GEP NEN: ESMO GUIDELINES

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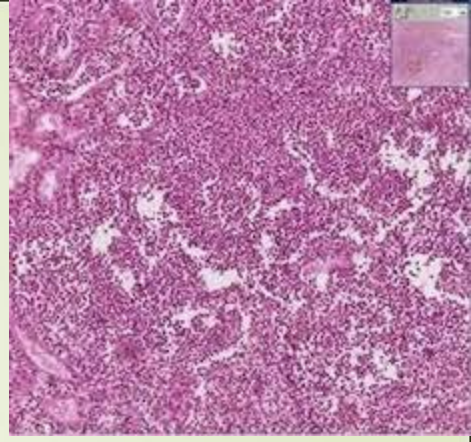
5 years OUTDATED, APOLOGIES….

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii124–vii130, 2012
doi:10.1093/annonc/mds295

Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

INCIDENCE EPIDEMIOLOGY



- Heterogeneous group of tumors with their origin in neuroendocrine cells of the embryological gut.
- The crude incidence has significantly increased over the last years and is now estimated to be 5.25/100 000/year.
- The highest incidence being from the fifth decade onward.
- Males to Females 5.5:4.5
- Hereditary syndromes: MEN 1, Von Hippel Lindau syndrome, NF1,2

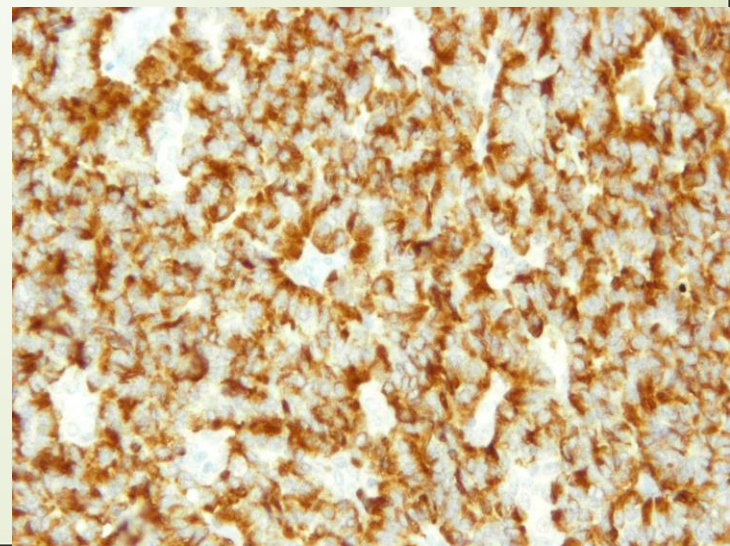
STAGING AND RISK ASSESSMENT

- Histology
- Pan-neuroendocrine markers: chromogranin A and synaptophysin, Neuron-specific enolase (NSE), CD56.

- Preoperative staging should include somatostatin receptor scintigraphy or 68Gallium-DOTA-TOC/-NOC/-TATE positron emission tomography (PET).
- The technique should always be complemented with computed tomography (CT) or magnetic resonance imaging (MRI).

- Endoscopy
- Echocardiography (Carcinoid syndrome)

- Plasma: CgA, NSE (gr 3), urine 5HIAA (small intestinal NET)
- Plasma in pNETs: glucagon, insulin, gastrin, VIP, PP



Intestinal neuroendocrine tumors (carcinoids, about 50% of GEP-NETs)

- with carcinoid syndrome (30% of carcinoids) flushing, diarrhea, endocardial fibrosis, wheezing caused by release of serotonin predominantly from liver metastases
- without carcinoid syndrome (70% of carcinoids)

Pancreatic endocrine tumors (PETs) (~30% of GEP-NETs)

Nonfunctioning (45%–60% of PETs)

Functioning (40%–55% of PETs)

- Gastrinoma, excessive gastrin production, Zollinger–Ellison syndrome
- Insulinoma, excessive insulin production, hypoglycemia syndrome
- Glucagonoma, excessive glucagons production, glucagonoma syndrome
- VIPoma, excessive production of vasoactive intestinal peptide (VIP), Watery diarrhea, hypokalemia–achlorhydria syndrome
- PPoma, excessive PP production, (generally classified as nonfunctioning PETs)
- Somatostatinoma, excessive somatostatin production
- CRHoma, excessive corticotropin-releasing hormones production
- Calcitoninoma, excessive calcitonin production
- GHRHoma, excessive growth hormone-releasing hormone production
- Neurotensinoma, excessive neurotensin production
- ACTHoma, excessive production of adrenocorticotropic hormone
- GRFoma, excessive production of growth hormone-releasing factor
- Parathyroid hormone-related peptide tumor

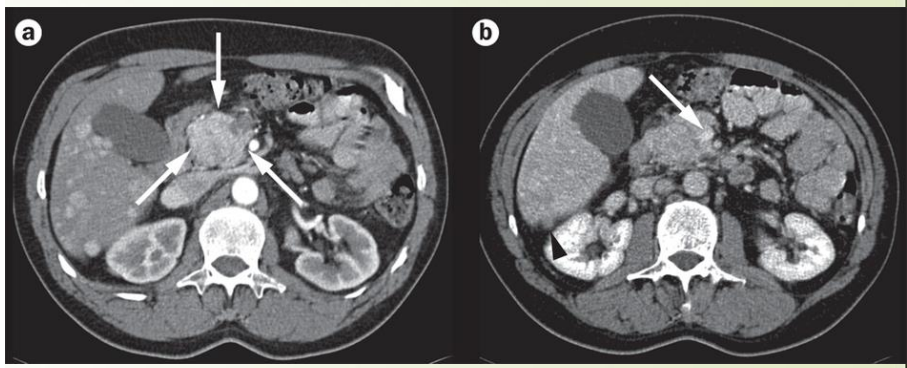


Table 2. Gastro entero pancreatic neoplasms: WHO Classification (2010)

WHO 1	NET G1, Ki-67 ≤2%
WHO 2	NET G2, Ki-67 3%–20%
WHO 3	NEC G3, Ki-67 >20%
	MANEC
	Tumor-like lesions

Grade	Mitotic count (10 HPF)[a]	Ki67 index (5)[b]
Grading proposal for neuroendocrine tumors		
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

Table 5. TNM classification for endocrine tumors of the pancreas (European Neuroendocrine Tumor Society)

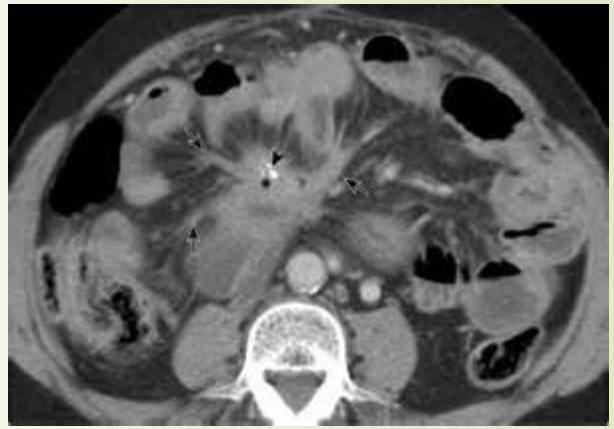
T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the pancreas and size ≤2 cm
T2	Tumor limited to the pancreas and size 2–4 cm
T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, and adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)
	For any T, add (m) for multiple tumors
N	Regional lymph nodes
NX	Regional lymph node cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M	Distant metastases
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

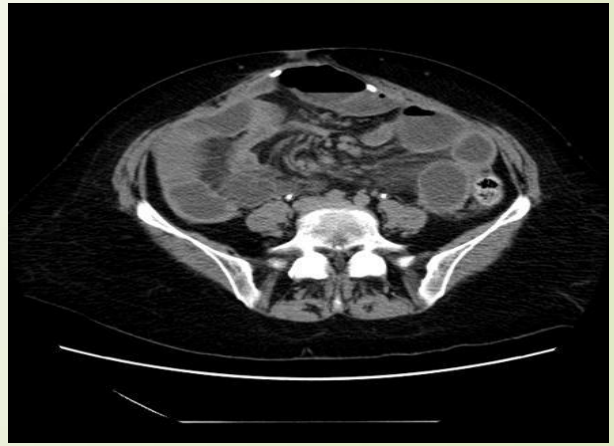
Table 6. TNM classification for endocrine tumors of lower jejunum and ileum (European Neuroendocrine Tumor Society)

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa and has a size ≤1 cm
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades subserosa
T4	Tumor invades peritoneum/other organs
	For any T add (m) for multiple tumors
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M	Distant metastases
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

- All patients with small intestinal NETs should be considered potential candidates for curative surgery in an interdisciplinary setting.
- Resection of the primary intestinal NET and regional lymph node metastases in patients with liver metastases is generally advocated to prevent development of mesenteric fibrosis, small-bowel/vascular obstruction.
- In patients with pancreatic NETs, curative surgery should be considered whenever possible even in the presence of resectable metastatic disease.
- It is a general agreement not to operate on G3 NEC.



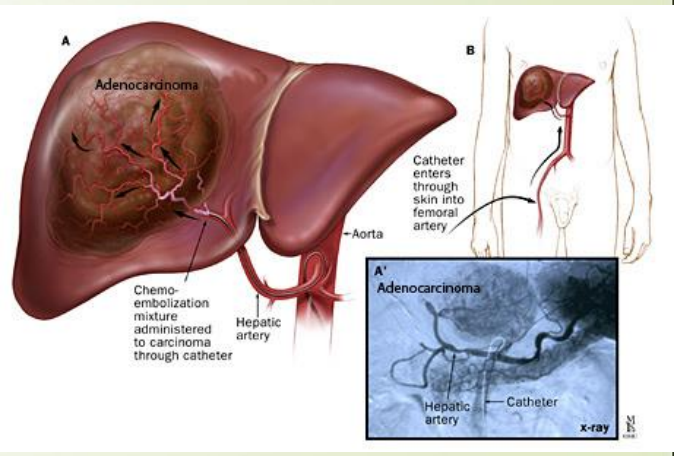


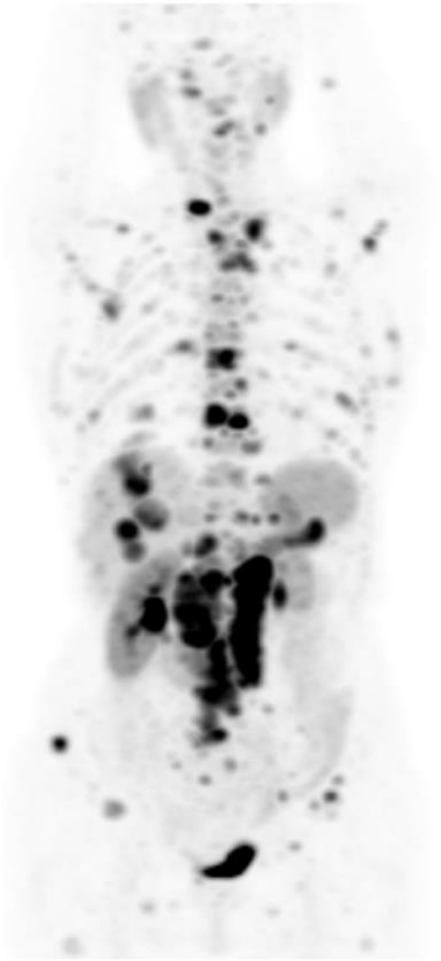
ABLATIVE MANAGEMENT OF ADVANCED DISEASE

- Cytoreductive surgery should be considered when metastatic disease is localized in the liver/abdomen and >70% of tumor load is thought resectable.

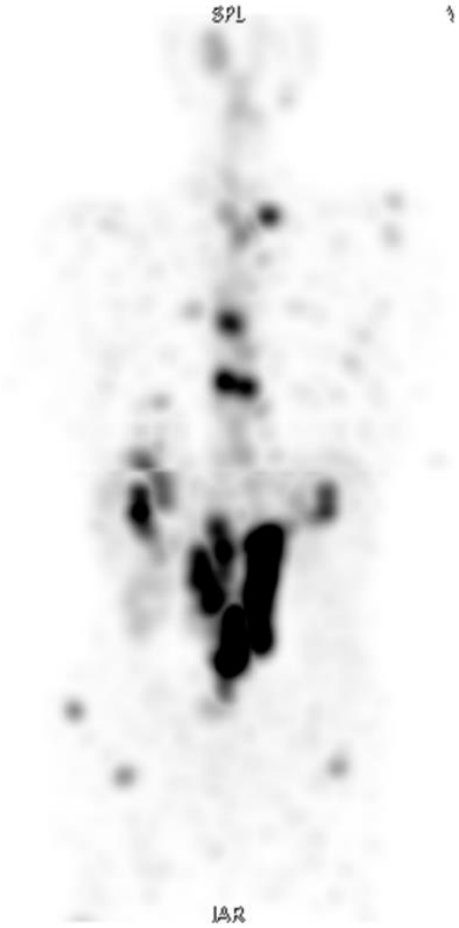
- RFA, TAE ,TACE, Y90 SIRT for liver metastases from Gr 1/2 NETs [III,B].

- Peptide receptor-targeted radiotherapy (PRRT) for NETs with liver metastases using 90Yttrium and 177Lutetium labeled DOTATOC or DOTATATE can be considered in both functioning and nonfunctioning NETs with positive somatostatin receptor scintigraphy irrespective of the primary tumor site [III,A].





DIAGNOSIS
68 Gallium-**Octreotate** PET/CT



THERAPY
177 Lutetium-**Octreotate** SPECT-CT

Applying the same tracer for both diagnostic as treatment applications is called "Theranostics".
The Figure illustrates this concept in the diagnosis and treatment of patients with metastatic neuroendocrine tumors resistant to all standard treatments.

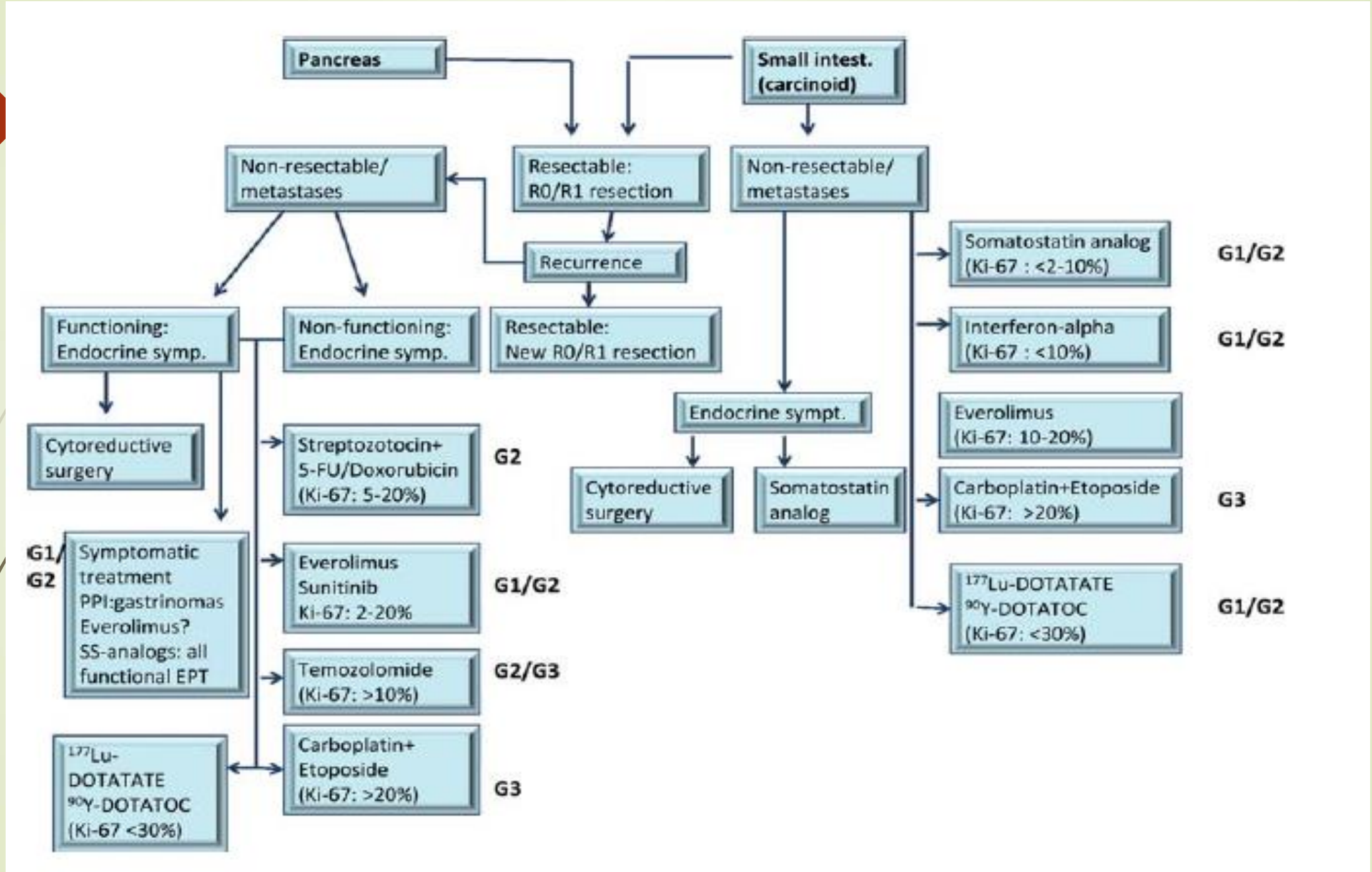
On the left the diagnostic imaging using whole body PET performed one hour after intravenous administration of 3 mCi 68Ga-octreotate showing an intense expression of the somatostatine receptor in all tumor sites in liver, bone and abdomen; and, on the right is the same patient imaged by whole body SPECT at 24 hours after administration of a radiotherapeutic dose of 177Lu-octreotate for selective targeted radiotherapy.

MEDICAL THERAPY

- Somatostatin analogs are the recommended first line therapy in nonfunctioning as well as functioning progressive G1/G2 NETs [II,A].
- In contrast, in metastatic NEC G3 regardless of the site of origin somatostatin analog treatment is not recommended (III, B).

- Everolimus (+/- SSA) in intestinal NETs, pNETs [I,A]
- Sunitinib in pNETs [I,A]

- Systemic cytotoxics are indicated in patients with inoperable progressive liver metastases from G1/G2 pancreatic NETs using a combination of streptozotocin and 5-fluorouracil (5-FU)/doxorubicin (II, B).
- Temozolomide-based chemotherapy is promising in pancreatic NETs either alone or combined with capecitabine giving high partial remissions (40%–70%) [III,B].
- In G3 NECs, cisplatinum/etoposide is recommended.


Pancreas
Small intest. (carcinoid)
Non-resectable/ metastases
Resectable: R0/R1 resection
Non-resectable/ metastases
Recurrence
Functioning: Endocrine symp.
Non-functioning: Endocrine symp.
Resectable: New R0/R1 resection
Cytoreductive surgery
Streptozotocin+ 5-FU/Doxorubicin (Ki-67: 5-20%)
G2
G1/ G2
Symptomatic treatment PPI:gastrinomas Everolimus? SS-analogs: all functional EPT
Everolimus Sunitinib Ki-67: 2-20%
G1/G2
Temozolomide (Ki-67: >10%)
G2/G3
177Lu-DOTATATE 90Y-DOTATOC (Ki-67 <30%)
Carboplatin+ Etoposide (Ki-67: >20%)
G3
Endocrine sympt.
Cytoreductive surgery
Somatostatin analog
Somatostatin analog (Ki-67 : <2-10%)
G1/G2
Interferon-alpha (Ki-67 : <10%)
G1/G2
Everolimus (Ki-67: 10-20%)
Carboplatin+Etoposide (Ki-67: >20%)
G3
177Lu-DOTATATE 90Y-DOTATOC (Ki-67: <30%)
G1/G2

FOLLOW UP

- In patients with R0/R1 resected NET G1/G2, it is recommended that imaging is performed every 3–6 months (CT or MRI), and in NEC G3, every 2–3 months.
- Somatostatin receptor imaging, either Octreoscan or PET/CT using 68Ga-DOTA-TOC/-NOC/-TATE is recommended after18–24 months if expression of somatostatin receptor has been proven on the tumor cells.
- In the case of rapid tumor progression, it may be necessary to re-biopsy liver metastases to re-assess the proliferative activity.
- If chromogranin A is not elevated, NSE represents an alternative biomarker.