

Neuroendocrine Neoplasms Introductory Lecture

NEN Pathology

Neuroendocrine Neoplasms are Heterogenous

Neuroendocrine Functionality

NENs can make, store and secrete hormones

Secretory Glands

1. Endocrine Glands (secrete into bloodstream)

Pancreas, thyroid, parathyroid, adrenal, pituitary

2. Exocrine Glands (secrete into ductal system)

GI, respiratory

Pathology

Neuroendocrine IHC Markers

Chromogranin

Proteins present in secretory granules

Synaptophysin

Glycoproteins present in synaptic vesicles

CD56

Neural cell adhesion molecule

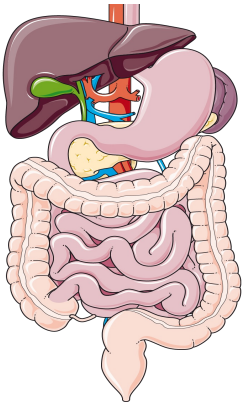
INSM1

Insulinoma associated protein

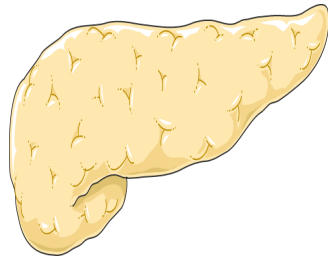
NEN Anatomy

Neuroendocrine Neoplasms occur diffusely
can arise throughout the neuroendocrine system

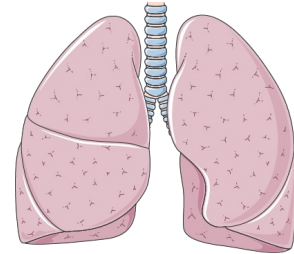
Common Tumor Sites



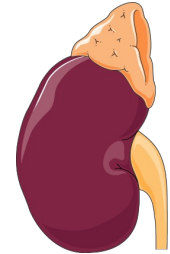
Gastrointestinal Track



Pancreas



Lungs



Adrenal Glands

NEN Initial Work Up

Imaging

Standard Imaging

Endoscopy
CT
MRI
FDG-PET

Somatostatin Receptor Scans

some NENs express somatostatin receptors

Newer scans: Radionuclide PET Scans

Radiotracer= Ga-68 or Cu-64
Somatostatin linker = Dotatate

Older scans: Octreotide Scintigraphy Scan

Radiotracer= indium-111
Somatostatin linker = Octreotide (somatostatin analogue)

Peripheral Blood Tests

Chromogranin A:

Non-specific marker
Can be falsely elevated by PPI, etc

Small Intestine Tumors:

Serotonin, 5HIAA (serum > urine)

Pancreatic Tumors:

Hypoglycemia: insulin, proinsulin, c-peptide
Hyperglycemia: glucagon, somatostatin
PUD: gastrin
Diarrhea: gastrin, VIP, somatostatin

Thoracic Tumors:

ACTH, cortisol

Adrenal Tumors:

ACTH, cortisol, renin, aldosterone, testosterone, DHEA, plasma/24-urine normetanephrine + metanephrines

NEN Grading & Prognosis

Grading: Metric of Tumor Differentiation

Grading Includes:

Mitotic Rate

Ki67 (proliferation index)

Necrosis

NE Tumors vs. NE Carcinoma

Low Grade/Well-differentiated Cancers =
Neuroendocrine Tumors (NETs)

High Grade/Poorly-differentiated Cancers =
Neuroendocrine Carcinomas (NECs)

Prognosis of NENs: varies significantly by grade

LOW GRADE NETs: Indolent

Prognosis can be >5-10 years (even if stage IV)

HIGH GRADE NECs: Aggressive

Prognosis can be weeks-months

* TNM staging less clinically relevant than in other solid cancers. Grade is more important for treatment decisions & prognostication

Carcinoid Tumors vs. Carcinoid Syndrome

Carcinoid Tumors

Originally meant “carcinoma-like”
because they behaved more benignly [*outdated term*]

Carcinoid Syndrome

Caused by increased secretion of serotonin

Occurs in NENs of midgut origin
(small intestine, appendix, ascending colon)

Carcinoid Syndrome

Serotonin Metabolism

neuroendocrine cells of GI tract produce serotonin
enterochromaffin/kulchitsky cells

tryptophan → serotonin → 5HIAA

Serotonin Metabolism

- Tryptophan is consumed to produce serotonin which can cause a niacin/B3 deficiency (pellagra: dermatitis, diarrhea, dementia)
- Small bowel NENs usually requires hepatic involvement to produce carcinoid syndrome because serotonin released from the small bowel is metabolized by the liver
- Unusual to have left-sided heart disease because serotonin is metabolized by the lung

Symptoms

Watery Diarrhea

Flushing

Wheezing/Bronchospasm

Hypotension

Palpitations

Right-sided heart disease (TR, PS)

Retroperitoneal Fibrosis

Management

Telotristat

Inhibits serotonin production

Somatostatin Analogues

Inhibits hormone secretion

* Octreotide HD IV or gtt if carcinoid crisis

Cardiac Monitoring

TTEs Q6-12 months

Gastrointestinal NEN Grading

Grade	Differentiation	Mitotic Count (per 10 HPF)	Ki-67 Index
(G1) Low Grade	Well Differentiated	<2	< 3%
(G2) Intermediate Grade	Well Differentiated	2-20	3-20%
(G3) High Grade	Well Differentiated	>20	> 20%
High Grade NEC	Poorly Differentiated	>20	> 20%
High Grade NEC	Poorly Differentiated	>20	> 20%

* Usually present with metastatic disease

Pancreatic NENs

NEN	Secreted Product	Presentation
Insulinoma	Insulin	hypoglycemia (Whipple's Triad), hypokalemia
Gastrinoma	Gastrin	Zollinger-Ellison Syndrome: Severe PUD
VIPoma	VIP Vasoactive intestinal polypeptide	Verner-Morrison Syndrome: watery diarrhea, hypokalemia, achlorhydria
Glucagonoma	Glucagon	DM, dermatitis, DVT, depression
Somatostatinoma	Somatostatin	cholelithiasis, hyperglycemia, steatorrhea
PPoma	PP Pancreatic polypeptide	No syndrome

*** Many pancreatic NENs are associated with MEN1 syndrome**
(tumors of pancreas, pituitary, parathyroid)

Thoracic NENs Presentation & Grading

Terminology	Grade	Typical Characteristics	Mitotic Count (per 10 HPF)
Typical Carcinoid	(G1) Low Grade	Central	<2
Atypical Carcinoid	(G2) Intermediate Grade	Peripheral + Smoking + Paraneoplastic	<2 – 10 (or necrosis)
Large Cell NEC	(G3) High Grade	Peripheral + Smoking	>10
Small Cell NEC	(G3) High Grade	Hilar/Perihilar + Smoking ++ Paraneoplastic	>10
Combined NEC/NSCLC	High Grade		

Adrenal NENs

presentation of:

Adrenal Cortical Carcinomas

Can be non-functional or functional (NENs)

work up of:

Adrenal Cortical Carcinomas

Peripheral Blood Tests:

ACTH, Cortisol (dex suppression, 24H urine, or midnight salivary)

Renin, Aldosterone

Plasma free metanephrines, 24H urine metanephrines, norepinephrine

Testosterone, DHEA

Imaging: suspicious findings

- > 4 cm
- Irregular/inhomogeneous
- Delayed washout

Adrenal NENs

Cushing's Syndrome

Labs:

ACTH (low)

Cortisol (high)

Presentation:

Hypertension

Hypokalemia

Metabolic alkalosis

Hyperglycemia

Pheochromocytoma

Labs:

Serum metanephrines (high)

24H Urine metanephrines (high)

Presentation:

Hypertension

Headache

Sweating

Tachycardia

Conn's Syndrome

Labs:

Renin (low)

Aldosterone (high)

Presentation:

Hypertension

Hypokalemia

Adrenal NENs

treatment of:

Adrenal Cortical Carcinomas

Non-Functional



**Observation
or Resection**

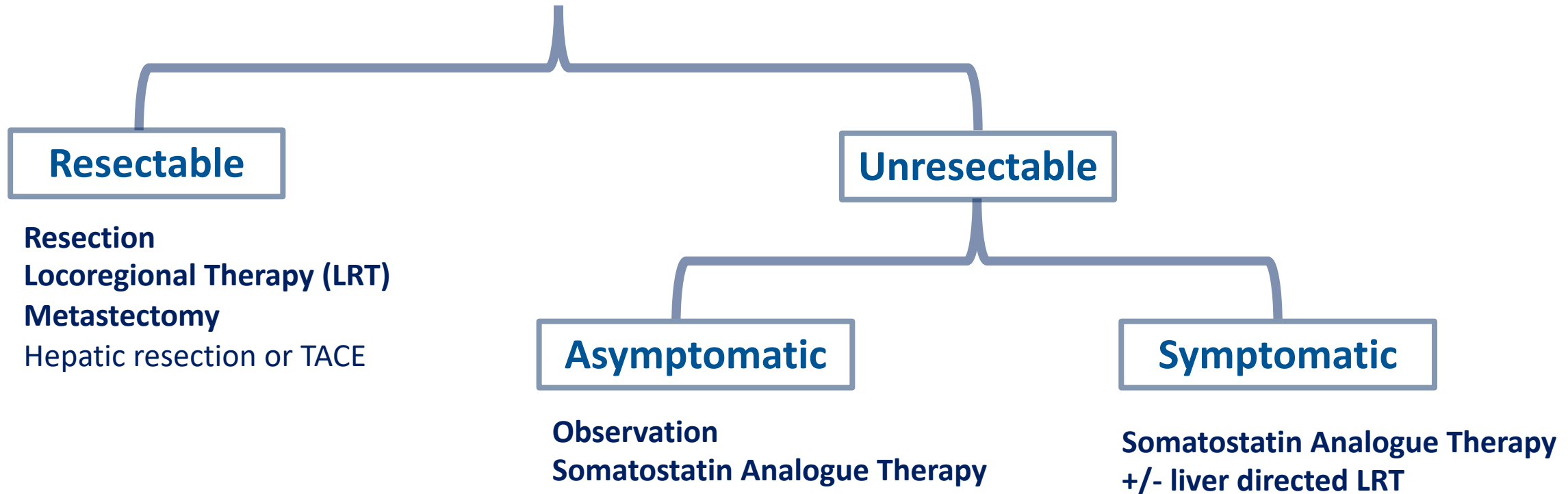
Functional



**Resection + LND
Consider adjuvant RT
Consider adjuvant mitotane**

** **Pheochromocytomas:** Give alpha-blocker (phenoxybenzamine, doxazosin, etc) pre-surgery. Don't give unopposed beta blockers*

Initial Treatment Paradigm for Low/Intermediate Grade NENs



** Pre-surgery: Consider octreotide pre/post surgery to prevent carcinoid crisis*

Front-Line Treatment of Low/Intermediate Grade NENs

Somatostatin Analogues

Somatostatin analogues target the somatostatin receptor that is present on the majority of NENs

Somatostatin Receptor Localization

Radionuclide PET scans (Ga-63 or Cu-64) are required to confirm presence of somatostatin receptors

Somatostatin Function

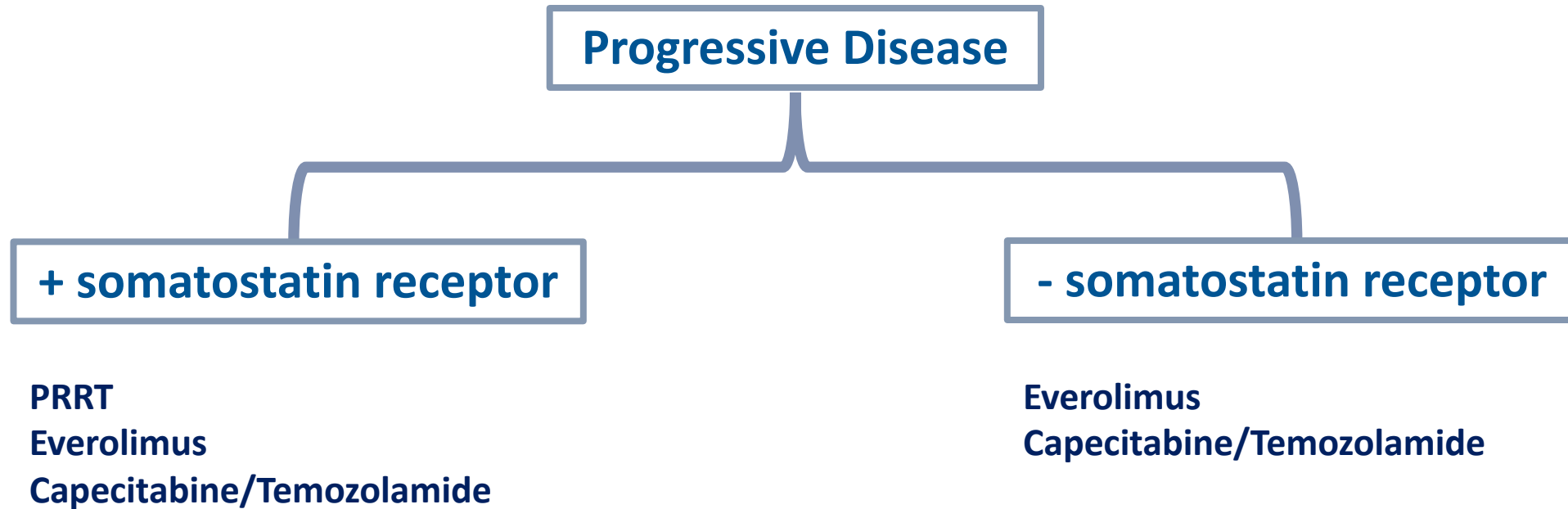
- (1) inhibits secretion of many hormones (Ach, glucagon, gastrin, GH, insulin, PP, serotonin, VIP, etc)
- (2) controls tumor growth

Somatostatin Analogues

Octreotide = intermediate-acting (BID dosing)

Lanreotide = long-acting (monthly dosing)

Second-Line Treatments of Low/Intermediate Grade NENs



** Consider Cap/Tem if concern for visceral crisis*

Second-Line Treatments of Low/Intermediate Grade NENs

Peptide Receptor Radioligand Therapy

PRRT = peptide receptor radioligand therapy

Somatostatin Linker = Dotate

Active Agent = Lutetium (Lu-177)

Localization:

Need somatostatin radionuclide PET first to determine if NEN has somatostatin receptors

Function:

Can shrink tumors

Adverse Effects:

Myelotoxicity, nephrotoxicity

Molecular Therapy

Everolimus (mTOR inhibitor)

Involved in VEGF/IGF signaling

Function:

Prevents tumor progression

Doesn't shrink tumors

Adverse Effects:

Stomatitis, hyperglycemia, diarrhea, pneumonitis

Third-Line Treatments of Low/Intermediate Grade NENs

Angiogenesis Agents (VEGF)

Bevacizumab
Cabozantinib
Lenvatinib
Sorafenib
Pazopanib
Sunitinib

Chemotherapy

Capecitabine +/- Temozolamide
FOLFOX
Dacarbazine
Doxorubicin

Treatment of High Grade NENs

Chemotherapy

Carboplatin/Etoposide

Capecitabine + Temozolamide

FOLFOX

FOLIRI

Ki-67 is associated with chemotherapy response

Ki-67 < 55% are less responsive to chemotherapy

Neuroendocrine Neoplasms Reference Handout

NEN Diagnosis

Heterogenous tumors can occur anywhere in NE system

Common Tumor Sites

Gastrointestinal
Pancreatic
Thoracic
Adrenal

Many NENs express somatostatin receptors

IHC Markers

Chromogranin
Synaptophysin
CD56
INSM1

Standard Imaging

Endoscopy
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Somatostatin Receptor Scans

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Adrenal Tumors:

ACTH, cortisol, renin, aldosterone, testosterone, DHEA, plasma/24-urine metanephrines

Carcinoid Syndrome

Neuroendocrine cells of GI tract secrete serotonin

Occurs in NENs of midgut origin

(small intestine, appendix, ascending colon)

Often with hepatic metastases

tryptophan → serotonin → 5HIAA

Symptoms

Watery Diarrhea

Flushing

Wheezing/Bronchospasm

Hypotension

Palpitations

Right-sided heart disease (TR, PS)

Retroperitoneal Fibrosis

* Low niacin/B3 from tryptophan consumption can cause pellagra (dermatitis, diarrhea, dementia)

Management

Telotristat

Inhibits serotonin production

Somatostatin Analogues

Inhibits hormone secretion

* Octreotide HD IV or gtt if carcinoid crisis

Cardiac Monitoring

TTEs Q6-12 months

NEN Grading

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High Grade/Poorly-differentiated Cancers = **Neuroendocrine Carcinomas (NECs)**

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PPoma	PP Pancreatic polypeptide	No syndrome

Adrenal NENs

Adrenal NENs can be functional or non-functional

Cushing's Syndrome

Labs:
ACTH (low)
Cortisol (high)

Presentation:
Hypertension
Hypokalemia
Metabolic alkalosis
Hyperglycemia

Conn's Syndrome

Labs:
Renin (low)
Aldosterone (high)

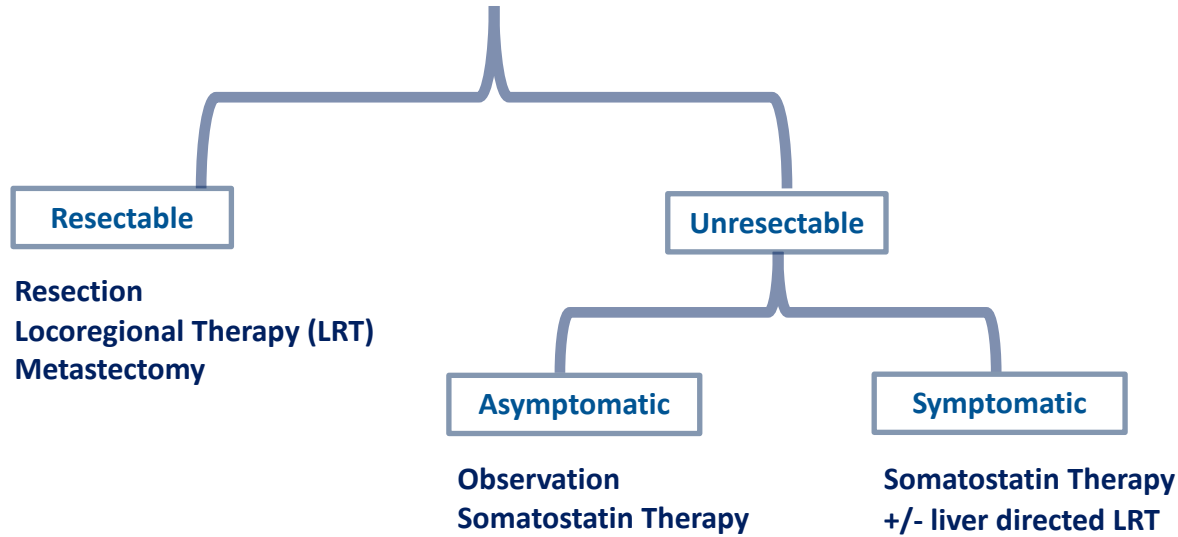
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Pheochromocytoma

Labs:
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Urine metanephrines (high)

Presentation:
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Headache
Sweating
Tachycardia

Low/Intermediate Grade NEN Front-Line Treatment



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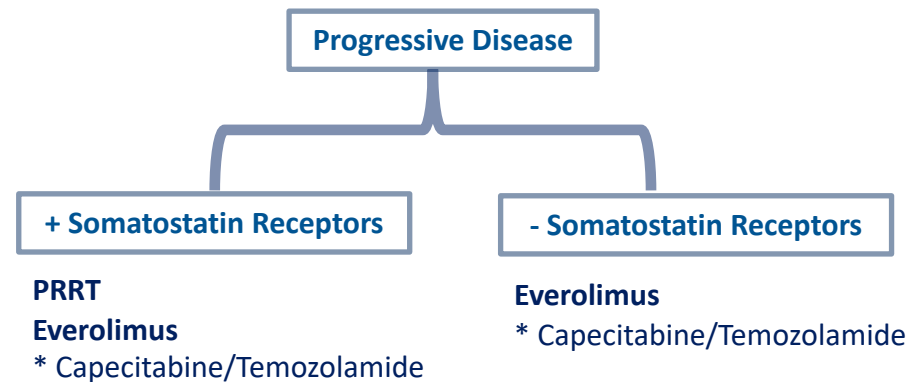
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Low/Intermediate Grade NEN Second-Line Treatment



High Grade NEN Treatment

Chemotherapy

Carboplatin/Etoposide

Capecitabine + Temozolamide
FOLFOX
FOLIRI

** Ki-67 < 55% are less responsive to chemo*