Neuroendocrine Tumors

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PRINCIPLES OF PATHOLOGY

Required Information:

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

2019 WHO Classification and Grading Criteria for Neuroendocrine Neoplasms of the Gastrointestinal Tract and Hepatopancreatobiliary Organs

Terminology	Differentiation	Grade	Mitotic rate[a] (mitoses/2 mm^2)	Ki-67 index[a] (percent)
NET, G1	Well-differentiated	Low	<2	<3
NET, G2	Well-differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well-differentiated	High	>20	>20
Neuroendocrine carcinoma (NEC), small cell type (SCNEC)	Poorly differentiated	High[b]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[b]	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm	Well or poorly differentiated[c]	Variable[c]	Variable[c]	Variable[c]

- Functioning NETs should have the same pathologic diagnosis as the non-functioning NETs at the same anatomic site, since the functional status is based upon clinical symptoms and should not alter the pathologic diagnosis.
- Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, and others.
- Although not entirely specific, lung origin is favored by thyroid transcription factor 1 (TTF-1); intestinal origin by CDX2; and pancreatic NETs by Isl1 and PAX8.

- Note that in cases where an accurate mitotic rate is precluded by inadequate tissue, such as in small biopsy samples including fine-needle aspiration (FNA), the Ki-67 index is the preferred method of establishing the proliferative rate.

- The liver is a common metastatic site for NET, and these metastatic lesions are often hypervascular. Therefore, multiphasic imaging of the liver with contrast enhancement (arterial and portal venous phase) should be performed whenever possible.

- Without a known tumor or specific clinical concern, imaging of the chest is optional for GI NET and imaging of the brain is generally not required for well-differentiated NET.
- For metastatic well-differentiated NET, anatomic imaging should generally be performed every 12 weeks–12 months based on clinical or pathologic signs of aggressiveness.
- Consider MRI over CT to minimize radiation risk.
- MRI preferred for pregnant patients.

- Evaluation with somatostatin receptor (SSR) imaging to assess receptor status and distant disease is appropriate. This is especially important for determining whether a patient may benefit from SSR-directed therapy.

- Octreotide SPECT/CT is much less sensitive for defining SSRpositive disease than SSR-PET/CT, and typically cannot be done in combination with multiphase CT or MRI. Therefore, SSR-PET/CT or SSR-PET/MRI is preferred.

- After potentially curative surgery, surveillance is recommended for at least 10 years for most patients. In certain cases, surveillance may be extended beyond 10 years based on risk factors such as age and risk of recurrence.

- Echocardiogram (transthoracic echocardiography, TTE) is important for the evaluation of carcinoid heart disease (CHD) and should include morphologic evaluation of the valves (especially tricuspid and pulmonic) and the right heart.

BIOCHEMICAL TESTING

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

SURGICAL PRINCIPLES

- Standard oncologic surgery (eg, distal pancreatectomy/splenectomy or pancreaticoduodenectomy) is appropriate for most resectable, non-metastatic pancreatic NETs.
- For patients with small (<2 cm) low-grade NETs, decisions on surgery versus active surveillance need to be individualized, based on tumor size/characteristics and patient characteristics:

◊ Tumors <1 cm have a lower malignant potential than tumors measuring 1–2 cm.

◊ Other radiographic characteristics of small tumors (homogeneous, well-circumscribed) may also correlate with benign behavior.

◊ Patient characteristics such as age and comorbidities are important when determining whether surveillance is appropriate.

- Resection of gastrointestinal NETs should include adequate regional lymph node resection (including all palpable disease where feasible) and thorough exploration of synchronous primary tumors (15%–30% incidence).

- Resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumor that has regressed should be considered for selected patients with adequate performance status.

- Cytoreductive surgery for distant metastatic disease (typically but not exclusively hepatic) is routinely recommended in patients in whom >90% of disease can be safely resected by surgery with or without ablation.
- This strategy is particularly appropriate for patients with relatively indolent metastatic small bowel NETs, and less appropriate for patients in whom rapid progression of disease is expected after surgery.
- Patients who are symptomatic from hormonal syndromes, such as carcinoid syndrome, typically derive palliation from cytoreductive surgery.

- Liver-directed therapies (eg, liver resection, thermal ablation, chemoembolization) for hepatic metastases from NETs following pancreatoduodenectomy are associated with increased risk for cholangitis and liver abscess.

- Octreotide therapy should be administered parenterally prior to induction of anesthesia in patients with functional NETs to prevent carcinoid crisis.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

- Systemic therapy may not be appropriate for every patient with locoregionally advanced or metastatic disease.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for NETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.

Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)[a,b,c]			
	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases (if progression on octreotide or lanreotide)[c]	• Everolimus[d,1,2] • PRRT with 177Lu-dotatate (if SSR-positive imaging and progression on octreotide/lanreotide) (category 1 for progressive mid-gut tumors)[e]	• None	• Consider (listed in alphabetical order): ▸ Cytotoxic chemotherapy, if no other options feasible (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.)

Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)			
	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases	• Everolimus[13] (category 1 for progressive disease) 10 mg by mouth, daily • Octreotide[a,b] LAR or lanreotide[a,5] (if SSR-positive imaging) • Sunitinib[14] (category 1 for progressive disease) 37.5 mg by mouth, daily • Temozolomide + capecitabine[15] (preferred when tumor response is needed for symptoms or debulking) • PRRT with 177Lu-dotatate (if SSR-positive imaging and progression on octreotide or lanreotide)[e]	• Cytotoxic chemotherapy options considered in patients with bulky, symptomatic, and/or progressive disease include: ◊ 5-FU + doxorubicin + streptozocin (FAS)[16] ◊ Streptozocin + doxorubicin[17] ◊ Streptozocin + 5-FU[18] ◊ FOLFOX (leucovorin + 5-FU + oxaliplatin)[19] ◊ CAPEOX (capecitabine + oxaliplatin)[20]	• Consider belzutifan in the setting of germline *VHL* alteration in patients with progressive PanNETs[h,21]

Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell (Extrapulmonary)		
Resectable disease: • Cisplatin + etoposide[10] • Carboplatin + etoposide[22] • FOLFOX • FOLFIRI • Temozolomide ± capecitabine	Locoregional Unresectable/Metastatic Disease: • Cisplatin + etoposide[10] • Carboplatin + etoposide[22] • Cisplatin + irinotecan • Carboplatin + irinotecan • FOLFOX • FOLFIRI • FOLFIRINOX[23,24] • Temozolomide ± capecitabine • Nivolumab + ipilimumab (category 2B) (only for metastatic disease with progression)[25] • Pembrolizumab[i]	Chemoradiation (concurrent/sequential) for locoregional unresectable disease • Cisplatin + etoposide • Carboplatin + etoposide

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) WITH 177LU-DOTATATE

- Lutetium 177Lu-dotatate is a radiolabeled SSA used as PRRT.
- It is approved by the FDA for the treatment of SSR-positive gastroenteropancreatic (GEP) NETs, including foregut, midgut, and hindgut NET in adults.
- Currently there are no randomized data, but there are reports of treatment efficacy and favorable outcomes when PRRT is used for PanNETs, pheochromocytomas, paragangliomas, and bronchopulmonary/thymic NETs.
- If feasible, participation in clinical trials of PRRT is strongly recommended for patients with such rare groups of NET.

- Key Eligibility:
- Well-differentiated NET
- SSR expression of NET as detected by SSR-PET/CT or SSR PET/MR.
- Adequate bone marrow, renal and hepatic function

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

PRINCIPLES OF LIVER-DIRECTED THERAPY FOR NEUROENDOCRINE TUMOR METASTASES

- **Indications for Hepatic Arterial Embolization**

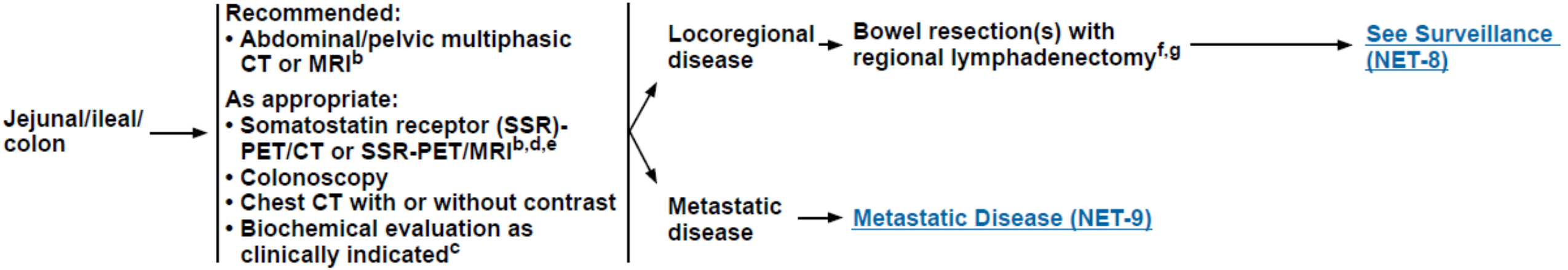
- Embolization is recommended for well-differentiated NETs with liver-dominant, unresectable metastases that are:
- Symptomatic on an SSA or following another form of systemic therapy
- Progressive on an SSA or following another form of systemic therapy
- Presenting with bulky liver disease; embolization may be employed as debulking therapy without waiting for progression.

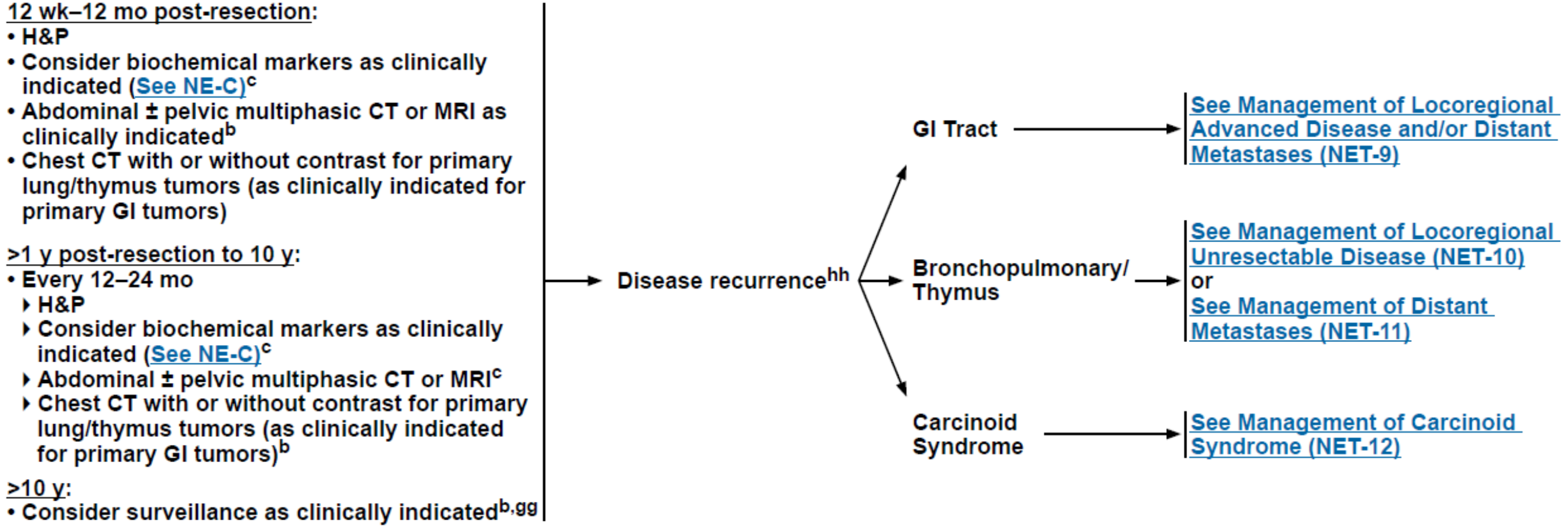
- Objective radiologic response rates average approximately 60%, with symptom palliation in approximately 85% of patients with hormonal syndromes.

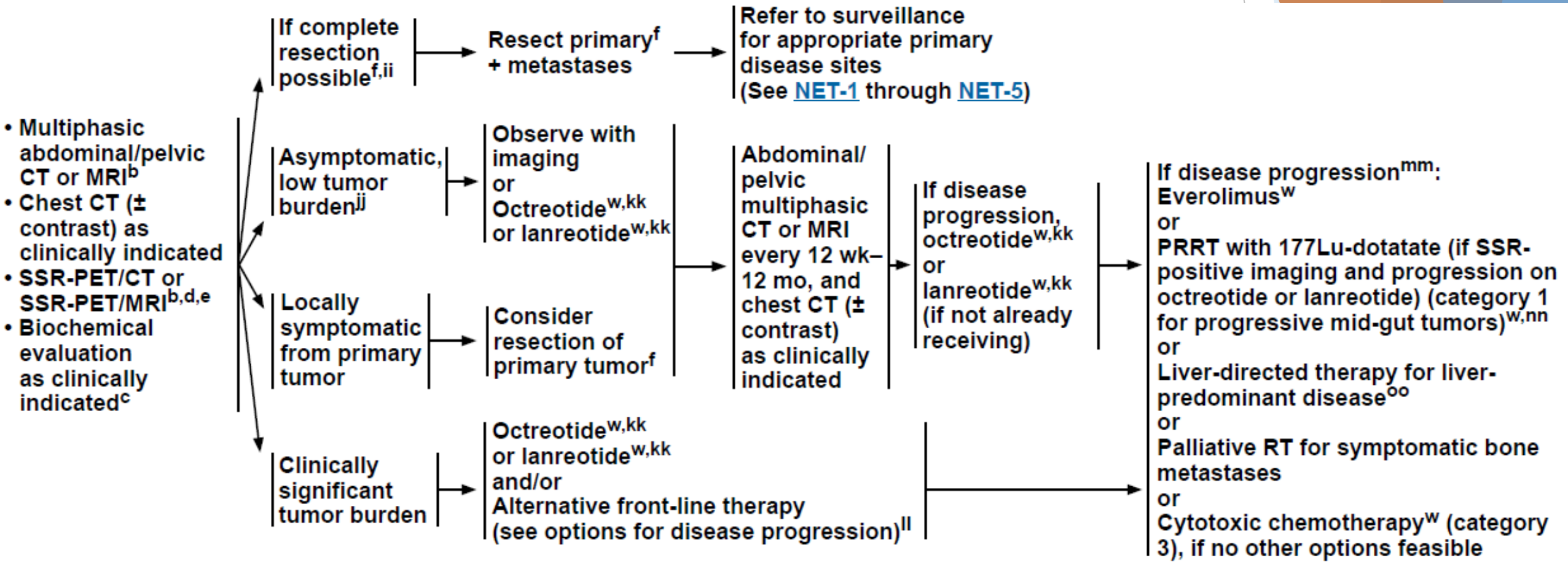
- Relative contraindications include significant baseline liver dysfunction (jaundice, ascites) and a liver tumor burden >70%.

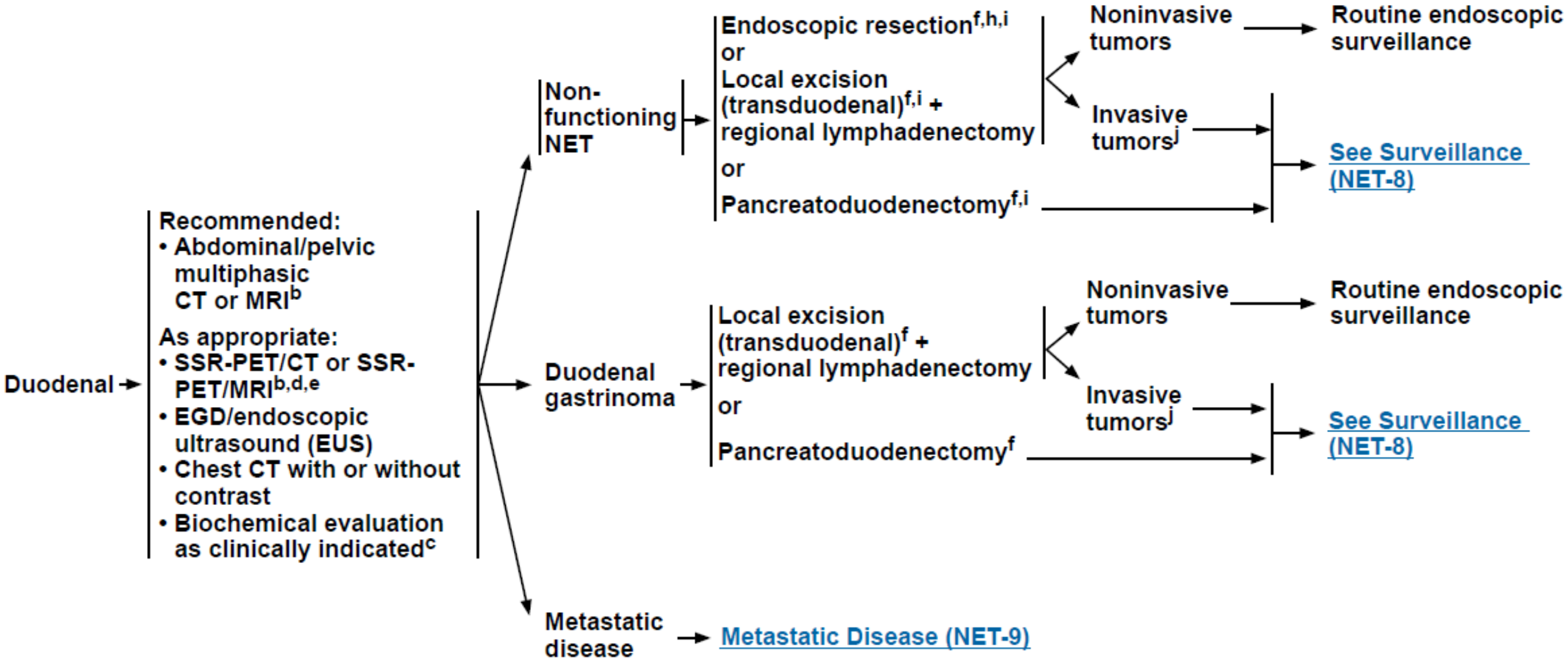
- Infectious complications occur in about 20% of cases following TAE/TACE and 8% after TARE, even with broad-spectrum antibiotic coverage.

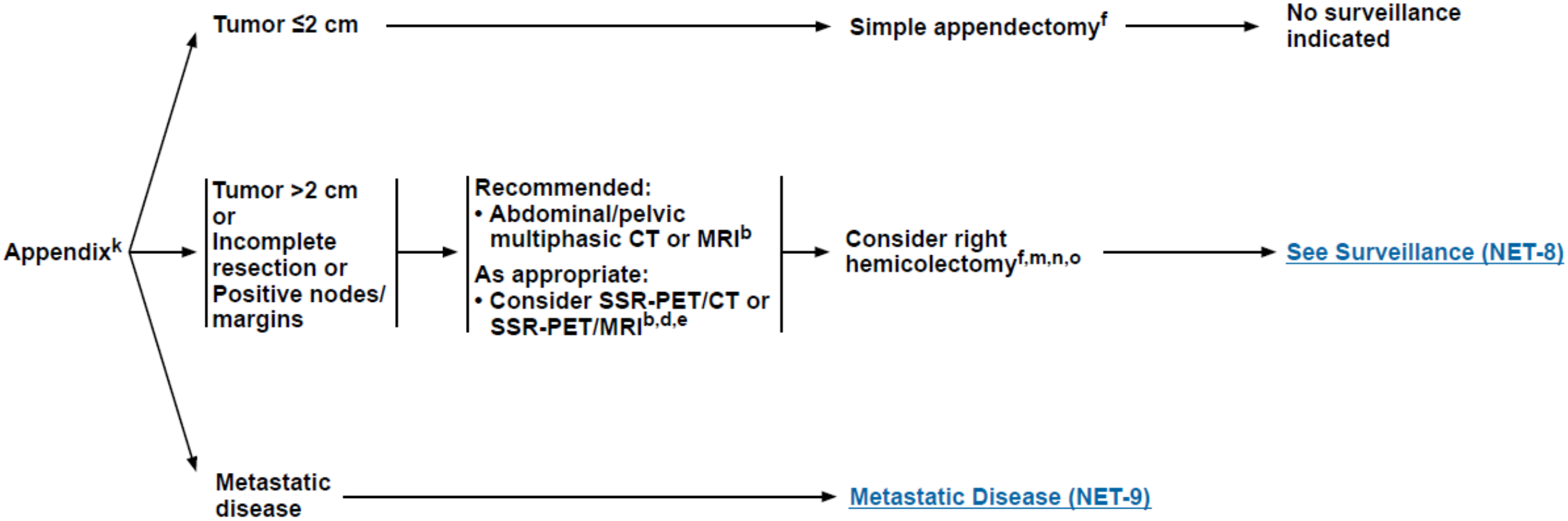
- Percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to four lesions each smaller than 3 cm.

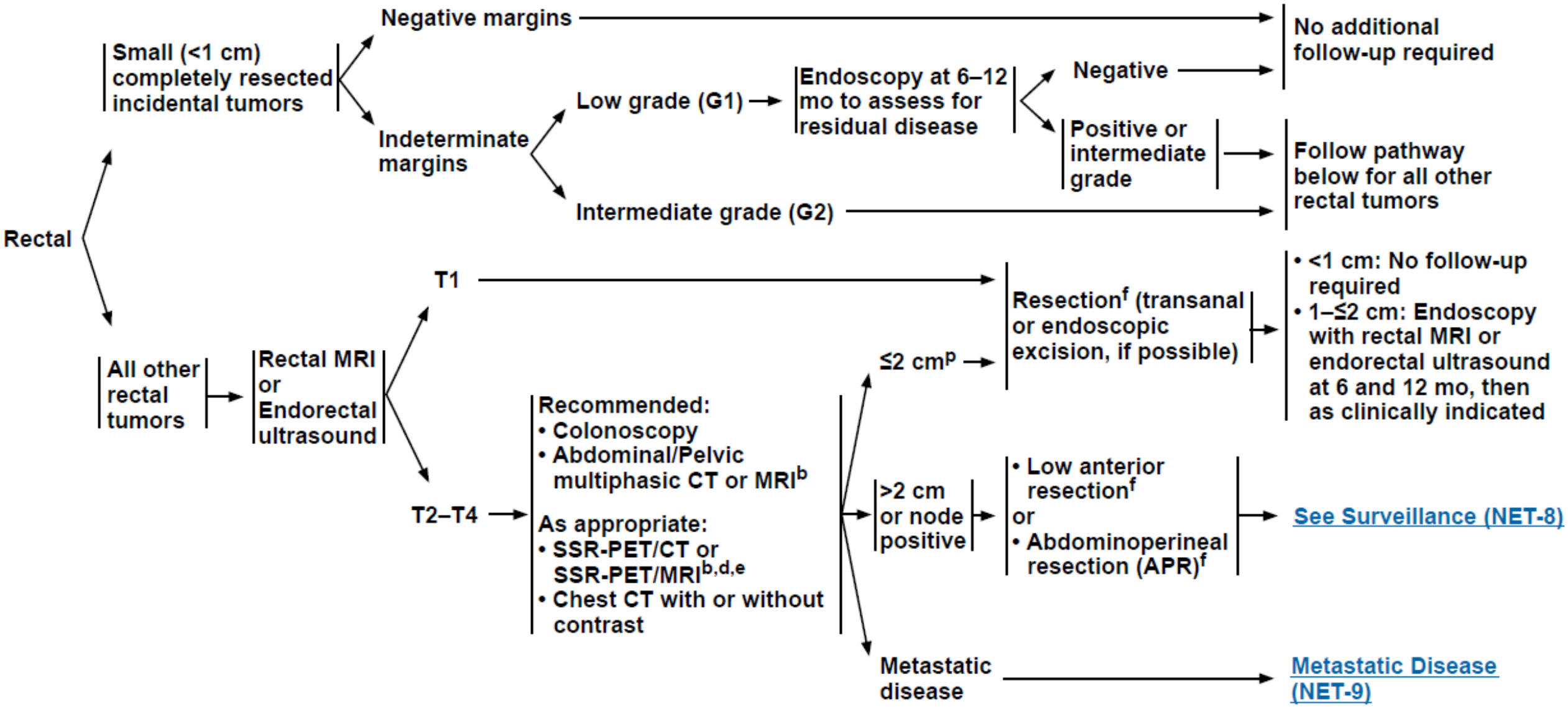

Jejunal/ileal/ colon
Recommended:
• Abdominal/pelvic multiphasic CT or MRI[b]
As appropriate:
• Somatostatin receptor (SSR)-PET/CT or SSR-PET/MRI[b,d,e]
• Colonoscopy
• Chest CT with or without contrast
• Biochemical evaluation as clinically indicated[c]
Locoregional disease
Bowel resection(s) with regional lymphadenectomy[f,g]
See Surveillance (NET-8)
Metastatic disease
Metastatic Disease (NET-9)

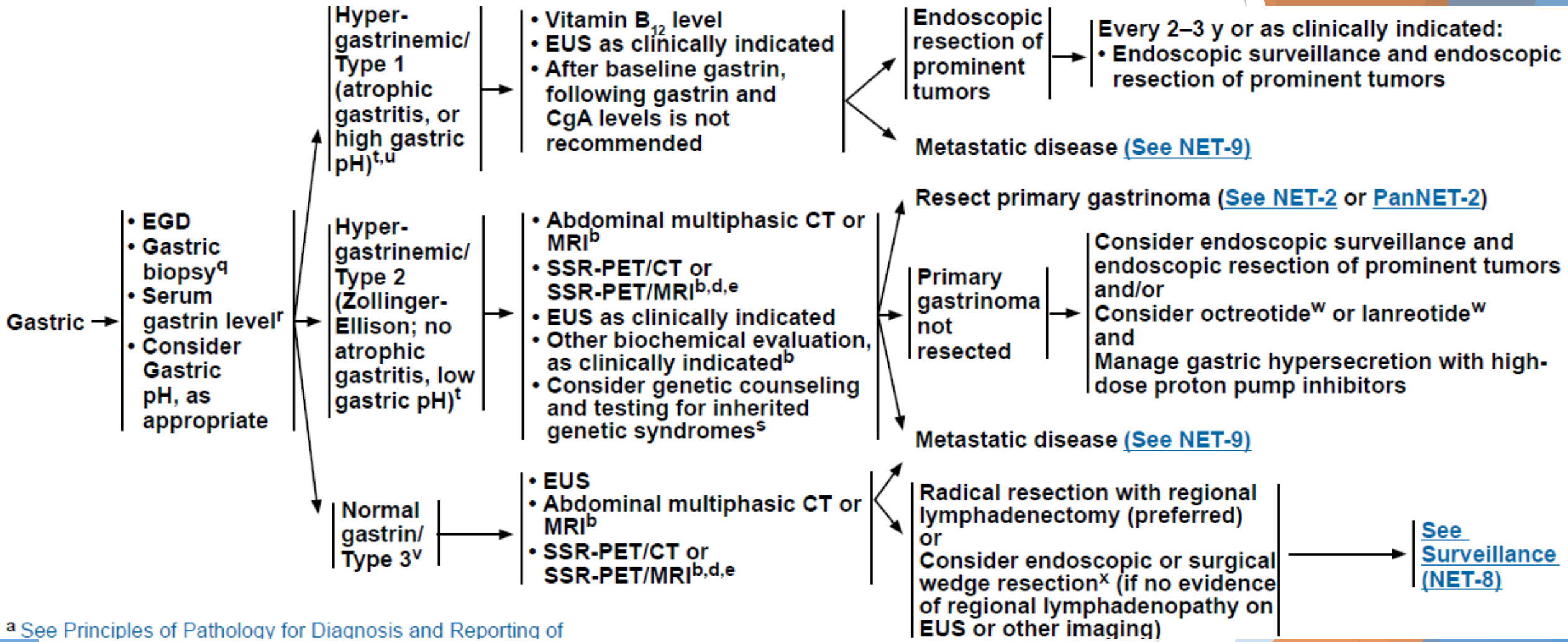

12 wk–12 mo post-resection:
• H&P
• Consider biochemical markers as clinically indicated (See NE-C)c
• Abdominal ± pelvic multiphasic CT or MRI as clinically indicatedb
• Chest CT with or without contrast for primary lung/thymus tumors (as clinically indicated for primary GI tumors)
>1 y post-resection to 10 y:
• Every 12–24 mo
▸ H&P
▸ Consider biochemical markers as clinically indicated (See NE-C)c
▸ Abdominal ± pelvic multiphasic CT or MRIc
▸ Chest CT with or without contrast for primary lung/thymus tumors (as clinically indicated for primary GI tumors)b
>10 y:
• Consider surveillance as clinically indicatedb,gg
Disease recurrencehh
GI Tract
See Management of Locoregional Advanced Disease and/or Distant Metastases (NET-9)
Bronchopulmonary/ Thymus
See Management of Locoregional Unresectable Disease (NET-10)
or
See Management of Distant Metastases (NET-11)
Carcinoid Syndrome
See Management of Carcinoid Syndrome (NET-12)


• Multiphasic abdominal/pelvic CT or MRI[b]
• Chest CT (± contrast) as clinically indicated
• SSR-PET/CT or SSR-PET/MRI[b,d,e]
• Biochemical evaluation as clinically indicated[c]
If complete resection possible[f,ii]
Resect primary[f] + metastases
Refer to surveillance for appropriate primary disease sites (See NET-1 through NET-5)
Asymptomatic, low tumor burden[jj]
Observe with imaging or Octreotide[w,kk] or lanreotide[w,kk]
Locally symptomatic from primary tumor
Consider resection of primary tumor[f]
Abdominal/ pelvic multiphasic CT or MRI every 12 wk–12 mo, and chest CT (± contrast) as clinically indicated
If disease progression, octreotide[w,kk] or lanreotide[w,kk] (if not already receiving)
Clinically significant tumor burden
Octreotide[w,kk] or lanreotide[w,kk] and/or Alternative front-line therapy (see options for disease progression)[ll]
If disease progression[mm]: Everolimus[w] or PRRT with 177Lu-dotatate (if SSR-positive imaging and progression on octreotide or lanreotide) (category 1 for progressive mid-gut tumors)[w,nn] or Liver-directed therapy for liver-predominant disease[oo] or Palliative RT for symptomatic bone metastases or Cytotoxic chemotherapy[w] (category 3), if no other options feasible


Duodenal
Recommended:
• Abdominal/pelvic multiphasic CT or MRI[b]
As appropriate:
• SSR-PET/CT or SSR-PET/MRI[b,d,e]
• EGD/endoscopic ultrasound (EUS)
• Chest CT with or without contrast
• Biochemical evaluation as clinically indicated[c]
Non-functioning NET
Endoscopic resection[f,h,i] or Local excision (transduodenal)[f,i] + regional lymphadenectomy or Pancreatoduodenectomy[f,i]
Noninvasive tumors
Routine endoscopic surveillance
Invasive tumors[j]
See Surveillance (NET-8)
Duodenal gastrinoma
Local excision (transduodenal)[f] + regional lymphadenectomy or Pancreatoduodenectomy[f]
Noninvasive tumors
Routine endoscopic surveillance
Invasive tumors[j]
See Surveillance (NET-8)
Metastatic disease
Metastatic Disease (NET-9)


Appendix[k]
Tumor ≤2 cm
Simple appendectomy[f]
No surveillance indicated
Tumor >2 cm or Incomplete resection or Positive nodes/ margins
Recommended:
• Abdominal/pelvic multiphasic CT or MRI[b]
As appropriate:
• Consider SSR-PET/CT or SSR-PET/MRI[b,d,e]
Consider right hemicolectomy[f,m,n,o]
See Surveillance (NET-8)
Metastatic disease
Metastatic Disease (NET-9)


Rectal
Small (<1 cm) completely resected incidental tumors
Negative margins
No additional follow-up required
Indeterminate margins
Low grade (G1)
Endoscopy at 6–12 mo to assess for residual disease
Negative
Positive or intermediate grade
Follow pathway below for all other rectal tumors
Intermediate grade (G2)
All other rectal tumors
Rectal MRI or Endorectal ultrasound
T1
Resection[f] (transanal or endoscopic excision, if possible)
• <1 cm: No follow-up required
• 1–≤2 cm: Endoscopy with rectal MRI or endorectal ultrasound at 6 and 12 mo, then as clinically indicated
≤2 cm[p]
T2–T4
Recommended:
• Colonoscopy
• Abdominal/Pelvic multiphasic CT or MRI[b]
As appropriate:
• SSR-PET/CT or SSR-PET/MRI[b,d,e]
• Chest CT with or without contrast
>2 cm or node positive
• Low anterior resection[f]
or
• Abdominoperineal resection (APR)[f]
See Surveillance (NET-8)
Metastatic disease
Metastatic Disease (NET-9)



[a] See Principles of Pathology for Diagnosis and Reporting of