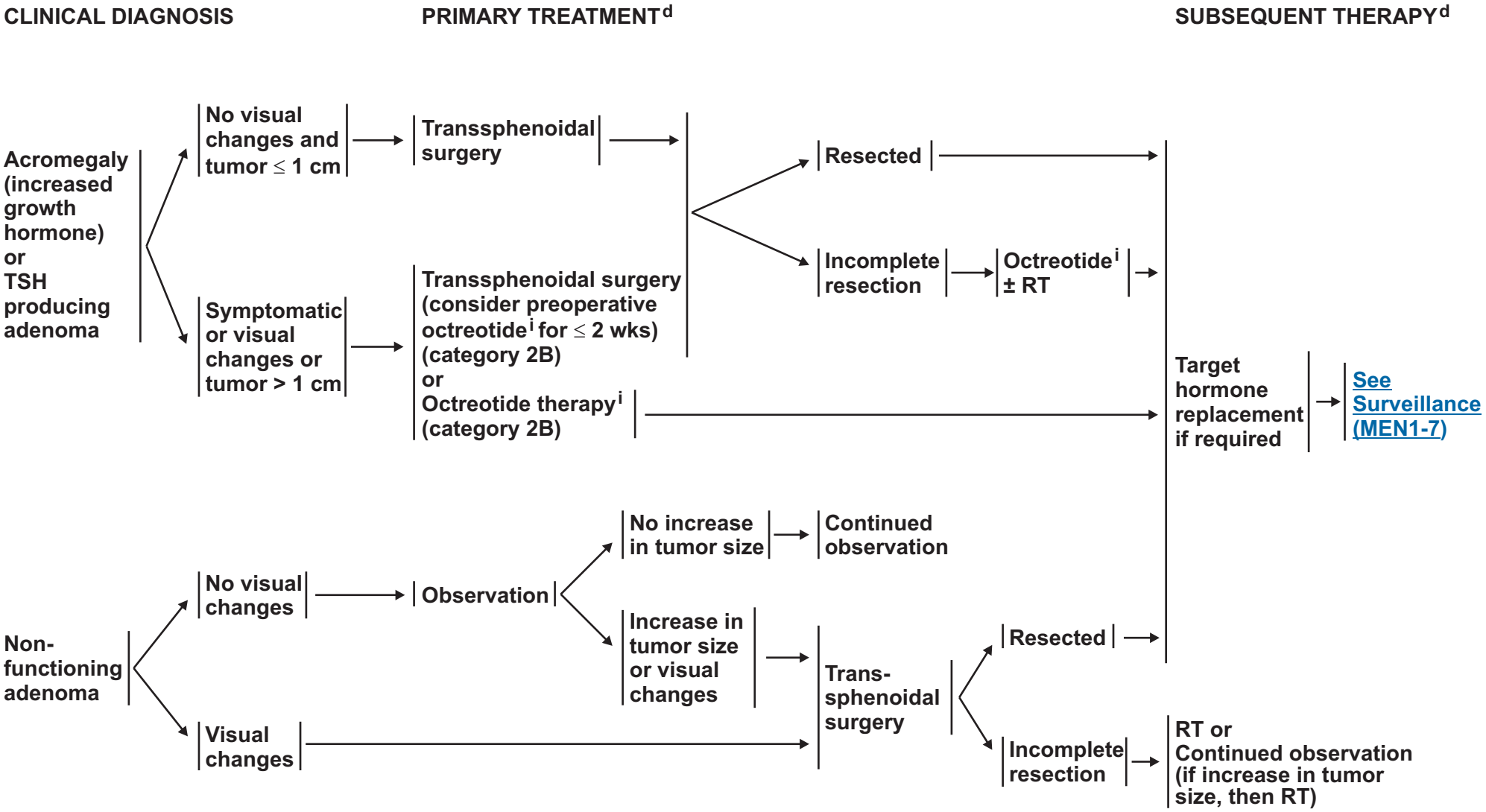


[d] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[m] Continue dopamine agonist or transsphenoidal resection of the tumor.
[n] Consider discontinuation of treatment, with clinical and hormonal monitoring, if tumor regression and hormone levels normal.
[o] Many of the treatments can be considered sequentially.

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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:
- CT/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

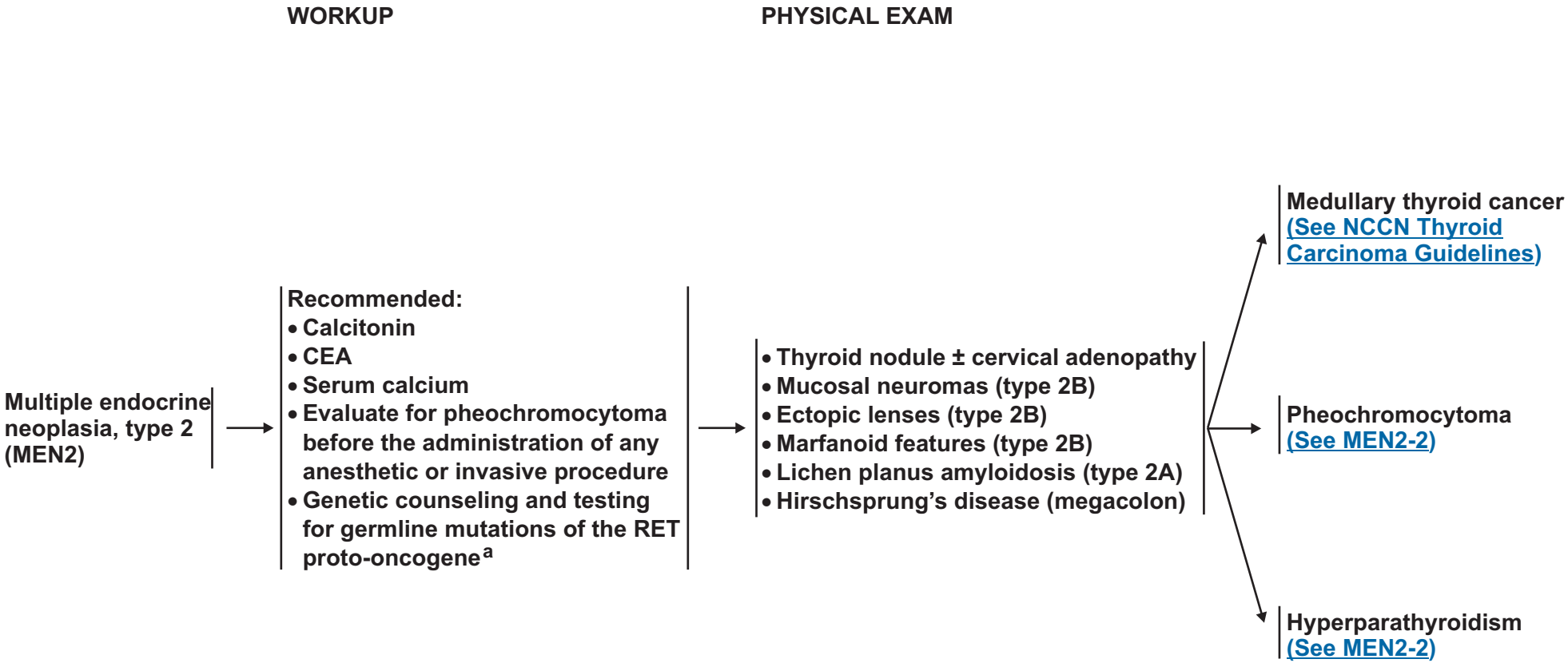
[p]Earlier, if symptoms.

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MEDULLARY THYROID CANCER, PHEOCHROMOCYTOMA, HYPERPARATHYROIDISM, LICHEN PLANUS AMYLOIDOSIS



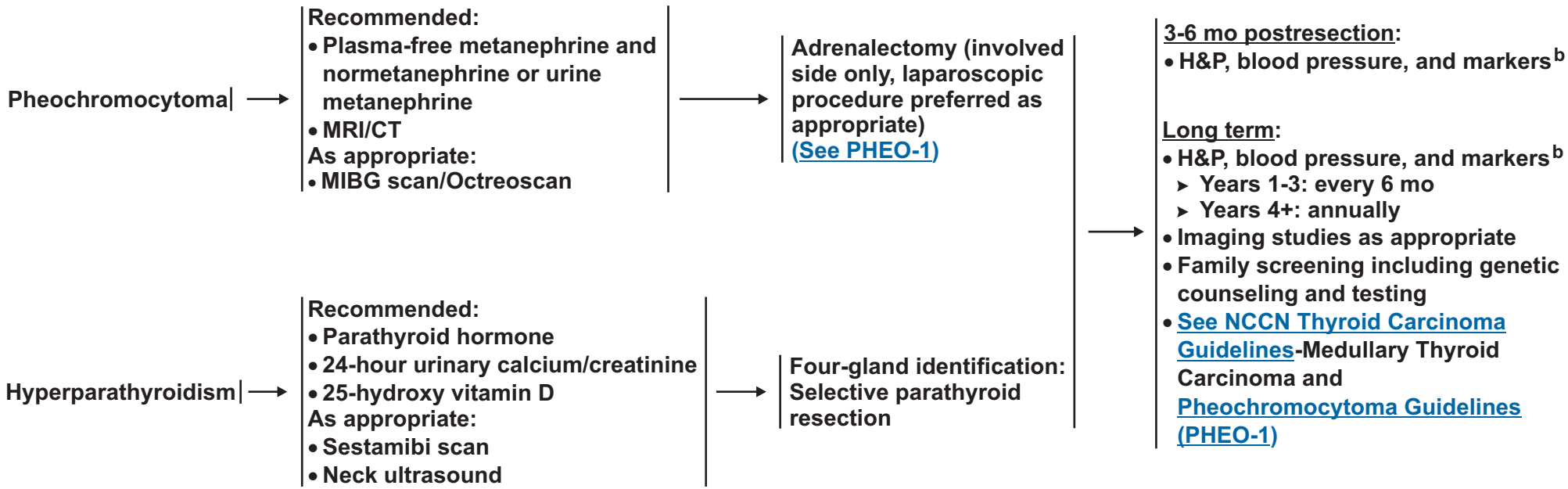
[a]Recommendations for prophylactic thyroidectomy based on individual RET mutations are detailed in the NCCN Thyroid Carcinoma Guidelines-Medullary Thyroid Cancer.

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Multiple Endocrine Neoplasia, Type 2



[b] See Stains and Laboratory Studies Indicated in the Workup of Neuroendocrine Tumors (NE-A).
[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).
[d] Earlier, if symptoms.

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IMMUNOHISTOCHEMICAL AND LABORATORY STUDIES INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS[1]

IMMUNOHISTOCHEMICAL STUDIES

- Basic for diagnosis
  - Chromogranin A
  - Synaptophysin
  - Cytokeratin
  - Ki67 (MIB-1)
- Tumor-specific confirmation
  - Gastrin
  - Somatostatin
  - Insulin
  - VIP
  - ACTH
  - Glucagon
  - Prolactin
  - Calcitonin
  - Pancreatic polypeptide
  - Alpha subunits
  - TSH
  - PTH
  - Proinsulin
  - LH/FSH
  - Growth hormone

GENERAL LABORATORY STUDIES

- Chemistries
  - Calcium
  - Phosphorus
  - Electrolytes
  - Magnesium
  - Chloride/phosphorus ratio

HORMONE-RELATED STUDIES (blood markers)

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

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

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, methyldopa, 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. This test should not be requested on patients who have recently received radioactive material.

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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 unresectable tumor that has regressed should be considered for selected patients with excellent performance status and loco regional recurrence or isolated distant metastases when complete resection can be achieved.**
- **For some patients, 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).**

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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)

Stomach

TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

Duodenum/Ampulla/Jejunum/Ileum

TNM

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

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

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Staging

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

Colon or Rectum

TNM

Primary Tumor (T)

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

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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.

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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**	**N0**	**M0**
	Any T	**N1**	**M0**
Stage IV	**Any T**	**Any N**	**M1**

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

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

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

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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 arise from cells throughout the nervous and endocrine systems which produce and secrete regulatory hormones. Common sites of origin of neuroendocrine tumors include the (1) endocrine pancreas; (2) parathyroid, adrenal, and pituitary glands; (3) calcitonin-producing cells of the thyroid (causing medullary thyroid carcinoma [MTC]); and (4) argentaffin cells of the gut (causing carcinoid tumors).

Neuroendocrine tumors are rare. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database showed an age-adjusted incidence of 5.25 cases per 100,000 people in the year 2004.[1]

Neuroendocrine tumors can be broadly subdivided into those with and those without a clinical syndrome and are accordingly termed "functional" or "nonfunctional" neuroendocrine tumors, respectively. Furthermore, neuroendocrine tumors can arise sporadically (nonhereditary tumors) or as a result of genetic predisposition (hereditary tumors). Functionally active neuroendocrine tumors present with clinical symptoms of excessive hormone release from the tumor cells. Examples of functionally active neuroendocrine tumors are insulinoma, gastrinoma, vasoactive intestinal polypeptidoma (VIPoma), glucagonoma, other rare pancreatic tumors and carcinoid tumors.

Most neuroendocrine tumors, (with the exception of insulinomas, which are usually benign), are malignant, and metastasize commonly to lymph nodes and the liver or less commonly to bone, lung, brain, and other organs. Despite the widespread metastases, these tumors are typically slow-growing with a low mitotic activity, and often have an insidious presentation.

Neuroendocrine Tumors are classified pathologically based on the grade of differentiation in to three broad categories: 1) Well-differentiated (low-grade) neuroendocrine tumors; 2) Moderately-differentiated (intermediate-grade) neuroendocrine tumors; and 3) Poorly-differentiated (high-grade) neuroendocrine tumors. The NCCN Neuroendocrine Tumors Guidelines are divided into the following categories: (1) carcinoid tumors (2) islet cell tumors (pancreatic endocrine tumors) (3) neuroendocrine tumors of unknown primary (4) adrenal gland tumors (including adrenal cortical tumors and incidentaloma) (5) pheochromocytoma/paraganglioma (6) poorly differentiated (high grade or anaplastic)/small cell tumors and (7) multiple endocrine neoplasia type 1 (MEN 1) which is associated with multiple tumors of the parathyroid, pituitary, and pancreatic glands as well as carcinoid tumors, adrenal tumors, multiple lipomas and angiomas;(8) Multiple endocrine neoplasia type 2 (MEN 2)

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characterized by MTC, pheochromocytoma often bilateral, and hyperparathyroidism; MEN 2B is characterized by Marfanoid habitus, multiple neuromas, especially on the tongue and marked flexibility.

The appropriate diagnosis and treatment of neuroendocrine tumors requires 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. The management of neuroendocrine tumors with surgical, medical, or radiation therapies is determined by the specific endocrine gland(s) involved, grade of differentiation, aggressiveness and stage of the tumor, amount of hormone produced, and specific patient needs.

These NCCN Neuroendocrine Guidelines discuss the diagnosis and management of the sporadic and hereditary neuroendocrine tumors as well as special considerations relating to these tumors. Oncologists should also note that unusual patient scenarios (presenting in less than 5% of patients) are not specifically discussed in these NCCN guidelines.

Sporadic, Nonhereditary Neuroendocrine Tumors

Carcinoid Tumors

Carcinoid tumors arise from argentaffin cells located in the foregut (ie, respiratory tract, thymus, pancreas, stomach, proximal duodenum), midgut (ie, jejunum, ileum, appendix, Meckel's diverticulum, ascending colon), and hindgut (ie, transverse and descending colon, rectum). Sixty six percent of carcinoid tumors arise in the midgut, with the small bowel being the most common site, followed by the appendix. The predominance of midgut tumors may be related to the incidental finding of carcinoid tumors in appendices removed for appendicitis or prophylactically excised during gynecologic operations. Carcinoid tumors associated with MEN 1 arise in the foregut (pancreas, thymus, lung, and proximal small intestine). Approximately 2500 new cases of malignant carcinoid tumor are diagnosed annually in the United States. About 50% of patients with malignant carcinoid tumors will live 5 years or more after diagnosis and initial treatment.[2]

Carcinoid tumors can secrete various hormones, including ACTH, gastrin, human chorionic gonadotropin, somatostatin, pancreatic polypeptide, serotonin, histamine, and tachykinins. The carcinoid syndrome [3] describes symptoms related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation resulting in classic symptoms, such as episodic cutaneous flushing, abdominal cramps, and diarrhea. Additionally, about 10-30% of those with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation or pulmonary stenosis. The occurrence and severity of the carcinoid syndrome are directly related to elevation of serotonin or its metabolites 5-hydroxyindoleacetic acid (5-HIAA), and tumor size in an area with direct access to the systemic circulation. Studies demonstrate that serum chromogranin-A levels are elevated in 56% to 100% of patients with carcinoid tumors, and the level correlates with tumor size.[4,5] The metabolic products released by the intestinal carcinoid tumor are rapidly destroyed by liver enzymes in the portal circulation, thus the classical syndrome 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. Therefore, in most cases, the carcinoid syndrome is associated with tumors of the midgut, because midgut tumors are the most common and frequently metastasize. Foregut tumors account for 2% to 33% of the carcinoid syndrome followed by hindgut tumors, which rarely produce such symptoms.[6-8]

The NCCN guidelines address 6 major presentations of carcinoid tumors: (1) small bowel/colon (2) appendix (3) rectal (4) gastric (5) thymus, bronchial, (6) atypical lung carcinoid.

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Evaluation of Carcinoid Tumors

For patients who present with carcinoid syndrome, evaluation with imaging studies to assess disease burden and possible primary location is recommended. Commonly used standard techniques include computed tomography, and magnetic resonance imaging (MRI). Triple phase technique is required when computed tomography (CT) scan is obtained for evaluation of liver metastasis. Carcinoid tumors possess high-affinity receptors for somatostatin in the majority of cases.[8,9] Therefore radiolabeled somatostatin receptor scintigraphy; performed using the radiolabeled somatostatin analogue [^{111}In-DTPA] octreotide (OctreoScan) may be used as appropriate. Patients with positive scans are more likely to respond to somatostatin treatment. Specific workup testing for individual carcinoid sites is outlined in the algorithms (see CARC-1, CARC-2, CARC-3, and CARC-4).

Primary Treatment of Carcinoid Tumors

Depending on the results obtained from the workup, the patient's disease is classified as locoregional or metastatic. Surgical resection of all neoplastic tissue should be performed for localized disease. However, the extent of the surgical resection depends on the location of the tumor, its size, its anticipated stage, and the general condition of the patient.

For patients presenting with tumors in the small bowel and colon, surgical resection is recommended. If octreotide therapy may be needed in the future, a prophylactic cholecystectomy should be considered in conjunction with surgical resection of a small bowel tumor, because possible subsequent treatment with octreotide increases the risk of developing gallstones.[10] If indicated, endoscopic resection of duodenal lesions is recommended (see CARC-1).

For appendiceal tumors 2 cm or less and confined to the appendix, simple appendectomy is sufficient.[11] However, if the tumor is more than 2 cm in diameter, the patients must have the surgical resection carefully evaluated for adequacy of resection and for the presence of locoregional spread to adjacent structures or lymph nodes. An inadequate resection is defined as a resection with narrow tumor-free or absent margins. These patients may require abdominal/pelvic CT or MRI scans, re-exploration, and a right hemicolectomy (see CARC-1).

The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, transanal or endoscopic resection (if possible) is recommended. However, for tumors more than 2 cm, which may show other signs of locally aggressive growth, a low anterior resection or an abdominoperineal resection (APR) should be considered[12] (see CARC-2).

Gastric carcinoids are first classified according to whether they are associated with hypergastrinemia or normal gastrin levels, because patients with the former usually have a benign course and patients with the latter have an aggressive course.[13] For hypergastrinemic patients whose tumors are 2 cm or less and either solitary or multiple, options include (1) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa; or (2) observation; or (3) octreotide for patients with Zollinger-Ellison syndrome (category 2B recommendation). For tumors larger than 2 cm either solitary or multiple, endoscopic resection (if possible) or surgical resection is indicated. Patients with normal gastrin levels are usually treated with radical resection of the tumor and removal of the perigastric lymph nodes (see CARC-3).

Localized and locoregional carcinoid tumors in the thymus are treated with surgical resection, and radiation therapy (RT) alone (category 2B for RT after complete resection) or with chemotherapy (category 3 for addition of chemotherapy). 5-fluorouracil or capecitabine at radiosensitizing doses may be considered. Cisplatin or carboplatin with etoposide may be appropriate for patients with moderately differentiated or atypical tumors. For localized or locoregional bronchial

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tumors, refer to the Lung Neuroendocrine Tumors algorithm, which is part of the NCCN Small Cell Lung Cancer Guidelines.

Surveillance

All patients with carcinoid tumors, should be re-evaluated 3-12 months after resection and annually thereafter with complete patient history and physical examination (H&P), and imaging studies such as CT (liver triple-phase) /MRI.

Plasma chromogranin A may be used as a tumor marker (category 3); while not diagnostic, elevated levels suggest recurrence.[14] 5-HIAA in a 24-hour urine sample may be considered in some cases. While monitoring patients, following treatment for 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 (see NE-A). 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 or Somatostatin Receptor scintigraphy) 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. For appendiceal tumors (2 cm or less) and rectal tumors (less than 1 cm), no follow-up is usually required (see CARC-1 and CARC-2). For rectal tumors between 1 and 2 cm, after primary therapy, proctoscopy is recommended at 6 and 12 months, and then as clinically indicated (see CARC-2). Surveillance for hypergastrinemic patients includes H&P (with esophagogastroduodenoscopy [EGD] for gastrinoma) every 6-12 months for the first 3 years and annually if no evidence of recurrence after 4 years. If clinically indicated, imaging studies should be performed. Antrectomy is considered if new lesions or increasing tumors are observed (see CARC-3).

Management of Recurrent or Unresected Carcinoid Tumors

Additional imaging recommendations for patients suspected to have distant metastatic disease include triple-phase technique CT or MRI.[15,16] Testing the levels of chromogranin-A (category 3) or 5-HIAA may be considered to monitor recurrence (discussed in the section above).

Resection of the primary tumor in patients with known metastatic disease is recommended particularly if the primary itself is symptomatic (this is usually not the case)

If no symptoms of carcinoid syndrome are present and the tumor is unresectable, the NCCN panel recommends either (1) observation with imaging studies as indicated every 3 to 6 months until the disease becomes symptomatic or progressive; (2) a clinical trial; or (3) octreotide therapy (see CARC-5). The interim results of a placebo controlled phase III trial (PROMID) showed that median time to tumor progression in the octreotide long-acting release (LAR) treated versus placebo groups was 14.3 and 6 months, respectively. 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.[17]

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For asymptomatic patients with resectable liver metastases as the only site of disease, liver resection is recommended. In limited unresectable disease, ablative techniques such as radiofrequency ablation (RFA) or partial hepatectomy (including removal of the intestinal primary tumor) can be considered. In such cases, the primary tumor should be surgically addressed when present, and prophylactic cholecystectomy should also be considered.

Octreotide is used to treat patients who have either the classical carcinoid syndrome or the watery diarrhea associated with vasoactive peptide secretion (VIPoma) and to prevent amine crisis associated with surgery, anesthesia, and chemotherapy in patients with functioning carcinoid tumors. A cardiology consultation and echocardiogram should be considered to assess whether the patient has carcinoid heart disease or before a major surgery.[10] Cardiac heart disease occurs in 11% to 66% of patients with the carcinoid syndrome.[18,19] The NCCN panel recommends (see CARC-5) that symptomatic patients with carcinoid syndrome, clinically significant tumor burden or progression (positive OctreoScan or increased biomarkers), or local effects (requires individual assessment) be treated octreotide.[10]

Doses of short-acting octreotide include 150-250 mcg administered subcutaneously (SubQ) 3 times daily (TID). The LAR formulation octreotide is used for the chronic (preventive) management of patients with the carcinoid syndrome; doses of LAR octreotide include 20 mg-30 mg intramuscularly (IM) every 3 to 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.[20-22]

The most common sites of metastases from carcinoids include regional/mesenteric lymph nodes, liver, bones, and lung. Whether symptomatic or not, resectable liver metastases should be considered for resection. For unresectable liver metastases, several options are recommended (see CARC-5), including (1) local ablative therapy (such as RFA, cryotherapy, microwave);[23,24] (2) hepatic regional therapy (arterial embolization, chemoembolization,[25] radioembolization)[26-31] (3) cytoreductive surgery may be considered if near complete resection can be achieved (category 2B); (4) clinical trial; (5) If no other options are feasible then systemic therapy (category 3) with cytotoxic agents such as interferon[21,32,33], temozolomide, dacarbazine, 5-fluorouracil and capecitabine can be used in patients with progressive metastases. Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a progression-free or overall survival benefit.

If painful bone metastases are present or weight-bearing bones are involved, recommended options include: (1) radiotherapy with or without bisphosphonates (category 2A for symptomatic and category 2B for asymptomatic disease); or (2) a clinical trial (see CARC-5).

For patients with lung metastases, resection is an option, if feasible. For patients with unresectable symptomatic lung lesions or tumor metastasis to the regional mesenteric lymph nodes, recommended options include a clinical trial or systemic therapy (if no other options are feasible)[34] (see CARC-5). Systemic therapy is an option (category 3) only when no other options are feasible because of the poor efficacy and toxicity of chemotherapy, Single-agent therapy and combination therapy with doxorubicin, 5-fluorouracil, dacarbazine, actinomycin-D, cisplatin, alkylating agents, etoposide, streptozotocin, and carboplatin have reported response rates ranging from 20% to 50%.[35-43]

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),[44-46] as well as inhibitors of mammalian target of rapamycin (mTOR).[29,47,48] Additionally, treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced

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carcinoid tumors.[49-52] Randomized trials to further evaluate the relative benefit and potential toxicities of many of these investigational treatments are anticipated.

Islet Cell Tumors (Pancreatic Endocrine Tumors)

The endocrine pancreas contains at least 5 types of cells that produce characteristic polypeptides. 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.[53] Although the peak incidence of occurrence is between ages 40 and 60 years, a significant number of patients diagnosed with islet cell tumors are under the age of 35.[53] Up to 50% of pancreatic endocrine tumors are non-functional, the remainder can manifest with clinically evident hormonal symptoms. The characteristics of functional endocrine tumors of the pancreas are summarized in Table 1.[54] Of these functioning tumors, up to 50% are insulinomas, and 90% of these are benign. About 50% are gastrinomas, and most (60% to 90%) of these are malignant with higher risk for the development of metastases. The remaining rare functioning islet cell tumors include glucagonoma, VIPoma, somatostatinoma, and pancreatic polypeptidoma (PPoma). Most of the nonfunctioning tumors (up to 90%) are malignant. Islet cell tumors occurring in patients with MEN 1 or MEN 2 are typically multiple, requiring different treatment strategies than those used for patients with sporadic pancreatic endocrine tumors that are usually solitary. Gastrinoma is the most common pancreatic islet cell tumor in patients with MEN 1 followed by insulinomas.

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, 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%.[55,56] Care should be taken in measuring Chromogranin A and interpreting the results as spuriously elevated levels of Chromogranin A have also 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.

Gastrinoma is often suspected in patients with severe gastroduodenal ulcer symptoms such as dyspepsia, sometimes accompanied by diarrhea. Evaluation includes measuring gastrin levels (basal and stimulated)[57] and gastric acidity. Diagnosis of gastrinoma can be confounded by the frequent use of proton pump inhibitors. 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 and 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 may be carried out as appropriate (see ISLT-1).

Insulinomas are generally small tumors that are best localized by transgastric ultrasound. Although 90% of insulinomas are benign, 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 supervised 72-hour fasting of the patient, with glucose and insulin testing (see ISLT-2). Patients with insulinoma have elevated levels of C-peptide. An insulin level greater than 3 mcIU/mL (usually greater than 6 mcIU/mL) when blood glucose is less than 40 to 45 mg/dL with an insulin-to-glucose ratio of 0.3 or

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less, reflecting the inappropriate secretion of insulin at the time of hypoglycemia document these tumors.[58-60]

Transgastric ultrasound has been shown to localize about 82% of pancreatic endocrine tumors.[61] Insulomas 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).[62] Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative.

For glucagonomas with diabetes, characteristic skin rash and diarrhea, the panel recommends a blood test for glucagon/blood glucose. 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.

Primary Treatment of Islet Cell Tumors (Pancreatic Endocrine Tumors)

Surgical resection is the optimal treatment for 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. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Octreotide should be used with caution in insulinomas because it can also suppress counter-regulatory hormones such as growth hormone, glucagon, and catecholamines. In this uncommon situation, octreotide can worsen hypoglycemia in some patients.[63]

Treatment of electrolyte imbalance with IV fluids, and octreotide may be useful (if OctreoScan positive) for stabilizing patients with glucagonoma or VIPoma.[10] Zinc supplementation is helpful in glucagonoma patients with severe skin rash. Venacaval filters and anticoagulation can be considered because of the increased risk of pulmonary emboli. Because of the severe weight loss, 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).

Laparoscopy should be considered for nonfunctioning tumors (see ISLT-1) to successfully locate and to stage the tumors. Depending on the size, location and type of tumor, recommended options for nonfunctioning pancreatic tumors include either (1) excision of the tumor with resection of peripancreatic lymph nodes; or (2) pancreaticoduodenectomy (ie, Whipple procedure) with dissection of peripancreatic nodes. For insulinomas, laparoscopic resection if possible is recommended. For rare functioning tumors such as somatostatinoma, ACTHoma, PTH-rp secreting tumors, 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 (category 2B); or (2) enucleation of tumors if identified at operation and duodenotomy with removal of periduodenal nodes (see ISLT-1). 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 with duodenectomy. Removal of the periduodenal nodes may be considered. Gastrinomas that are deeper or invasive 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

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pancreatectomy or tumor enucleation, with spleen preservation when possible.

The primary treatment for locoregional insulinoma, because they are primarily benign, is enucleation. This 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 the location of the tumor within the pancreas or invasion, then the following options may be considered (1) segmental resection of the pancreas; (2) pancreaticoduodenectomy; or distal pancreatectomy if possible with the preservation of the spleen depending on the site of the tumors (category 2B) (see ISLT-2).

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. Patients should receive trivalent vaccine before splenectomy.

As with nonfunctioning tumors, depending on the size, location and invasion of the tumor, recommended options for VIPoma, include either (1) excision of the tumor, distal pancreatectomy, and resection of peripancreatic lymph nodes and spleen; or (2) pancreaticoduodenectomy with dissection of peripancreatic nodes for tumors in the head of the pancreas (see ISLT-3).

Surveillance

All patients with pancreatic endocrine tumors should be followed-up 3-12 months after resection and annually thereafter with an H&P, appropriate tumor markers, and imaging studies such as CT /MRI (see ISLT-4).

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

Surgical resection is recommended for resectable locoregional recurrence (see ISLT-4).

Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases. Surgical excision, of both the primary tumor and liver metastases should be considered when possible. Caution is advised when performing resection, ablation, or intraarterial therapies after or during pancreaticoduodenectomy as these patients are at higher risk for hepatic septic complications due to the contaminated biliary tree. For extrahepatic or unresectable islet cell tumors, asymptomatic patients should either (1) undergo observation and follow-up with tumor markers and CT or MRI every 3 to 12 months; or (2) participate in a clinical trial (see ISLT-5).

For symptomatic or clinically significant tumor burden or significant disease progression, patients with a positive OctreoScan or elevated biomarkers can be treated with short-acting octreotide 150-250 mcg subcutaneously three times a day (category 2B). If this octreotide dose is tolerated and patients have a symptomatic response, then the panel recommends considering an initial monthly dose of 20-30 mg LAR octreotide intramuscularly. Subsequently, the number of injections and dose of LAR octreotide may be gradually increased, based on the patient's tolerance and response. In addition, specific agents (including diazoxide or histamine H2 antagonists) for controlling symptoms may be used, and clinical syndromes should be managed accordingly. If a tumor can be resected, either in the liver or lungs, the metastases with or without the primary tumor should be resected because such treatment can produce clinically significant palliation and prolonged survival.[64]

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Systemic chemotherapy is recommended for patients with unresectable liver or lung metastases. Trials using chemotherapeutic drugs including doxorubicin, streptozocin, 5-FU, temozolomide, and dacarbazine have established cytotoxic effects in pancreatic tumors (see ISLT-5). The combination of doxorubicin and streptozocin has a reported 69% objective response rate in the treatment of patients with advanced islet cell carcinoma.[65] A retrospective review from the M. D. Anderson Center, reported an objective response rate of 39% with the combination of 5-FU, doxorubicin and streptozocin.[66] Ramanathan et al.[67] reported on an ECOG study of single agent dacarbazine, which demonstrated a response rate of 34%. An oral regimen using temozolomide and thalidomide was found to be useful in a number of neuroendocrine malignancies. Regimens using temozolomide-based chemotherapy have also been studied in prospective trials that included small numbers of patients with pancreatic neuroendocrine tumors but need confirmation in larger studies.[68-70] In a phase II study in 29 patients with metastatic neuroendocrine tumors, temozolomide (150 mg/m^2 for seven days every 2 weeks) plus thalidomide (dose range 50-400 mg daily) was shown to produce response rates of 45% in islet cell tumors and 7% in carcinoids.[69]

A number of investigational therapies have shown preliminary evidence of activity in patients with advanced pancreatic neuroendocrine tumors. These include VEGF pathway inhibitors as well as inhibitors of mammalian target of rapamycin (mTOR). Sunitinib (category 2B) and everolimus (category 2B) have been added to the list of systemic therapy options for patients with advanced pancreatic endocrine tumors (see ISLT-5).

A phase III trial of sunitinib versus placebo in patients with metastatic pancreatic cancer showed that sunitinib prolonged progression free survival (11.5 versus 5.5 months). The overall response rate seen with sunitinib was 9.3% and it displayed an acceptable safety profile.[71] Independent Data Monitoring Committee recommended stopping this study early due to differences in efficacy.[71] An open-label, phase II study assessed the clinical activity of everolimus in patients with metastatic pancreatic neuroendocrine tumors who experienced progression on or after chemotherapy. Patients were stratified by prior octreotide therapy to either everolimus alone (n = 115) or everolimus plus long acting octreotide (n = 45).[14] This study confirmed that everolimus was well tolerated in patients with advanced pancreatic neuroendocrine tumors, either alone or in combination with octreotide LAR.

For patients with incurable liver metastases with dominant metastases, options include hepatic regional therapies such as arterial embolization, radioembolization,[26-30] and chemoembolization;[72] and local ablative therapy (RFA, cryotherapy, microwave),[23,24] which may provide effective cytoreductive therapy of the liver metastases (category 2B).

For painful bony metastases, systemic chemotherapy; or radiotherapy with or without bisphosphonates (category 2A for symptomatic and category 2B for asymptomatic disease) can be considered. Clinical trials are an option for all patients with unresectable metastatic disease.

Neuroendocrine Unknown Primary Tumors

Neuroendocrine carcinomas of unknown primary site are uncommon. According to a SEER database analysis a primary tumor site could not be found in 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

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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. 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); thereby OctreoScan has greatly improved the sensitivity and specificity in localizing certain neuroendocrine tumors.[73] In addition, radionucleotide bone imaging (bone scan) is recommended to evaluate patients suspected of having metastatic bone disease. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan can be occasionally useful in finding a primary tumor.

If the primary tumor site is found by imaging studies, the tumors are managed as per the treatment algorithms for individual sites (see NE-1). If a primary tumor is not identified, additional workup includes core needle or fine needle aspiration biopsy. Functional adrenal neoplasms and suspected carcinoid tumor syndrome needs to be ruled out prior to biopsy or invasive procedures.

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 (see NE-A). Blood chromogranin levels are usually elevated in patients with neuroendocrine tumors. The grade of differentiation is also useful for profiling these tumors and predicting prognosis and should be included in the evaluation.[74]

Primary Treatment of Neuroendocrine Unknown Primary Tumors

The endpoint of the evaluation is the pathologic categorization of the 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 in section below “Poorly Differentiated (High Grade or Anaplastic)/ Small Cell tumors” (also see ANAP-1). Well and moderately differentiated tumors should be treated similarly to typical “Carcinoids Tumors” described above (also see CARC-5).

Adrenal Gland Tumors

Adrenocortical carcinomas (ACCs) are rare (incidence 1-2 per million).[74-76] 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.[77,78] 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).[79-83] 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, usually Cushing’s syndrome with or without virilization.[75,88-90] Signs and symptoms associated with hypersecretion of cortisol 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]

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Evaluation of Adrenal Gland Tumors

Functional evaluation: The following tests can be considered for evaluation of hypercortisolemia: Fasting serum glucose; 24-hour urinary free cortisol; dexamethasone suppression test (1mg of dexamethasone at bedtime followed by a fasting serum cortisol at 8 AM).[88] For evaluation of sex steroids serum dehydroepiandrosterone sulfate (DHEA-S), androstenedione, testosterone, 17-OH-progesterone are helpful.[88] For evaluation of mineralocorticoid excess: potassium and aldosterone to renin ratio can be determined. The kidney hormone renin normally stimulates the adrenal glands to release aldosterone. High levels of both renin and aldosterone are normally present when the body is trying to conserve fluid and salt (sodium). Patients with primary aldosteronism, in contrast have elevated plasma levels of aldosterone and low levels of renin activity. The plasma aldosterone-renin ratio in patients with primary hyper-aldosteronism is usually greater than 30.[92] A pheochromocytoma should always be excluded with normal plasma free metanephrine or normetanephrine levels or a 24-hour urine fractionated metanephrine (see AGT-1).

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.[93] Because the lung and liver are the most common sites of metastatic spread, thoracic and abdominal scans are integral to the staging workup of ACCs. 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]

Primary Treatment of Adrenal Gland Tumors

Laparoscopic excision of the tumors is the preferred method of removal of benign adrenal tumors. When tumors are thought to be malignant, an open or laparoscopic assisted operation should be done as these malignant tumors are prone to rupture.[96,97]

Patients who experience symptoms secondary to adrenocortical steroid secretion may require treatment for palliation of symptoms such as hypertension, hyperglycemia, hypokalemia, and muscle atrophy. Mitotane with steroid replacement is often used as a first-line agent due to its tumor lytic effects,[78] but is not tolerated by some patients. Other adrenostatic agents include ketoconazole, metyrapone, and mitotane.

Ketoconazole is most commonly used at doses of 400-1200 mg per day due to its easy availability and relatively tolerable toxicity profile.

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.[98-100] The largest study retrospectively analyzed 177 patients with resected ACC (stages I-III) treated in Italy and Germany.[101] In the Italian cohort, nearly half received adjuvant mitotane (47/102 patients) at doses ranging from one to five 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 control, 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. Due to the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisone) should be prescribed in order to prevent adrenal insufficiency. For patients with high grade adrenal carcinoma suspected of having gross

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residual disease due to invasion and incomplete resection the NCCN panel recommends adjuvant mitotane therapy or radiation therapy to the adrenal tumor bed. For functional tumors, the NCCN panel suggests follow-up with imaging and biomarkers every 3-6 months (see AGT-5).

Treatment of Metastatic or Unresectable Adrenal Carcinoma

Surgical resection of the tumor with removal of the adjacent lymph nodes is recommended in patients with localized adrenal carcinoma. Open adrenalectomy is preferred due to increased risk for local recurrence when done laparoscopically.

Treatment strategies for metastatic adrenal carcinomas include resection with or without adjuvant chemotherapy and/or radiation for low grade tumors or palliative chemotherapy or radiation for high grade tumors.

For functional metastatic adrenal carcinomas that are low grade, according to the NCCN panel, resection may be considered if greater than 90% of the tumor can be removed. Otherwise the option is systemic therapy preferably in a clinical trial (see AGT-5). 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, yielding an overall response rate of 49% (by WHO criteria) and a complete hormonal response in 9 of 16 patients with functioning tumors.[102] Another study examined the combination of mitotane with streptozocin and reported an objective response rate of 36%.[103] There are no randomized data to support these findings, and 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. However, enrolling the patients in clinical trials is preferred.

In patients with high grade metastatic disease, external beam radiation therapy may be of benefit to the metastatic sites or to adrenal tumor bed.

Pheochromocytoma/Paragangliomas

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla, and they occur in 0.1% to 1% of hypertensive patients. 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, whereas extra-adrenal pheochromocytomas usually occur within the para-aortic sympathetic chain. Ectopic pheochromocytomas/paragangliomas are more likely to be malignant, (about 40% versus 10%). Paragangliomas are extra adrenal pheochromocytomas that arise from extra adrenal sympathetic ganglia. About 40% of paragangliomas are functional, secreting norepinephrine and normetanephrine.

Evaluation of Pheochromocytoma/paragangliomas

If pheochromocytoma is suspected, plasma-free metanephrine or normetanephrine tests and/or 24-hour urine level for metanephrine, catecholamines, creatinine, and optional dopamine establishes the diagnosis in most patients. Imaging studies including chest/abdominal CT scan and MRI are recommended. An MIBG scan is highly effective in localizing pheochromocytomas (including extra-adrenal tumors) and

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is recommended, especially when the tumor is not identified by either MRI or CT scan.[104] 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 (see PHEO-1). Genetic counseling…

Primary Treatment of Pheochromocytoma/paraganglioma

Surgical resection is the mainstay of treatment. All patients must receive preoperative blocking agent to counteract the effects of the catecholamines on target tissues.[105] 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, a non-selective [alpha]-blocker) and forced hydration for at least 7 days (see PHEO-1). Adrenergic blockage of [alpha] 1-receptors with prazosin or doxazosin can also be performed,[106] when long term therapy is required for metastatic pheochromocytoma. 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.

A laparoscopic approach, when feasible, is the preferred treatment for adrenal medullary tumors, including pheochromocytomas.[107] If possible, cytoreductive resection is also recommended for the treatment of isolated distant metastases. Cytoreductive resection, if possible, with or without RT is recommended for locally unresectable disease. 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 dacarbazine[108] (see PHEO-2); (3) iodine-131-MIBG therapy may be considered as compassionate use on a clinical trial after confirming dosimetrically that tumors take up MIBG.[109,110]

Surveillance

Surveillance intervals are similar to those for other neuroendocrine tumors. H&P blood pressure and tumor markers should be measured 3-12 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 (see PHEO-2). In addition, imaging studies should be done if 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 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/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 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.

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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, 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 Neoplasias (MEN)

The MEN syndromes are caused by tumors that affect endocrine organs. There are 2 main types of MEN: MEN 1 and MEN 2. MEN1 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 associated with medullary thyroid cancer (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 *MEN 1* (chromosomal locus 11q13)[111] whereas MEN 2, and familial MTC are associated with germline-activating mutations of the proto-oncogene *RET* (chromosomal locus 10q11.2).[112] Table 2 summarizes the tumors in patients with multiple endocrine neoplasia. Of interest, the somatic mutation of the menin gene is the most common in sporadic or nonhereditary tumors-parathyroid adenomas, gastrinomas, insulinomas, and bronchial carcinoids.[81] Somatic *RET* mutations are also found in sporadic MTC.[113] All patients with MTC should be tested for germline mutation as about 10% of patients with presumed sporadic MTC have a de novo mutation of the *RET* oncogene.

MEN 1

MEN 1 (or Wermer's 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.[81] About 35% of patients have functioning tumors of the pituitary, and an additional 20% of patients also have or develop nonfunctioning islet cell tumors.[114] 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, Cushing's syndrome or acromegaly related to a pituitary tumor, solitary or bilateral adrenal tumors (which can cause Cushing's syndrome). Ectopic Cushing's syndrome may be caused by a pancreatic islet cell tumor, thymic carcinoid or a bronchial carcinoid tumor, or MTC. Cushing's

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syndrome may 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 approximately 60% of gastrinomas are malignant.[115,116] 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 2.

Evaluation of MEN1 syndromes

The algorithm lists 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 hormonal levels, and (2) imaging tests needed to localize the site of the tumor or hyperplasia, (3) additionally, genetic counseling for patients suspected of having MEN 1 syndrome, which may include genetic testing to identify one of the characteristic predisposing germline mutations. 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 the MEN1 gene.

Pancreatic Tumors in MEN1

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 Table2. The workup for pancreatic islet cell tumors (see MEN1-1, MEN1-2, MEN1-3) in the context of MEN 1 is similar to that for sporadic islet cell tumors (see ISLT-1, ISLT-2). For details on the evaluation for pancreatic tumors, see the section on “Islet Cell Tumors (Pancreatic Neuroendocrine Tumors).”

Parathyroid Tumors in MEN1

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 (see MEN1-3). 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. Also, genetic counseling of the patient and family is recommended which may also include genetic testing.

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

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accurate and the abnormal parathyroid glands are best identified during surgery.[117,118] However as mentioned sestamibi scanning can identify ectopically situated parathyroid tumors.

Pituitary Tumors in MEN1

Various laboratory tests are available for evaluating suspected pituitary tumors. These tests include an overnight dexamethasone suppression test or a 24-hour urinary free cortisol test for patients with Cushing's syndrome, and an optional corticotropin-releasing hormone (CRH) stimulation test with bilateral petrosal vein sampling for adrenocorticotrophic hormone (ACTH) in patients with suspected pituitary Cushing's syndrome (see MEN1-4). The latter procedure can distinguish between a possible ACTH-secreting pituitary tumor and an ectopic source of ACTH (basal and after CRH, 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 (see MEN1-4). 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, together with IGF-1, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol also aid in the recognition of nonfunctioning tumors. In addition, an MRI of the sella with contrast is recommended to evaluate whether a pituitary adenoma is present (see MEN1-4). Additionally as mentioned previously, if MEN 1 is suspected, genetic counseling of the patient and family is recommended which may also include genetic testing.

Primary Treatment of MEN1 Syndromes

Primary therapy 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.

Primary Treatment of Pancreatic Tumors in MEN1

All patients who might require splenectomy should receive trivalent vaccine (ie, pneumococcus, haemophilus influenza b, and meningococcus group C), preoperatively. 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 benign or malignant) tumors in the setting of MEN1. 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 preoperatively or with intraoperative ultrasound (see MEN1-2).[119]

For gastrinomas, before surgical intervention, any symptoms of gastrin hypersecretion may be treated with histamine H2-receptor antagonists or with proton pump inhibitors. If the tumor is occult and primary tumor is not found, the panel recommends several options: (1) observation (category 2B) (see MEN1-1); (2) duodenotomy and tumor enucleation with periduodenal node dissection with or without spleen-preserving distal pancreatectomy (category 2B). In patients with sporadic MEN 1,

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70% of gastrinomas are associated with extrapancreatic tumors in the duodenum; thus, treatment includes tumor enucleation and duodenotomy with excision of small tumors with periduodenal lymph node dissection. 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 with proximity to the main pancreatic duct should be managed by pancreaticoduodenectomy with periduodenal node dissection. Gastrinomas suspected to be in the distal pancreas are treated with either distal pancreatectomy with spleen preservation or tumor enucleation and duodenotomy with regional lymphadenectomy.

Insulinomas are not found in the duodenum but may occur anywhere throughout the pancreas. Recommended options for resectable sporadic insulinomas include laparoscopic removal or open surgery with tumor enucleation or distal pancreatectomy. For patients with MEN1 in contrast most recommend subtotal pancreatectomy and excision of tumors from the head of the pancreas.

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 (see MEN1-2). Splenectomy is almost always performed, because the tumors are usually malignant, relatively large, and situated in the tail of the pancreas. For unresectable disease, prophylactic cholecystectomy is recommended, and octreotide therapy should be considered.[10]

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 (see MEN1-3). For PPoma, somatostatinoma and other nonfunctional tumors of the pancreas, the panel recommends resection with lymph node dissection (see MEN1-3).

Primary Treatment Parathyroid Tumors in MEN1

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 (see MEN1-3). 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.[120,121] 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 would include determining blood calcium levels at 6 months and yearly thereafter.

Primary Treatment of Pituitary Tumors in MEN1

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 dopamine-agonist (bromocriptine, pergolide.[122] For a patient with a symptomatic pituitary

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prolactinoma (as evidenced by visual changes or increasing pituitary size), and for those with no response or intolerance to dopamine agonist, or with disease of sudden onset (indicating intratumoral hemorrhage) surgery may be necessary. If complete resection is not achieved, recommendations include re-excision and postoperative radiotherapy followed by target-organ hormone replacement therapy and medical suppression with dopamine-agonist therapy if elevated prolactin levels persist. If mass effects are present or pregnancy is desired, resection is recommended (see MEN1-5).

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 be considered (see MEN1-5). 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 less without associated visual changes. However, treatment with octreotide for 2 weeks or less (category 2B) may be considered before surgery for larger tumors (more than 1 cm), those associated with visual changes, or symptoms. 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 (see MEN1-6).

Surveillance

All patients with MEN1 should be followed with an H&P, tumor marker and calcium levels as appropriate and with imaging studies such as CT /MRI every 3-6 months for the first year after resection. The follow-up tests must be repeated every 6 months, 1-3 years after surgery and annually thereafter (see MEN1-7). All close family members of patients with MEN1 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 1. 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 also have (or develop) pheochromocytoma (usually bilateral, 50%) and hyperparathyroidism (about 25%). Most patients with MEN 2B in addition to MTC also have mucosal neuromas, intestinal ganglioneuromas, or ectopic lenses as well as a Marfanoid habitus; 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 proceeded 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*.[123,124]

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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, facial flushing), or pheochromocytoma (headaches, increased perspiration, rapid heart rate) or hyperparathyroidism. In addition, nearly all MEN 2B patients have a Marfanoid habitus, mucosal neuromas, poor dentition, 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 (see MEN2-1).

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 MEN2A, 2B and familial MTC

Before surgery, basal calcitonin and carcinoembryonic antigen (CEA) levels should be measured, because these test results help guide the extent of nodal dissection, 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. 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. In patients with a positive RET oncogene test that are scheduled for a prophylactic thyroidectomy, 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.[125,126] MTC patients should have catecholamine and metabolite measurements to rule out a diagnosis of a coexisting pheochromocytoma (see next paragraph) before they have a thyroidectomy and lymph node dissection. 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.[127,128] The urinary dopamine level tests are optional, according to the panel recommendation. Localization tests include CT or MRI with 0.5-cm sections through the adrenal area and with optional use of MIBG scan or OctreoScan (see MEN2-2). These radionucleotide scans may be useful if the CT/MRI scans are negative.

A parathyroid workup consists of blood calcium levels, PTH determinations, and a 24-hour urine collection to assess both calcium and creatinine levels. A neck ultrasound, or a sestamibi scan, in patients with primary hyperparathyroidism is optional. As previously mentioned evaluation for pheochromocytoma is essential before the administration of any anesthetic or before an invasive procedure (see MEN2-2).

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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 NCCN Thyroid Carcinoma Guidelines and also see PHEO-1), respectively. 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[125,126] and before the age of six for patients with MEN 2A and familial MTC. As mentioned previously, a total of about 25% of patients with MEN 2A either have or will develop hyperparathyroidism. Patients with MEN 2 and familial MTC are also more prone to post-operative hypoparathyroidism, because the thyroid gland is removed for treatment of C-cell hyperplasia or MTC. Most surgeons recommend, when possible, leaving normal parathyroid glands that are marked with a clip or stitch in situ during thyroid surgery. When a normal parathyroid gland cannot be preserved in patients with MEN 2A, it should be autotransplanted to the forearm. If hyperparathyroidism recurs documenting an elevated PTH level in the ipsilateral basilic vein localizes the tumor which can be removed or subtotally resected. Recurrent primary hyperparathyroidism occurs in almost 20% of patients with MEN 2A and 33% of MEN1, but only rarely in patients with sporadic hyperparathyroidism. 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. Some surgeons recommend prophylactic parathyroidectomy of all normal parathyroid glands with immediate autotransplantation in patients with MTC. The consensus of the NCCN panel was for selective resection of abnormal parathyroid glands and for leaving normal parathyroid glands in situ when possible. When the blood supply to a parathyroid gland is possibly compromised the parathyroid gland should be autotransplanted.

Surveillance

For MEN 2 patients, a routine H&P including blood pressure and markers should be performed 3 -6 months after thyroid resection, then every 6 months during the first 3 years, and annually thereafter. Imaging studies (eg, ultrasound, CT, MRI) should be performed selectively, as clinically indicated. After surgery for MTC, repeat calcitonin and CEA tests should be performed at 3-6 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.

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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	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

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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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