Taipei Veterans General Hospital Practices Guidelines for

Pancreatic neuroendocrine tumor

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WHO classification of GEP NETs 1980 – 2017

WHO 1980	WHO 2000/2004	WHO 2010	WHO 2017
Islet cell tumour (adenoma/ carcinoma)	Well-differentiated endocrine tumour/carcinoma (WDET; WDEC)	Neuroendocrine tumour NET G1/G2	Neuroendocrine tumour **NET G1/G2/G3** (Well differentiated neuroendocrine neoplasm)
Poorly differentiated endocrine carcinoma	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	Neuroendocrine carcinoma NEC G3 large or small cell type	Neuroendocrine carcinoma **NEC G3** (Poorly differentiated neuroendocrine neoplasm), large or small cell type
	Mixed exocrine-endocrine carcinoma MEEC	Mixed adeno-neuroendocrine carcinoma MANEC	Mixed neuroendocrine-nonneuroendocrine neoplasm **MiNEN**
Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions	

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

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm^2)	Ki-67 index*
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High†	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated‡	Variable‡	Variable‡	Variable‡

LCNEC, Large-cell neuroendocrine carcinoma; MiNEN, Mixed neuroendocrine – non-neuroendocrine neoplasm; NEC, Neuroendocrine carcinoma;
NET, Neuroendocrine tumour; SCNEC, Small-cell neuroendocrine carcinoma.

Histopathology 2020, 76, 182 – 188.

Well Differentiated Pancreatic Neuroendocrine Tumor (NET grade 1,2,3)

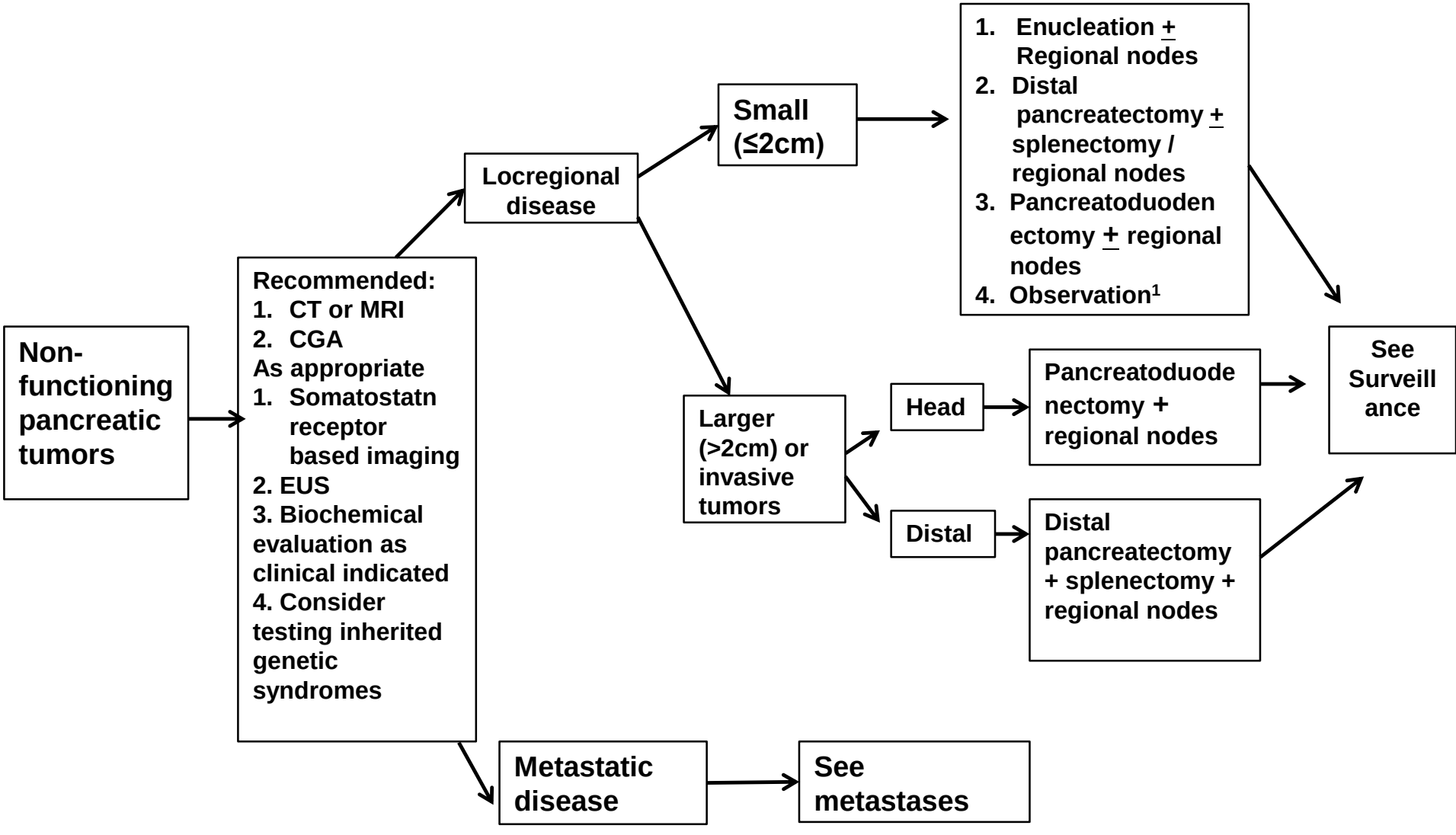
Pretreatment work-ups- Pancreatic neuroendocrine tumor

- **History and physical exam**
- **CBC, platelets, PT/APTT and chemistry profile**
- **Multiphasic CT or MRI**
- **Tumor markers: CGA, NSE**
- **Hormone (See next page)**
- **Optional studies**
  - Gene analysis : MEN-1 and VHL gene (小兒科牛道明實驗室)
  - WBBS if Symptoms (+)
  - Octreoscan/Ga68 PET CT
  - FDG PET CT

Hormone related studies

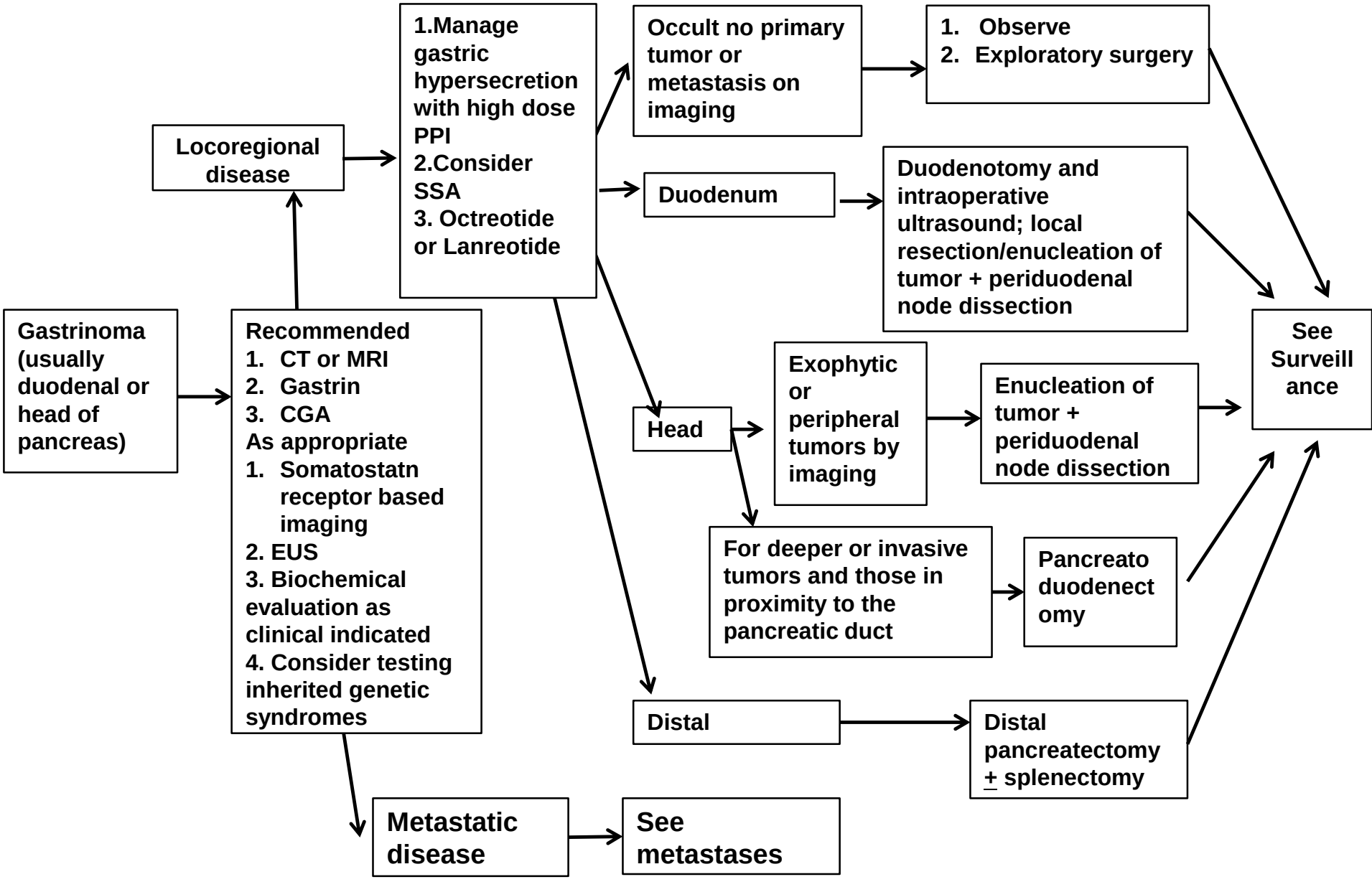
- Carcinoid tumors
  - 5-HIAA (24-h urine)
  - Chromogranin A (category 3)
- PanNET
  - Chromogranin A (category 3)
- Gastrinoma
  - Gastrin
- Insulinoma
  - Proinsulin
  - Insulin/glucose ratio
  - C-peptide
- VIPoma
  - VIP
- Glucagonoma
  - Glucagon
  - Blood glucose
  - CBC
- Other pancreas
  - Somatostatin
  - Pancreatic polypeptide
  - Calcitonin
  - PTH-related peptide
- Pheochromocytoma/paraganglioma
  - Metanephrines (plasma and urine)
  - Catecholamines (urine)
  - Dopamine (urine)[2]
- Pituitary
  - Growth hormone/IGF-1
  - Prolactin
  - LH/FSH
  - TSH
  - Alpha subunits
  - ACTH
- Ectopic hormones
  - ACTH
  - GRH
  - GHRH

Non-Functional PNET

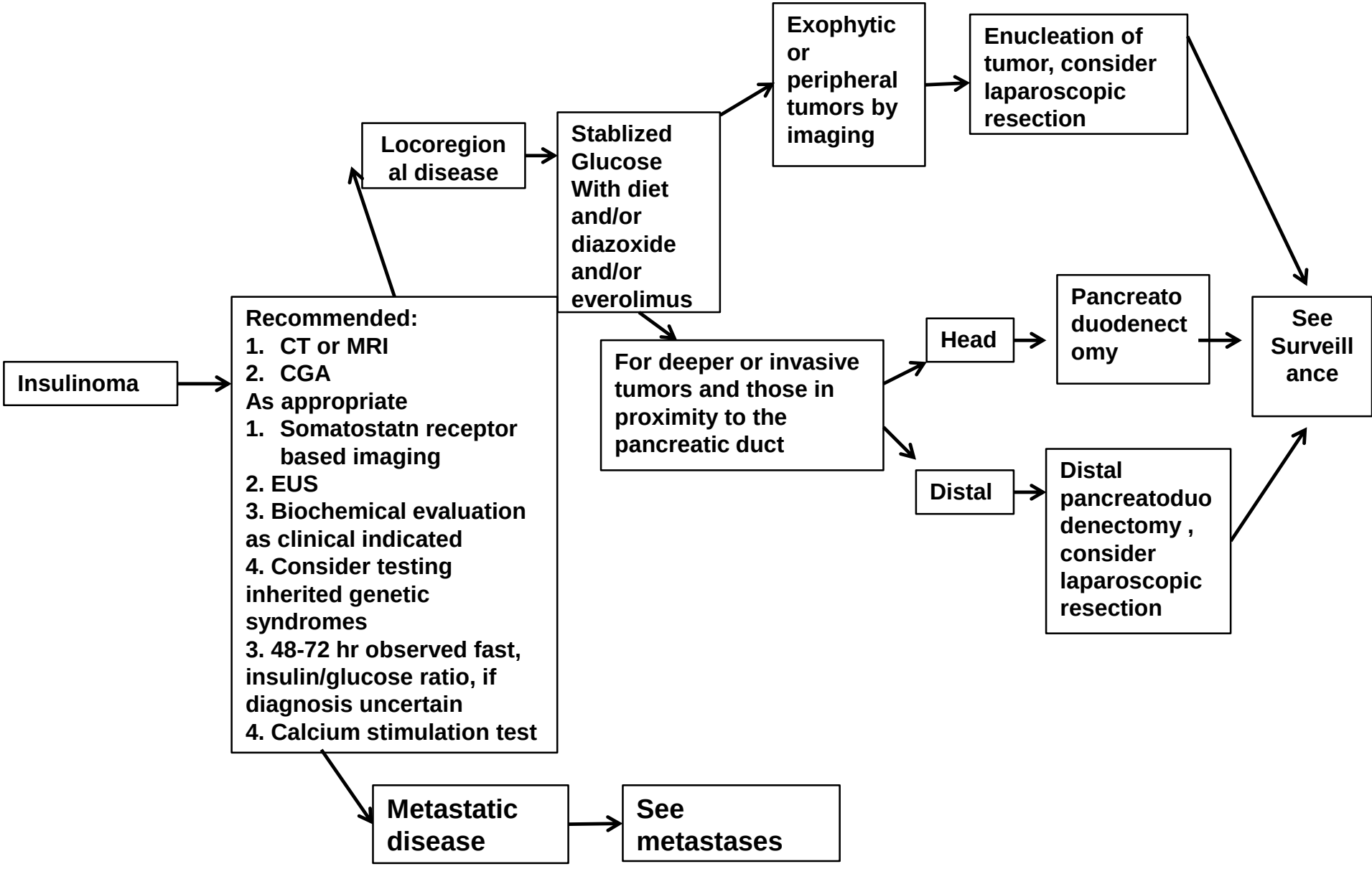


Observation in only selected cases: tumor ≤ 2cm, incidentaly discovered, low grade, non-functional, low expression in PET CT . Decision based on estimated surgical risk, site of tumor and patient comorbidities

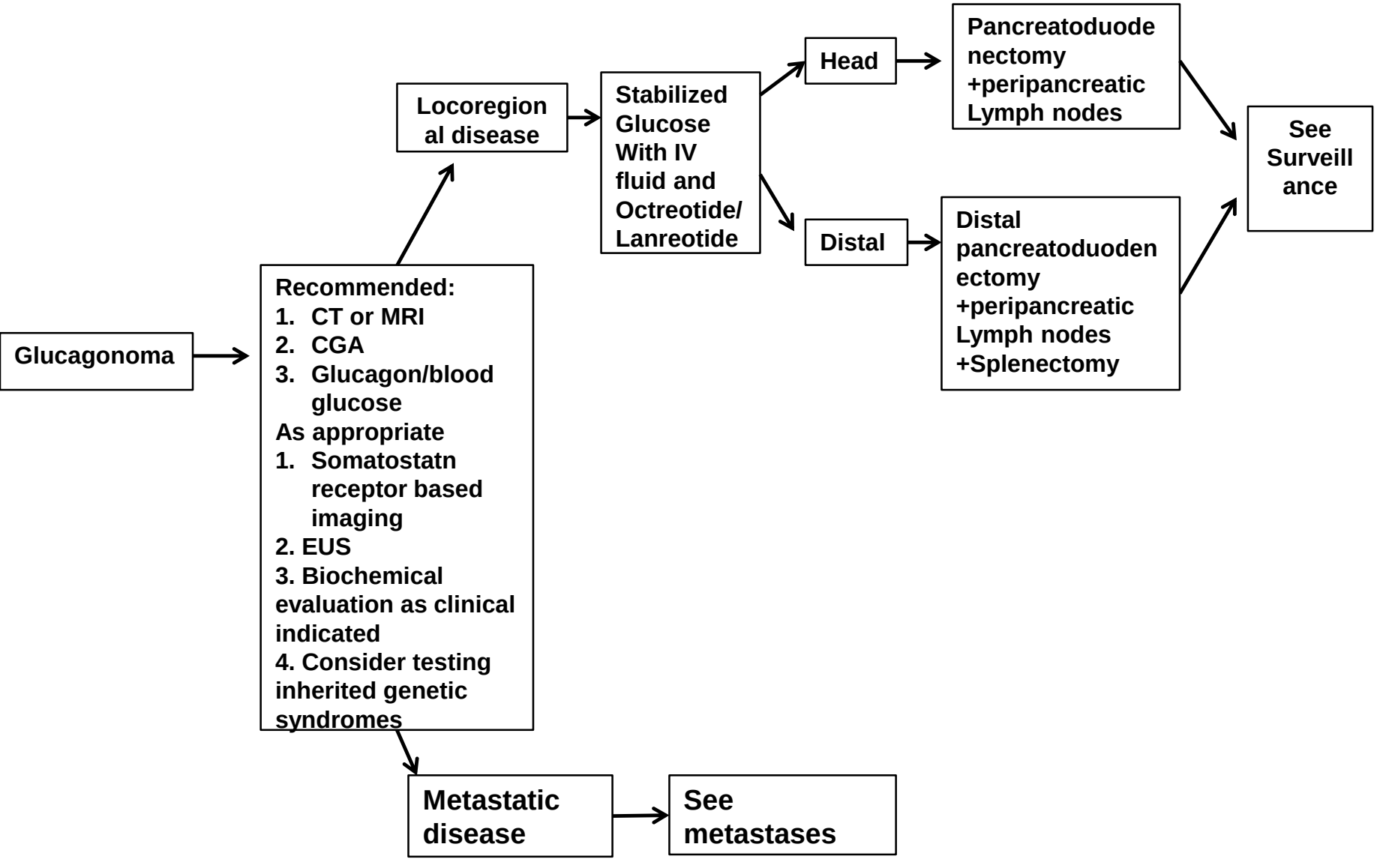
Gastrinoma


Gastrinoma (usually duodenal or head of pancreas)
Recommended
1. CT or MRI
2. Gastrin
3. CGA
As appropriate
1. Somatostatn receptor based imaging
2. EUS
3. Biochemical evaluation as clinical indicated
4. Consider testing inherited genetic syndromes
Locoregional disease
1.Manage gastric hypersecretion with high dose PPI
2.Consider SSA
3. Octreotide or Lanreotide
Occult no primary tumor or metastasis on imaging
1. Observe
2. Exploratory surgery
Duodenum
Duodenotomy and intraoperative ultrasound; local resection/enucleation of tumor + periduodenal node dissection
Head
Exophytic or peripheral tumors by imaging
Enucleation of tumor + periduodenal node dissection
For deeper or invasive tumors and those in proximity to the pancreatic duct
Pancreato duodenect omy
Distal
Distal pancreatectomy + splenectomy
See Surveill ance
Metastatic disease
See metastases

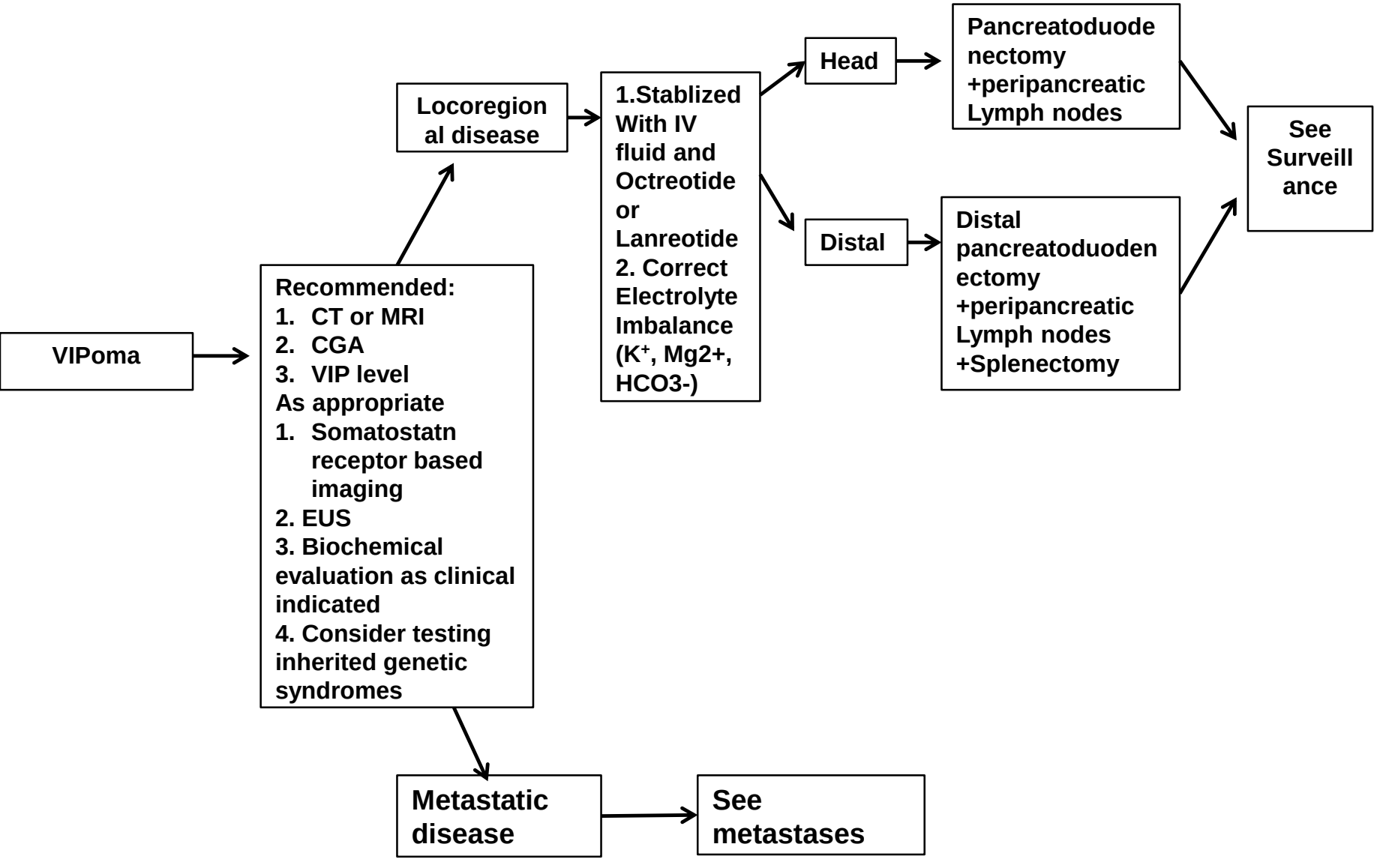
Insulinoma


Insulinoma
Recommended:
1. CT or MRI
2. CGA
As appropriate
1. Somatostatn receptor based imaging
2. EUS
3. Biochemical evaluation as clinical indicated
4. Consider testing inherited genetic syndromes
3. 48-72 hr observed fast, insulin/glucose ratio, if diagnosis uncertain
4. Calcium stimulation test
Locoregional disease
Stablized Glucose With diet and/or diazoxide and/or everolimus
Exophytic or peripheral tumors by imaging
Enucleation of tumor, consider laparoscopic resection
For deeper or invasive tumors and those in proximity to the pancreatic duct
Head
Pancreatoduodenectomy
Distal
Distal pancreatoduodenectomy , consider laparoscopic resection
See Surveillance
Metastatic disease
See metastases

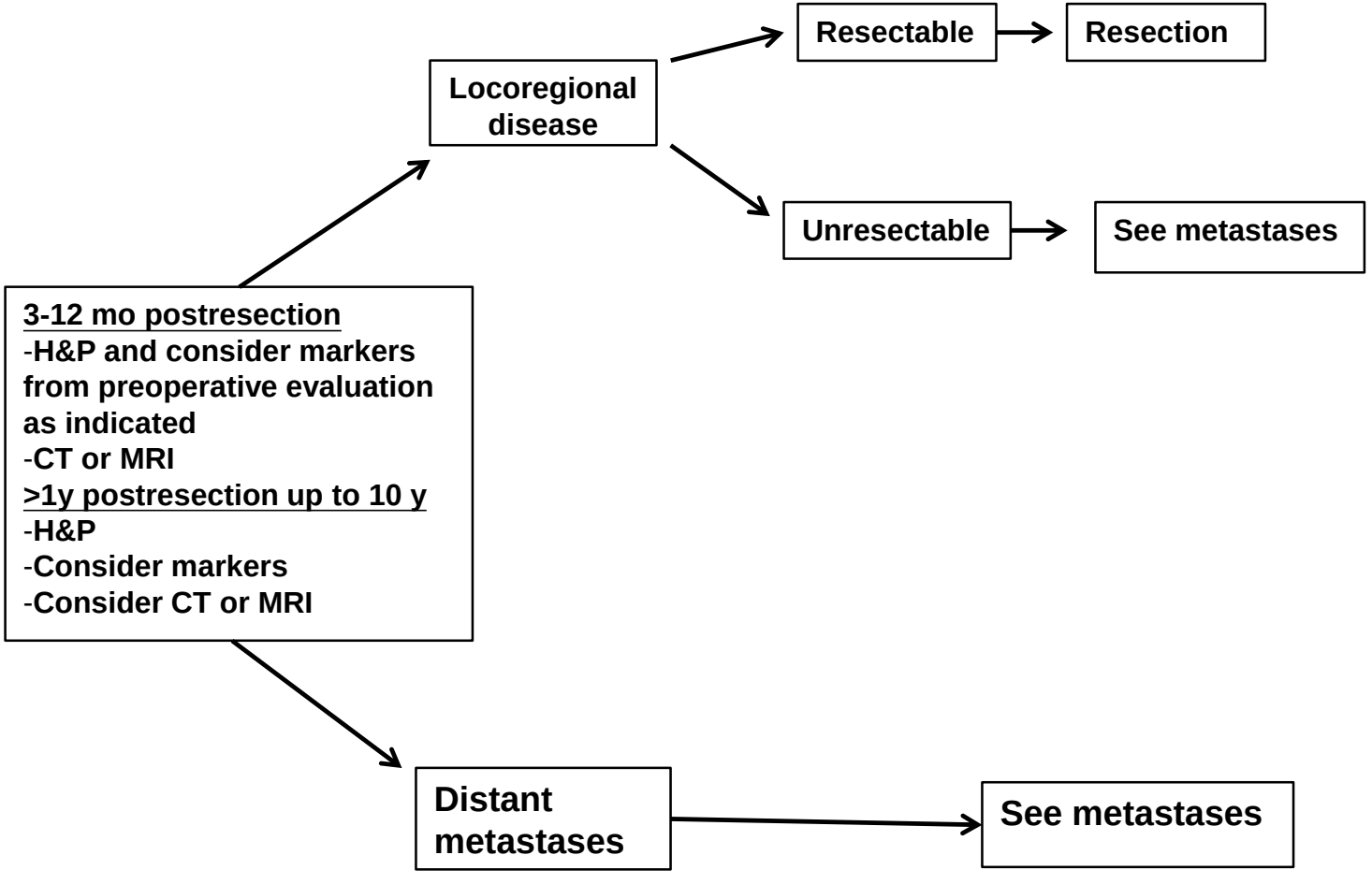
Glucagonoma



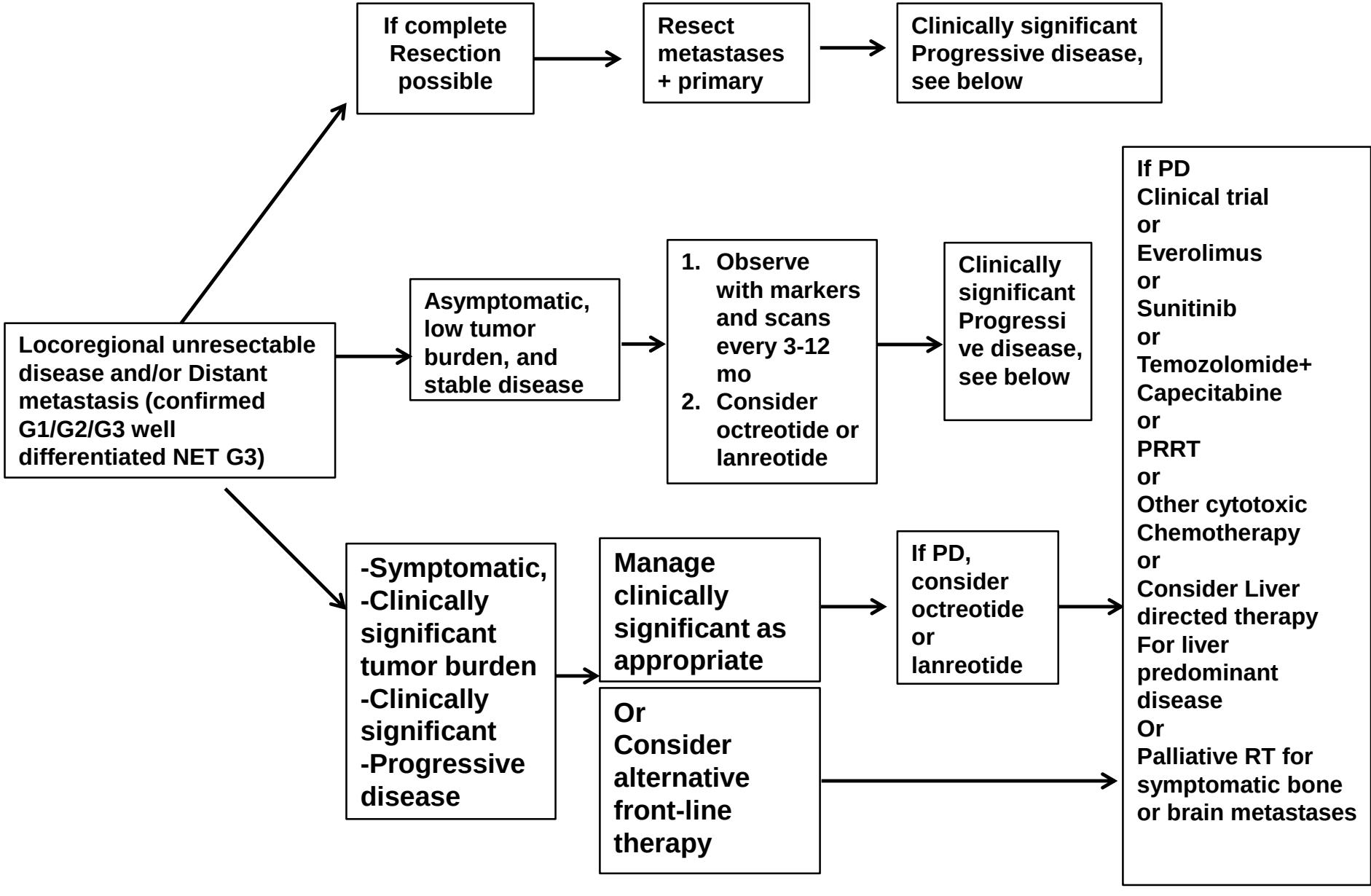
VIPoma


VIPoma
Recommended:
1. CT or MRI
2. CGA
3. VIP level
As appropriate
1. Somatostatn receptor based imaging
2. EUS
3. Biochemical evaluation as clinical indicated
4. Consider testing inherited genetic syndromes
Locoregional disease
1.Stablized With IV fluid and Octreotide or Lanreotide
2. Correct Electrolyte Imbalance (K+, Mg2+, HCO3-)
Head
Pancreatoduodenectomy +peripancreatic Lymph nodes
Distal
Distal pancreatoduodenectomy +peripancreatic Lymph nodes +Splenectomy
See Surveillance
Metastatic disease
See metastases

Surveillance

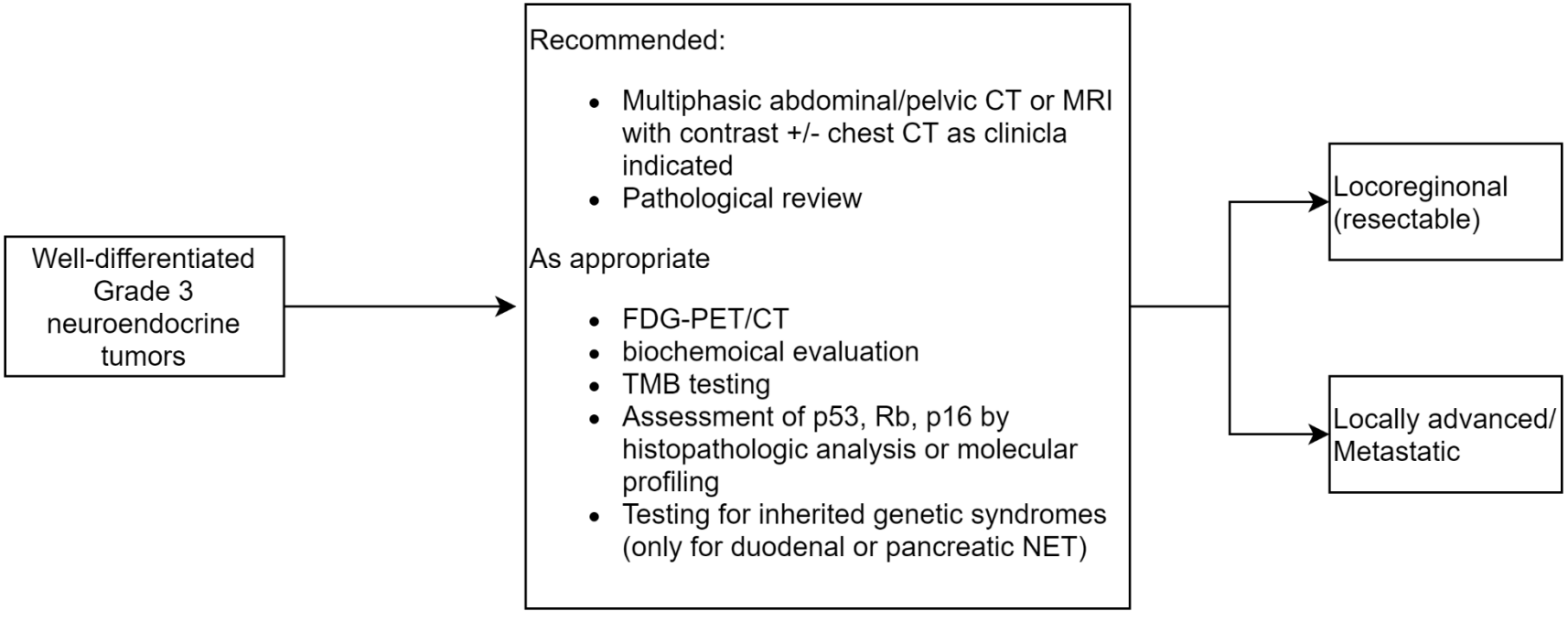


Metastases

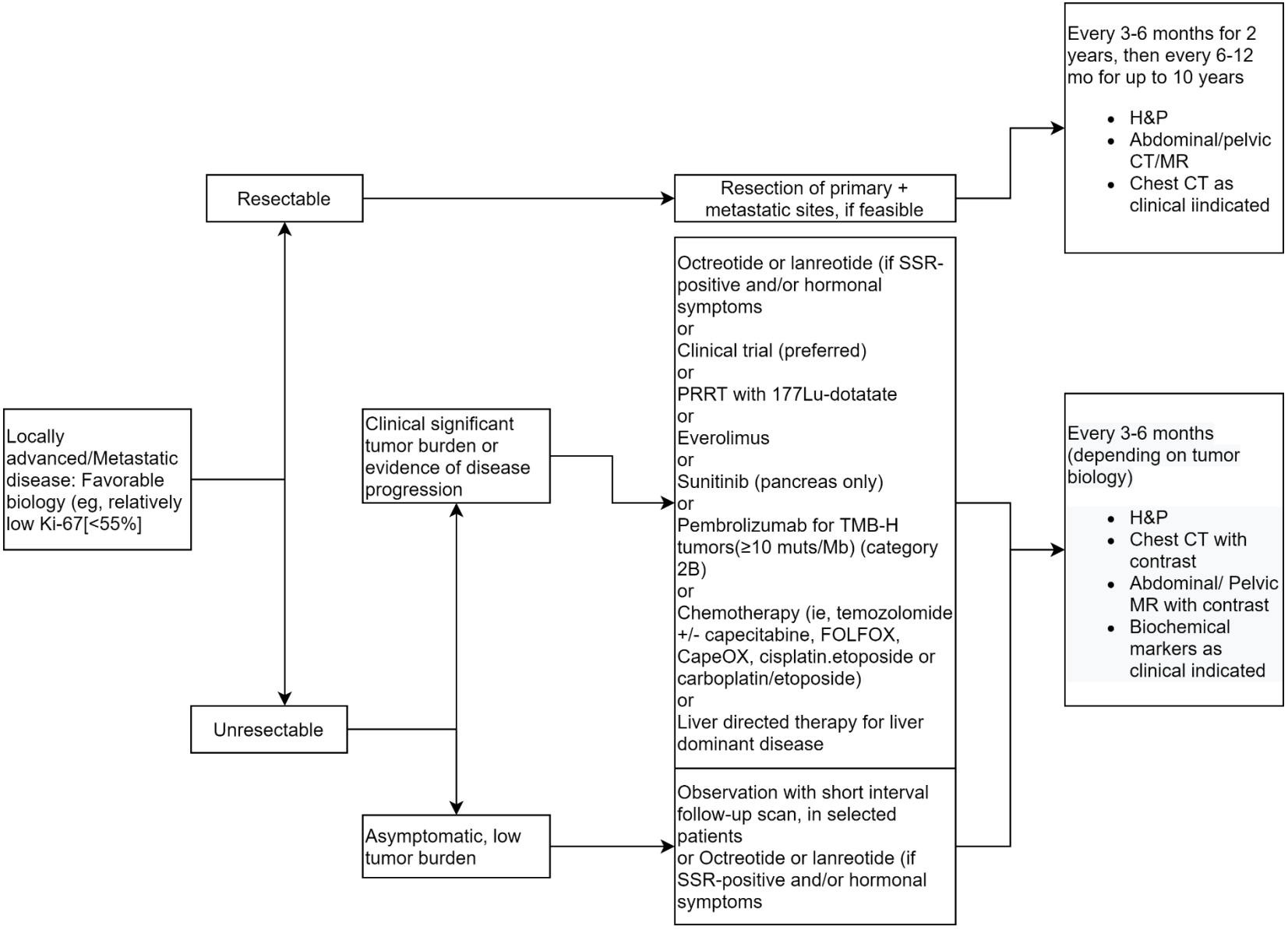

If complete Resection possible
Resect metastases + primary
Clinically significant Progressive disease, see below
Locoregional unresectable disease and/or Distant metastasis (confirmed G1/G2/G3 well differentiated NET G3)
Asymptomatic, low tumor burden, and stable disease
1. Observe with markers and scans every 3-12 mo
2. Consider octreotide or lanreotide
Clinically significant Progressive disease, see below
-Symptomatic,
-Clinically significant tumor burden
-Clinically significant
-Progressive disease
Manage clinically significant as appropriate
Or
Consider alternative front-line therapy
If PD, consider octreotide or lanreotide
If PD
Clinical trial
or
Everolimus
or
Sunitinib
or
Temozolomide+ Capecitabine
or
PRRT
or
Other cytotoxic Chemotherapy
or
Consider Liver directed therapy
For liver predominant disease
Or
Palliative RT for symptomatic bone or brain metastases

Well Differentiated Pancreatic Neuroendocrine Tumor (NET grade 3)

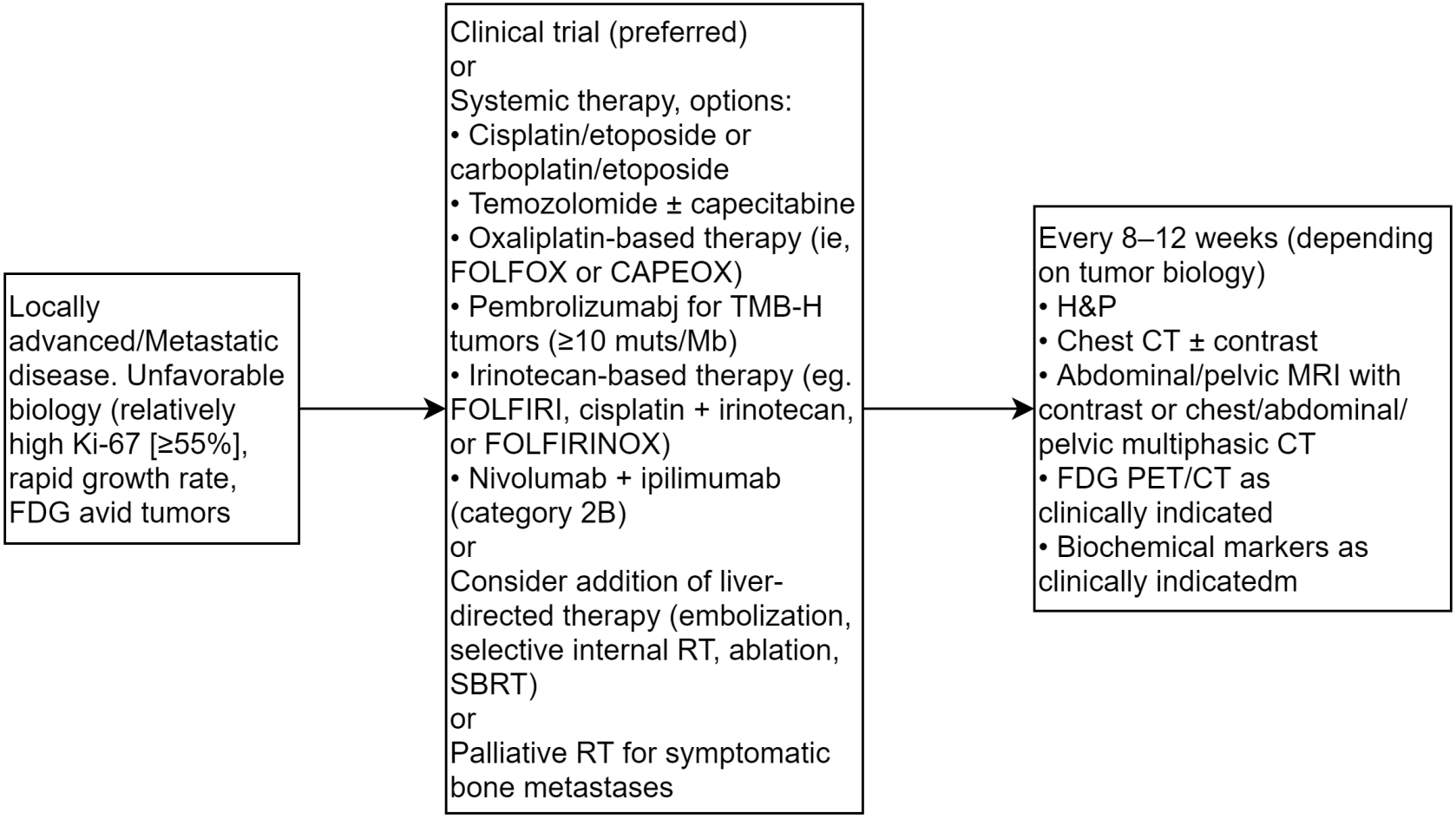
Pancreatic neuroendocrine tumor



Pancreatic neuroendocrine tumor

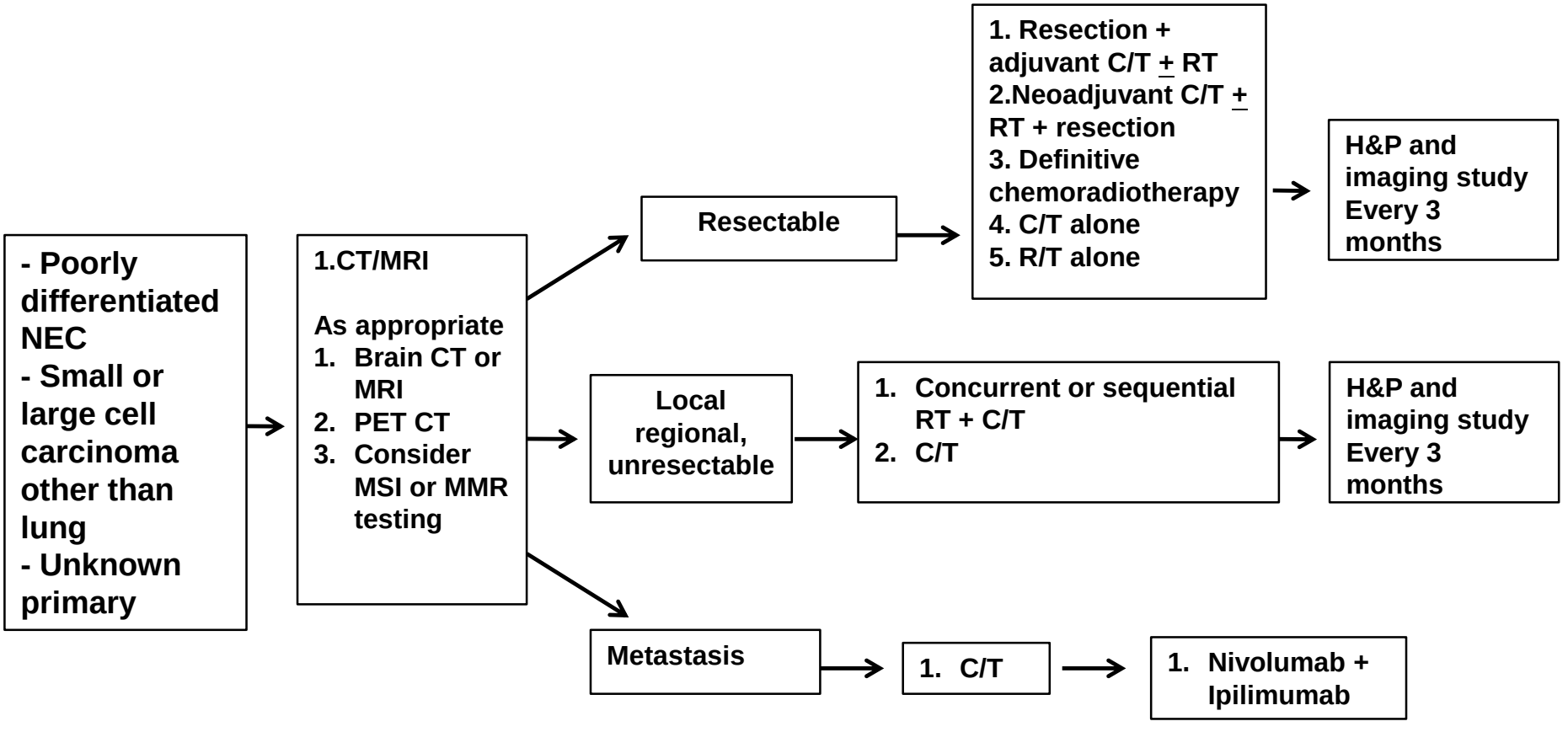


Pancreatic neuroendocrine tumor



Poorly Differentiated Pancreatic Neuroendocrine Tumor (NEC grade 3)

WHO grade 3



Chemotherapy options include cisplatin/etoposide, carboplatin/etoposide, FOLFOX, FOLFIRI and temozolomide +/- capecitabine. When combine with RT, chemotherapy options are limited to cisplatin/etoposide or carboplatin/etoposide.

Recommended regimens of well differentiated PNETS (G1,2,3)

Standard regimen

- Everolimus[1]
  10mg QD
- Sunitinib[2]
  37.5mg QD
- Temazolamide + Capecitabine[3]
  Capecitabine (750 mg/m² twice daily, days 1-14) and
  Temazolomide (200 mg/m² once daily, days 10-14) every 28 days.
- DTIC +5-FU± Epirubicin[4]
  Dacarbazine (200 mg/m², D1-3), Epirubicine (20 mg/m² , D1-3),
  5-FU (500 mg/m², D1-3) every 21 days
- Cytotoxic chemotherapy
  - FOLFOX
  - XELOX

Other Consideration

- Belzutifan in the setting of germline VHL alterations in progressive PNET[11]

Recommended regimens of poorly differentiated PNETS (NEC G3)

- Etoposide + cisplatin[5]

  Cisplatin (25 mg/m2, D1-3) and Etoposide (80 mg/m2, D1-3) every 21 days
- Etoposide + carboplatin[5]

  Carboplatin (AUC=4, dose= 4x (25+CCr)mg, D1) and Etoposide (80 mg/m2, D1-3) every 21 days
- Irinotecan + cisplatin[6]

  Cisplatin (60 mg/m2, D1) and Irinotecan (60 mg/m2, D1, D8 D15) every 28 days
- Cytotoxic chemotherapy
  - FOLFOX
  - XELOX
- Pembrolizumab
  - If MSI-H or TMB-H (≥10 mut/Mb)
- Irinotecan-based therapy
  - FOLFIRI, Cisplatin + Irinotecan pr FOLFIRINOX
- Atezolizumab and chemotherapy[10]
- Nivolumab + Ipilimumab (category 2B)[12,13]

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Recurrent, Locoregionally Advanced, and/or Distant Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)

- Systemic therapy may not be appropriate for every patient with recurrent, locoregionally advanced and/or distant metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, liver-directed therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for NETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms for GI tumors, see NET-9. For management of carcinoid syndrome, see NET-12.

Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)[a,b,c]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Recurrent, Locoregional Advanced Disease, and/or Distant Metastases (if progression on octreotide LAR or lanreotide)[c]	• Everolimus[d,1,2] • PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR/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 disease. (See Discussion for details.)

[a] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered.
[b] The PROMID trial showed an antitumor effect of octreotide LAR in advanced neuroendocrine tumors of the midgut.[3] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 GEP NETs.[4]
[c] If clinically significant disease progression, treatment with octreotide LAR or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; these regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide LAR or lanreotide with 177Lu-dotatate, see NE-G.
[d] Effectiveness of everolimus in the treatment of patients with carcinoid syndrome has not been established.
[e] See Principles of PRRT with 177Lu-dotatate (NE-G).

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

References

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Recurrent, Locoregionally Advanced, and/or Distant Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)

- Systemic therapy may not be appropriate for every patient with recurrent, locoregionally advanced and/or distant metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, liver-directed therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for NETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms for GI tumors, see NET-9. For management of carcinoid syndrome, see NET-12.

Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)[a,b,c]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Recurrent, Locoregional Advanced Disease, and/or Distant Metastases (if progression on octreotide LAR or lanreotide)[c]	• Everolimus[d,1,2] • PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR/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 disease. (See Discussion for details.)

[a] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered.
[b] The PROMID trial showed an antitumor effect of octreotide LAR in advanced neuroendocrine tumors of the midgut.[3] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 GEP NETs.[4]
[c] If clinically significant disease progression, treatment with octreotide LAR or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; these regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide LAR or lanreotide with 177Lu-dotatate, see NE-G.
[d] Effectiveness of everolimus in the treatment of patients with carcinoid syndrome has not been established.
[e] See Principles of PRRT with 177Lu-dotatate (NE-G).

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NCCN Guidelines Version 1.2022
Neuroendocrine and Adrenal Tumors

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Recurrent, Locoregionally Advanced, and/or Distant Metastatic Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)

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

Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)[c]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Recurrent, Locoregional Advanced Disease, and/or Distant Metastases	• Everolimus[12] (category 1 for progressive disease) 10 mg by mouth, daily • Octreotide LAR[a,b] or lanreotide[a,5] (if SSTR-positive) • Sunitinib[13] (category 1 for progressive disease) 37.5 mg by mouth, daily • Temozolomide + capecitabine[14,15] (preferred when tumor response is needed for symptoms or debulking) • PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR 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[g,21]

[a] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered.

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

[c] If clinically significant disease progression, treatment with octreotide LAR or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; these regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide LAR or lanreotide with 177Lu-dotatate, see NE-G.

[e] See Principles of PRRT with 177Lu-dotatate (NE-G).

[g] The study excluded patients with prior systemic anticancer therapy, including anti-vascular endothelial growth factor therapy, patients needing immediate surgical intervention for tumor treatment, or patients with evidence of metastatic disease on screening imaging. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med 2021;385:2036-2046.

References

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

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Neuroendocrine and Adrenal Tumors

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Well-Differentiated, Grade 3 Neuroendocrine Tumors

Well-Differentiated, Grade 3 Neuroendocrine Tumors

Locally Advanced/Metastatic Disease with Favorable Biology (Unresectable with Clinically Significant Tumor Burden or Evidence of Disease Progression)	Locoregional Disease (Resectable) with Unfavorable Biology	Locally Advanced/Metastatic Disease with Unfavorable Biology
• Octreotide LAR[a] or lanreotide[a] (if SSTR-positive and/or hormonal symptoms) • Clinical trial (preferred) • PRRT with 177Lu-dotatate[h] (if SSTR-positive) • Everolimus • Sunitinib (pancreas only) • Pembrolizumab[i] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Chemotherapy (ie, temozolomide ± capecitabine,[j,14] FOLFOX, CAPEOX, cisplatin/etoposide, or carboplatin/etoposide)	• Clinical trial (preferred) • Neoadjuvant chemotherapy on a case-by-case basis (eg, Ki-67 >55%) ‣ Temozolomide ± capecitabine[j] ‣ Oxaliplatin-based therapy (FOLFOX, CAPEOX) ‣ Cisplatin/etoposide or carboplatin/etoposide	• Clinical trial (preferred) • Cisplatin/etoposide or carboplatin/etoposide • Temozolomide ± capecitabine[j,14] • Oxaliplatin-based therapy (ie, FOLFOX or CAPEOX) • Pembrolizumab[i] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Irinotecan-based therapy (eg, FOLFIRI, cisplatin + irinotecan, or FOLFIRINOX) • Nivolumab + ipilimumab[22,23] (category 2B)

[a] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered.
[h] Consider trial of SSA before PRRT. Preliminary data suggest reduced efficacy if high Ki-67 and/or FDG-PET avid. See Principles of PRRT with 177Lu-dotatate (NE-G).
[i] Pembrolizumab can be considered for patients with dMMR, MSI-H, or advanced TMB-H tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[j] Temozolomide ± capecitabine may have more activity in tumors arising in the pancreas compared to GI NETs.

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

References

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Extrapulmonary Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/ Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

Extrapulmonary Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

Resectable disease	Locoregional unresectable disease: Chemoradiation (concurrent/sequential)	Locoregional unresectable/metastatic disease: Systemic therapy
• Cisplatin + etoposide[10] • Carboplatin + etoposide[24] • FOLFOX • FOLFIRI • Temozolomide ± capecitabine	• Cisplatin + etoposide • Carboplatin + etoposide • Capecitabine (when etoposide + platinum is not feasible)	• Cisplatin + etoposide[10] • Carboplatin + etoposide[24] • Cisplatin + irinotecan • Carboplatin + irinotecan • FOLFOX • FOLFIRI • FOLFIRINOX[25,26] • Temozolomide ± capecitabine • Nivolumab + ipilimumab [22,23,27] (category 2B) (only for metastatic disease with progression) • Pembrolizumab[i] (if MSI-H, dMMR, or TMB-H tumors [≥10 mut/Mb])

[i] Pembrolizumab can be considered for patients with dMMR, MSI-H, or advanced TMB-H tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.

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

References

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregional Unresectable/Metastatic Adrenocortical Carcinoma[k]

Locoregional Unresectable/Metastatic Adrenocortical Carcinoma		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cisplatin + etoposide[28] ± doxorubicin ± mitotane[l,m,29] • Carboplatin + etoposide ± doxorubicin ± mitotane[l,m]	• Pembrolizumab[30,31] ± mitotane[l,m] • Mitotane monotherapy[l,m]	• Streptozocin ± mitotane[l,m,29]

[k] See Discussion for further information regarding the phase III FIRM-ACT trial.
[l] Monitor mitotane blood levels. Some institutions recommend target levels of 14–20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Life-long hydrocortisone ± fludrocortisone replacement usually is required with mitotane.
[m] Mitotane may have more benefit for control of hormone symptoms than control of tumor.

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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Paraganglioma/Pheochromocytoma

Paraganglioma/Pheochromocytoma

Locally Unresectable	Distant Metastases
• Clinical trial (preferred) • SSAs (octreotide LAR or lanreotide)[a,n] • Sunitinib 37.5 mg once daily • HSA iobenguane I 131[o] or other 131I-MIBG (requires prior positive MIBG scan) • Consider PRRT with 177Lu-dotatate (if SSTR-positive)[p,q]	• Clinical trial (preferred) • SSAs (octreotide LAR or lanreotide)[a,n] • Sunitinib 37.5 mg once daily • Systemic chemotherapy (eg, CVD[r] or temozolomide) • HSA iobenguane I 131[o] or other 131I-MIBG (requires prior positive MIBG scan) • Consider PRRT with 177Lu-dotatate (if SSTR-positive)[p,q]

[a] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered.
[n] SSAs may be used for indolent, low-volume progressing disease for antiproliferative effect and/or antisecretory effect. Data about anti-proliferative effects are limited.
[o] HSA iobenguane I 131 is an FDA-approved option.
[p] SSTR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, and 68Ga-DOTATOC.
[q] Data are limited on the use of PRRT with 177Lu-dotatate in this setting. See Principles of PRRT with 177Lu-dotatate (NE-G).
[r] CVD = cyclophosphamide, vincristine, and dacarbazine.

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