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Treatment of Neuroendocrine Tumours: Approach of GEP-NETS

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Neuroendocrine tumours (NETs) represent a rare entity, with various anatomic primary tumour sites, three different grades, a functional or non-functional status, and differences in somatostatin receptor expression, making NETs a heterogeneous disease. The management of these tumours is challenging and varies from a simple watch-and-wait strategy to more complex multi-modality treatment combinations. The choice of treatments depends on the previously mentioned factors. NETs most frequently arise from the gastro-entero-pancreatic (GEP) tract. The article reviews the classification, diagnosis, and staging of well-differentiated GEP-NETS, and discusses different therapeutic options.

Introduction

Neuroendocrine tumours (NETs) derive from neuroendocrine cells that are disseminated in the body, and most frequently arise from the gastro-entero-pancreatic (GEP) and bronchopulmonary tracts. It is a rare neoplasm representing 1–2% of all digestive cancers. The majority of NETs are sporadic, and about 20% of cases are part of a hereditary syndrome. GEP-NETS represent about 60% of NET localizations and are most frequently detected in the midgut and, more specifically, in the small intestine (SI). The incidence has increased particularly in the small bowel and rectum, primarily due to incidental diagnosis upon screening endoscopic procedures.¹ The World Health Organization (WHO) classification, updated in 2022, separates neuroendocrine neoplasms (NENs) into well-differentiated NETs and poorly differentiated neuroendocrine carcinoma (NEC).² NETs, representing 80 to 90% of NEN, are divided into three grades based on mitotic count and the Ki67 proliferative index (**Table 1**). NETs are often indolent, with a median overall survival (OS) of 9.3 years.¹ Prognosis depends on the grade, primary site, and extent of the disease. Localized and G1 NETs are associated with the longest OS (up to 30 years for localized G1 appendix NETs). Pancreatic NETs (pNETs) have a less favourable prognosis than SI-NETs. In this article, we will review the classification, diagnosis, and staging of well-differentiated GEP-NETS, and discuss the different therapeutic options.

Diagnosis and Staging

Diagnosis of GEP-NETS may be an incidental finding or suspected from clinical symptoms (e.g., bowel obstruction, diarrhea, flushing). NENs produce hormones in about 30–45% of cases^{3,4} and symptoms are related to the type of hormone secreted (e.g., insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptide [VIP]oma, somatostatinoma). Carcinoid syndrome (CS), a result of serotonin and other vasoactive substance secretion (e.g., tachykinins, prostaglandins), is characterized by flushing, diarrhea, and right-sided valvular heart disease. It is particularly associated with liver metastasis since it bypasses the hepatic metabolism that inactivates the hormones.⁵ CS has been associated with shorter survival.⁴

Histological diagnosis based on surgical specimen or core biopsy is essential for pathological diagnosis and classification of NENs. It is important to keep in mind that NENs are heterogeneous, even within the same tumour or between different lesions, and this may evolve over time. Intra-tumoural heterogeneity can be detected in up to 30% of NENs, especially in tumours with Ki67 expression >10% and sized ≥ 2 cm. Inter-tumoural heterogeneity, i.e., between different locations, is the result of molecular alterations—some trials reported a higher Ki67 in metastases than primary tumours—and is related to tumour size >4 cm.⁶

	Grade	Mitotic index (/10 HPF)	Ki67 index (%)
Well-differentiated NEN	G1 - low	<2	<3
	G2 - intermediate	2–20	3–20
	G3 - high	>20	>20
Poorly-differentiated NEN = NEC	G3	>20	>20

Table 1. WHO 2022 classification of neuroendocrine neoplasms of the gastroenteropancreatic system²; courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.

Abbreviations: HPF: high-power field, **NEC:** neuroendocrine carcinoma, **NEN:** neuroendocrine neoplasm, **WHO:** World Health Organization

Measurement of 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of serotonin, has an excellent 90 percent sensitivity and specificity for carcinoid syndrome. However, the sensitivity is low in the absence of CS.⁷ Dosage of chromogranin A (CgA), a hormonally inactive glycoprotein secreted by neuroendocrine cells, is generally not recommended for follow-up, mainly because of a lack of specificity. False positive results were reported due to drugs (proton pump inhibitors), food, non-oncologic comorbidities (e.g., renal failure, atrophic gastritis, pancreatitis), and malignancies (e.g., hepatocellular carcinoma, breast and colon cancers).⁸

Diagnostic imaging should combine anatomical and functional modalities. Regular computed tomography (CT)-scans are essential for staging and follow-up. Well-differentiated NETs express the somatostatin receptor (SSTR) on the cell surface in about 80% of cases. Nuclear medicine modalities have a major role in diagnosis and staging and represent a new therapeutic option. The type of positron emission tomography (PET) to be used depends on the grade of the tumour. ⁶⁸Ga-DOTATATE-PET, in combination with CT, is the modality of choice for low-grade and differentiated tumours.⁹ Considering the previously discussed tumoural heterogeneity, for G2/G3 NETs, both ⁶⁸Ga-DOTATATE-PET and fluorodeoxyglucose (FDG)-PET may be indicated to separate low-grade lesions from poorly differentiated ones.¹⁰ In case of metachronous metastases or unexpected progression, a new biopsy could be considered.

Treatment

Surgery

Localized Well-differentiated G1&G2 NETs

For well-differentiated G1 and G2 NETs, surgery is the treatment of choice. The modality and extent of surgery depend on the site and size of the tumour, the local invasiveness, and the risk of lymph node metastasis.¹¹ An endoscopic resection for small size (<1 cm) duodenal, rectal, and type 1 and 2 gastric NETs is a valid option. Non-functional pancreatic NETs sized 2 cm or smaller generally have an indolent course for which an observation strategy may be considered.¹² For young patients, avoiding long-term surveillance with multiple imaging tests and their resulting costs could be an argument for upfront surgery. There is a clear indication of surgery for functional pancreatic NETs, irrespective of tumour size. To prevent carcinoid crisis during surgery, perioperative octreotide treatment has traditionally been recommended. However, its indication is now controversial as a review and meta-analysis showed limited benefit.¹³ An intravenous injection of octreotide should be available in case of hemodynamic instability during surgery, in addition to intravenous fluid resuscitation. There is currently no data to support an adjuvant systemic treatment. Surveillance imaging after curative surgery is recommended for up to 10 years.¹⁴

Advanced and Metastatic Disease

Resection of the primary tumour could lead to prolonged survival in metastatic G1 or G2 GEP-NET cases.¹⁵ Nevertheless, there is a lack of prospective data to conclude a clear strategy. SI-NETs are a particular situation where palliative surgical resection of the primary lesion should be considered because of the frequent association with desmoplasia and fibrosis, which can lead to a bowel obstruction or ischemia. This is particularly true in symptomatic patients with abdominal pain or symptoms of intestinal obstruction.

In cases of GEP-NETs with only liver metastases that can be completely resected, surgery can improve quality of life and survival.¹⁶ When the liver is the predominant site of metastasis but without any surgical possibility, a liver-directed approach like hepatic embolization (e.g., trans-arterial embolization, chemoembolization, or radioembolization) may be a valuable alternative.¹⁷

Liver transplantation could be considered in selected cases of patients <60 years with unresectable liver metastases without other metastatic sites, with a minimum of 6 months of disease stabilization, as assessed by an experienced multidisciplinary team. A systematic review has reported recurrence rates of 33% to 57%.¹⁸

Systemic Treatments Options (Table 2)

Systemic therapy has the dual aim of controlling symptoms and improving survival outcomes. Whether to watch and wait or to treat depends on the tumour characteristics, grade, ki67 expression, sites, and metastatic burden, as well as the presence of symptoms and the aim of the treatment (curative versus palliative). All available options must be explained and discussed with the patient.

Somatostatin Analogs (SSA)

SSA allow tumour-related symptom relief by 70-80% and are the first-line treatment for NETs. Two long-acting SSA are approved and used in Canada: subcutaneous lanreotide autogel (120 mg) and intramuscular long-acting release octreotide (30 mg), which are both given every 4 weeks. Subcutaneous short-acting somatostatin is reserved for rapid control of functional symptoms

and can be given multiple times daily alone or in combination with any of the long-acting SSA. In cases of persistent diarrhea that is refractory to SSA and related to serotonin secretion, telotristat ethyl, an oral tryptophan hydroxylase inhibitor, has shown efficacy in two Phase 3 trials, the TELESTAR and TELECAST trials.¹⁹

Besides their role in symptom control, SSA have an anti-proliferative effect through the inhibition of growth factors, inhibition of angiogenesis, and modulation of the immune system. They are also indicated for both functional and non-functional advanced GEP-NETs with Ki67 <10%, as first-line treatment, alone or in combination with other systemic treatments. In the PROMID trial, long-acting octreotide showed a delayed tumour progression by 8.3 months compared to placebo in patients with advanced G1 midgut NETs.²⁰ The CLARINET trial, which included a larger patient population with advanced non-functional G1/G2 (ki67 <10%) GEP-NETs, showed a significant prolonged progression-free survival (PFS) in patients receiving lanreotide, but no OS benefit.²¹ In situations where there is progression on standard lanreotide dosing, reducing the interval between injections to 21 or 14 days could be an option. This strategy demonstrated encouraging PFS results in the Phase 2 trial CLARINET FORTE, particularly in patients with Ki-67 <10%.²²

Peptide Receptor Radionuclide Therapy (PRRT)

PRRT is a type of targeted therapy that uses a radiopeptide somatostatin analog (DOTATATE or DOTATOC) combined with a radioactive compound (generally ¹⁷⁷Lutetium [¹⁷⁷Lu]) that binds to receptors on tumour cells to deliver radioactivity cytotoxicity. For patients with SSTR-positive GEP-NETs, PRRT is a valid option in the first-line setting, as well as in the second-line after progression on SSA.

The NETTER-1 Phase 3 trial included patients with midgut NET G1 or G2, after progression on SSA, and randomized them to either four injections of ¹⁷⁷Lu-dotatate or double-dosing of octreotide long-acting repeatable (LAR) (60 mg; q4w). In this study, treatment improved PFS (28.4 months versus 8.5 months, $p < 0.001$), but not OS.²³

Indication		Pan		SI		mPFS (months)	mOS (months)	ORR (%)	References/trials
G1-G2	G3	G1-G2	G3	G1-G2	G3				
SSA (vs. placebo) Lanreotide octreotide	1 st line (84%), <u>GEP-NETs</u> , Ki67 <10%, NF					NR vs. 18, $p<0.001$	84.7 vs 83.7, $p=0.51$	2%	CLARINET ²¹
	1 st line, G1, <u>SI-NETs</u>					TTP: 14.3 vs. 6 months, $p=0.000072$		2%	PROMID ²⁰
Everolimus (vs. placebo)	1 st line or later, <u>GEP-NETs</u> , CS					16.4 vs. 11.3, SNS*	29.2 vs. 35.2, NS		RADIANT-2 ²⁷ (SSA + everolimus vs. placebo + SSA)
	1 st line or later (40% not pre-treated), <u>pNETs</u> , G1-G2					11 vs. 4.6, $p<0.001$	44 vs. 37.7, $p=0.3$	<10%	RADIANT-3 ²⁸
	≥1 line, NF, <u>GEP-NETs</u>					11 vs. 3.9, $p<0.00001$	27.3 vs. NA, $p=0.037$		RADIANT-4 ²⁹
SSA + EVEROLIMUS (vs. everolimus)	1 st line, <u>GEP-NETs</u> , NF					29.7 vs. 13.6, $p=0.00016$	NE, HR 0.74 [95% CI: 0.25-2.24]	23 vs. 8.3	STARTER-NET ³⁰
	≥1 line (chemotherapy/SSA/local treatment), <u>pNETs</u> , NF&F					11.4 vs. 5.5, $p<0.001$	38.6 vs. 29.1, $p=0.02$	9.3 vs. 0	Raymond et al, NEJM 2011 ²⁵
SUNITINIB (vs. placebo)	≥1 line (chemotherapy/SSA/local treatment), <u>pNETs</u> , NF&F								
	≥1 line (everolimus/PRRT/TMZ), NF, <u>GEP-NETs</u>					-Pan: 13.8 vs. 4.4, $p<0.001$ -GI: 8.5 vs. 5.6, $p=0.007$	21.9 vs. 19.7**, HR 0.86, [95% CI: 0.56-1.31]	19 vs. 0 1 vs. 0	CABINET ²⁶
PRRT (vs. double dose SSA)	NF&F: 1 st line, <u>GEP-NETs</u>					22.8 vs. 8.5, $p<0.0001$	pending	43 vs. 9.3	NETTER-2 ²⁴
	≥1 line, <u>SI-NETs</u>					28.4 vs. 8.5, $p<0.0001$	48 vs. 36.3, $p=0.3$	18 vs. 3	NETTER-1 ²³
Chemotherapy CAPTEM (vs. TMZ)	≥1 line, G1-G2					22.7 vs. 14.4, $p=0.022$	58.7 vs. 53.8, $p=0.42$	39.7 vs. 33.8	Kunz et al., JCO 2022 ³³
	≥1 line, G1-G3					6.9 vs. 12, $p=0.093$		56.4 vs. 27.3	Apostolidis et al., Cancers 2021 ³⁵ →retrospective trial
FOLFOX (vs. CAPTEM)									

Table 2. Indications and outcomes of systemic treatment for GEP-NET; courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.

■ : selected population

* mPFS significantly longer after adjusting for randomization imbalances such as baseline chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA), age, World Health Organization (WHO) performance score (PS), liver involvement, bone metastasis, lung as the primary site.

** pNET +epNET

Abbreviations: **CAPTEM:** capecitabine – temozolomide, **CI:** confidence interval, **epNET:** extra-pancreatic neuroendocrine tumours, **FOLFOX:** 5-FU-leucovorin-oxaliplatin, **GEP-NETs:** gastro-entero-pancreatic neuroendocrine tumours, **GI:** gastro-intestinal, **HR:** hazard ratio, **mOS:** median overall survival, **mPFS:** median progression-free survival, **NET:** neuroendocrine tumours, **NF:** non-functional, **NF&F:** non-functional and functional, **NR:** not reached, **NS:** non-significant, **ORR:** overall response rate, **pan:** pancreas, **pNETs:** pancreatic NETs, **PRRT:** peptide receptor radionuclide therapy, **CS:** carcinoid syndrome, **SI:** small intestine, **SI-NETs:** small intestine-NETs, **SSA:** somatostatin analogues, **TTP:** time to progression, **TMZ:** temozolomide

The NETTER-2 Phase 3 trial enrolled patients newly diagnosed with advanced GEP-NETs G2-G3 (Ki67 10–55%) and randomized them to either four injections of ¹⁷⁷Lu-dotatate plus octreotide LAR (30 mg; q4w), or octreotide LAR (60 mg; q4w).²⁴ The trial showed a significant gain in PFS (22.5 months versus 8.5 months), and the OS results are pending. NETTER-2 set up PRRT as a new first-line option for G2/G3 (Ki67 10–55%) GEP-NET. It is noteworthy to mention the 2–3% risk of myelodysplasia associated with PRRT. This rate seems even higher in patients who previously received chemotherapy.

Tyrosine Kinase Inhibitor (TKI)

Sunitinib

Sunitinib, an oral multi-targeted TKI, was compared to placebo in a Phase 3 trial that included patients with progressing pancreatic NETs who were previously treated with SSA, chemotherapy, or local therapy. In this study, the median PFS was significantly longer with sunitinib (11.4 months versus 5.5 months)²⁵ Although the survival benefit favoured sunitinib, the median OS could not be estimated because of the high number of censored events.

Cabozantinib

Cabozantinib, another oral multi-targeted TKI, has been evaluated in a recent Phase 3 trial, CABINET, in which patients with advanced G1-G3 NETs (32% pancreatic) who progressed after one or more prior lines (everolimus, sunitinib, or ¹⁷⁷Lu-dotatate). A gain in PFS (8 months versus 4 months) was observed for G1-G2 GEP-NETs, with similar effects found for OS.²⁶

Lenvatinib, sorafenib, pazopanib, axitinib

Lenvatinib, sorafenib, and pazopanib have been evaluated in small Phase 2 trials in patients with GI-NETs, and a signal of activity was detected with response rates of about 22% for pazopanib to 44% with lenvatinib. Axitinib was evaluated in the Phase 3 trial AXINET in combination with SSA for patients with G1-G2 extrapancreatic NETs and

showed a response rate of 13.2% and a PFS of 16.6 months (versus 9.9 months for placebo).

Mammalian Target of Rapamycin (mTOR) Inhibitors

Everolimus has been evaluated in several Phase 3 trials in G1-G2 advanced GEP-NETs. The first trial, RADIANT-2, included mostly patients with progressing SI-NETs associated with CS, who were randomized to receive everolimus 10 mg daily versus placebo, plus octreotide LAR (30 mg; q4w).²⁷ A first analysis did not show a statistically significant gain in PFS. In a subsequent analysis with adjustment for prognostic factors, such as performance status and CgA level, everolimus was found to improve PFS with a 38% reduction risk of progression, but did not benefit OS. The second trial, RADIANT-3, included patients with advanced pan-NETs, and showed a PFS benefit in favour of the everolimus arm (11 months versus 4.6 months).²⁸ Finally, the RADIANT-4 trial included patients with advanced pre-treated non-functional GI-NETs (24%) and lung NETs, randomly assigned to everolimus versus placebo.²⁹ A statistically significant gain in PFS was observed (11 months versus 3.9 months), as well as a trend towards improved OS. The response rate in all these trials was <10%.

Recently, everolimus plus lanreotide versus everolimus alone as a first-line treatment was evaluated in the Phase 3 STARTER-NET trial in G1/G2 GEP-NETs.³⁰ The combination arm showed a statistically significant benefit in PFS (29.7 versus 13.6 months) and ORR (23% versus 8.3%), but not in OS.

The combination of everolimus/bevacizumab versus everolimus alone was addressed in a randomized Phase 2 trial in pancreatic NETs. The combination arm showed a better ORR (31% versus 12%), a minor gain of PFS (16.7 months versus 14 months), no OS benefit, and significant toxicity.³¹ This combination is not approved in Canada.

Chemotherapy

The role and place of chemotherapy in the treatment of NETs have yet to be defined. The primary site, the tumour grade, Ki67 expression, and the burden and aggressiveness of the disease are among the factors determining the indication for cytotoxic drugs. Streptozocin and/or doxorubicin and/or fluorouracil have historically been used and emerged from controversial trials.³²

The most commonly used chemotherapy regimens are capecitabine plus temozolomide (CAPTEM) and 5-FU, leucovorin, and oxaliplatin (FOLFOX). In a phase 2 trial, CAPTEM versus temozolomide alone in pre-treated but chemotherapy-naïve G1/G2 advanced pancreatic-NETs demonstrated a gain in PFS (22.7 months versus 14.4 months) and ORR (40% versus 34%).³³ A systematic review confirmed these data and suggests that this regimen is more effective in pancreatic than non-pancreatic NETs.³⁴

In a retrospective analysis of patients with G3 GEP-NETs who received chemotherapy in the first-line setting, FOLFOX was shown to result in the best ORR (56.4%), and CAPTEM in the longest PFS (12 months).³⁵

Among patients with G1/G3 pancreatic-NETs previously treated with CAPTEM, FOLFOX seems to be effective according to a small retrospective trial (ORR: 45.2%, disease control rate: 93.5%).³⁶

A platinum-based chemotherapy plus etoposide regimen is indicated for neuroendocrine carcinomas, but showed no efficacy in G1/G2 or G3 differentiated NETs.³⁷

Immunotherapy

Trials with immune checkpoint inhibitors have been disappointing, and their role in NETs has yet to be defined.³⁸ The combination of an immune checkpoint inhibitor and anti-vascular endothelial growth factor (VEGF) therapy has shown objective responses and encouraging PFS in a small single-arm trial.³⁹

Sequencing Therapies

The sequence of treatment depends on the localization of the primary tumour site, tumour grade, functional or non-functional status, expression or absence of somatostatin receptor, as well as widespread and growth development of the disease. There is no established consensus on treatment sequencing because trials are lacking. We propose an algorithm of treatment in **Figure 1**. Clinical and radiological surveillance is an acceptable option for asymptomatic disease with a low tumour burden. Choosing between cytotoxic chemotherapy or PPRT for rapidly progressive NETs with high Ki67 should take into consideration the above-mentioned factors and the accessibility to each treatment. The ongoing Phase 3 COMPOSE trial compares these two options, which will inform the best therapeutic strategy.

Conclusion

GEP-NET remains a rare and heterogeneous disease with no clear consensus on the optimal sequencing of therapy. Understanding and predicting the behaviour of the disease depends on multiple above-mentioned disease characteristics. With increasing incidence and prevalence, more patients will be able to enroll in clinical trials, which will help choose the most adequate treatment for patients with NET. Since GEP-NETs are generally indolent and have an expected survival of several years, the indication and effectiveness of treatments with preservation of quality of life must be properly balanced.

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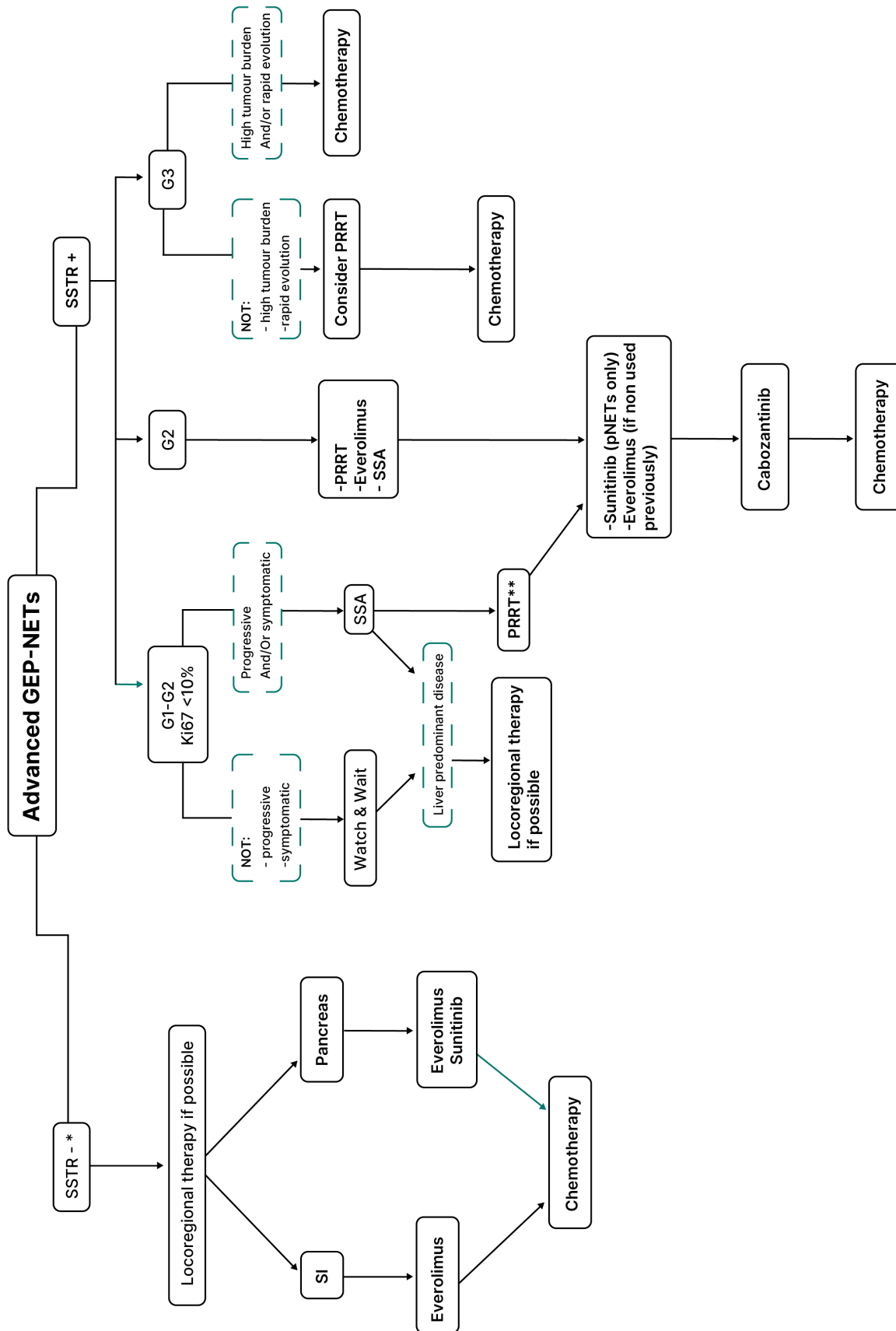


Figure 1. Algorithm for advanced GEP-NETs treatment; courtesy of Nathalie Baudoux, MD and Mustapha Tehfe, MD, MSC.

*SSA could be considered. Positive SSTR status is not predictive of response

**only SI-NETs were included in NETTER-1

Abbreviations: SSTR: somatostatin receptor, SSA: somatostatin analog, PRRT: peptide receptor radionuclide therapy

References

- Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncology*. 2017;3(10):1335–1342. doi:10.1001/jamaoncol.2017.0589.
- WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol.10). <https://publications.iarc.fr>.
- Fottner C, Ferrata M and Weber M.M, Hormone secreting gastro-entero-pancreatic neuroendocrine neoplasias (GEP-NENS): when to consider, how to diagnose? *Rev. Endocr. Metab. Disord*. 2017;18:393-410.
- Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18(4):525–534. doi: 10.1016/S1470-2045(17)30110-9.
- Onaitis MW, Kirshbom PM, Hayward TZ, Quayle FJ, Feldman JM, Seigler HF, et al. Gastrointestinal carcinoids: characterization by site of origin and hormone production. *Ann Surg*. 2000;232(4):549–56. doi: 10.1097/00000658-200010000-00010.
- Bourdeleau P, Couvelard A, Ronot M, Lebtahi R, Hentic O, Ruszniewski P, et al. Spatial and temporal heterogeneity of digestive neuroendocrine neoplasms. *Ther Adv Med Oncol*. 2023;15:17588359231179310. doi: 10.1177/17588359231179310.
- O'Toole D, Grossman A, Gross D, Delle Fave G, Barkmanova J, O'Connor J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biochemical markers. *Neuroendocrinology*. 2009;90(2):194–202. doi: 10.1159/000225948.
- Vezzosi D, Walter T, Laplanche A, Raoul JL, Dromain C, Ruszniewski P, et al. Chromogranin A measurement in metastatic well-differentiated gastroenteropancreatic neuroendocrine carcinoma: screening for false positives and a prospective follow-up study. *Int J Biol Markers*. 2011;26(2):94–101. doi: 10.5301/IBM.2011.8327.
- Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology*. 2017;105(3):212–244. doi: 10.1159/000471879.
- Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010;16(3):978–85. doi: 10.1158/1078-0432.CCR-09-1759.
- Eto K, Yoshida N, Iwagami S, Iwatsuki M, Baba H. Surgical treatment for gastrointestinal neuroendocrine tumors. *Ann Gastroenterol Surg*. 2020;4(6):652–659. doi: 10.1002/ags3.12396.
- Aziz H, Howe JR, Pawlik TM. Surgery vs observation for patients with small pancreatic neuroendocrine tumors. *JAMA Surg*. 2021;156(5):412–413. doi: 10.1001/jamasurg.2020.5640.
- Xu A, Suz P, Reljic T, Are AC, Kumar A, Powers B, et al. Perioperative carcinoid crisis: a systematic review and meta-analysis. *Cancers (Basel)*. 2022;14(12):2966. doi: 10.3390/cancers14122966.
- Singh S, Moody L, Chan DL, Metz DC, Strosberg J, Asmis T, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumors. *JAMA Oncol*. 2018;4(11):1597–1604. doi: 10.1001/jamaoncol.2018.2428.
- Tierney JF, Chivukula SV, Wang X, Pappas SG, Schadde E, Hertl M, et al. Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery*. 2019;165(3):644–651. doi: 10.1016/j.surg.2018.09.006.
- Norton JA, Warren RS, Kelly MG, Zuraek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery*. 2003;134(6):1057–63. doi: 10.1016/j.surg.2003.07.025. PMID: 14668741.
- Kennedy A, Bester L, Salem R, Sharma RA, Parks RW, Ruszniewski P; NET-Liver-Metastases Consensus Conference. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference. *HPB (Oxford)*. 2015;17(1):29–37. doi: 10.1111/hpb.12326.
- Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. *Surgery*. 2017;162(3):525–536. doi: 10.1016/j.surg.2017.05.006.
- Dillon JS, Kulke MH, Hörsch D, Anthony LB, Warner RRP, Bergsland E, et al. Time to sustained improvement in bowel movement frequency with telotristat ethyl: analyses of phase III studies in carcinoid syndrome. *J Gastrointest Cancer*. 2021;52(1):212–221. doi: 10.1007/s12029-020-00375-2.
- Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide lar in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. *Neuroendocrinology*. 2017;104(1):26–32. doi: 10.1159/000443612.
- Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224–33. doi: 10.1056/NEJMoa1316158.

22. Pavel M, Ćwikła JB, Lombard-Bohas C, Borbath I, Shah T, Pape UF, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur J Cancer*. 2021;157:403-414. doi: 10.1016/j.ejca.2021.06.056.
23. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376(2):125-135. doi: 10.1056/NEJMoa1607427.
24. Singh S, Halperin D, Myrehaug S, Herrmann K, Pavel M, Kunz PL, et al. [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus highdose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403(10446):2807-2817. doi: 10.1016/S0140-6736(24)00701-3.
25. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-13. doi: 10.1056/NEJMoa1003825. Erratum in: *N Engl J Med*. 2011;364(11):1082.
26. Chan JA, Geyer S, Zemla T, Knopp MV, Behr S, Pulsipher S, et al. Phase 3 Trial of cabozantinib to treat advanced neuroendocrine tumors. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2403991. Epub ahead of print.
27. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012. doi: 10.1016/S0140-6736(11)61742-X.
28. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-23. doi: 10.1056/NEJMoa1009290.
29. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977. doi: 10.1016/S0140-6736(15)00817-X.
30. Hijoka S, Honma Y, Machida N, Mizuno N, Hamaguchi T, Boku N, et al. A phase III study of combination therapy with everolimus plus lanreotide versus everolimus monotherapy for unresectable or recurrent gastroenteropancreatic neuroendocrine tumor (JCOG1901, STARTER-NET). *J Clin Oncol*. 2025;43(4_suppl). Doi:10.1200/JCO.2025.43.4_suppl.6.
31. Kulke MH, Ou FS, Niedzwiecki D, Huebner L, Kunz P, Kennecke HF, et al. Everolimus with or without bevacizumab in advanced pNET: CALGB 80701 (Alliance). *Endocr Relat Cancer*. 2022;29(6):335-344. doi: 10.1530/ERC-21-0239.
32. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22(23):4762-71. doi: 10.1200/JCO.2004.04.024. Erratum in: *J Clin Oncol*. 2005;23(1):248.
33. Kunz PL, Graham NT, Catalano PJ, Nimeiri HS, Fisher GA, Longacre TA, et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). *J Clin Oncol*. 2023;41(7):1359-1369. doi: 10.1200/JCO.22.01013.
34. Arrivi G, Verrico M, Roberto M, Barchiesi G, Faggiano A, Marchetti P, et al. Capecitabine and temozolomide (CAPTEM) in advanced neuroendocrine neoplasms (NENs): a systematic review and pooled analysis. *Cancer Manag Res*. 2022;14:3507-3523. doi: 10.2147/CMAR.S372776.
35. Apostolidis L, Dal Buono A, Merola E, Jann H, Jäger D, Wiedenmann B, et al. Multicenter Analysis of Treatment Outcomes for Systemic Therapy in Well Differentiated Grade 3 Neuroendocrine Tumors (NET G3). *Cancers (Basel)*. 2021;13(8):1936. doi: 10.3390/cancers13081936.
36. Al-Toubah T, Morse B, Pelle E, Strosberg J. Efficacy of FOLFOX in patients with aggressive pancreatic neuroendocrine tumors after prior capecitabine/temozolomide. *Oncologist*. 2021;26(2):115-119. doi: 10.1002/onco.13611.
37. Donadio MD, Brito ÂB, Riechelmann RP. A systematic review of therapeutic strategies in gastroenteropancreatic grade 3 neuroendocrine tumors. *Ther Adv Med Oncol*. 2023;15:17588359231156218. doi: 10.1177/17588359231156218.
38. Albertelli M, Dotto A, Nista F, Veresani A, Patti L, Gay S, et al. Present and future of immunotherapy in neuroendocrine tumors. *Rev Endocr Metab Disord*. 2021;22(3):615-636. doi: 10.1007/s11154-021-09647
39. Halperin DM, Liu S, Dasari A, Fogelman D, Bhosale P, Mahvash A, et al. Assessment of clinical response following atezolizumab and bevacizumab treatment in patients with neuroendocrine tumors: a nonrandomized clinical trial. *JAMA Oncol*. 2022;8(6):904-909. doi: 10.1001/jamaoncol.2022.0212.