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Systemic therapies for advanced gastroenteropancreatic neuroendocrine tumors

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\textbf{ABSTRACT}

\textbf{Introduction:} Neuroendocrine tumors are a heterogeneous group of malignancies, characterised by production of hormones and vasoactive peptides. The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NET) is rising, and they have the highest prevalence amongst upper gastro-intestinal tumors. Diagnosis remains challenging due to wide variations in presentation and slow onset of symptoms. A multi-disciplinary approach is vital in appropriately managing the diverse spectrum of GEP-NET.

\textbf{Areas covered:} Investigations in GEP-NET and biomarkers are described. Moreover, all available therapeutic options for GEP-NET including surgery, somatostatin analogues, targeted agents, Peptide Receptor Radionuclide Therapy and chemotherapy are also discussed.

\textbf{Expert commentary:} The landscape of management has changed significantly in the last decade as a result of many practice-changing clinical trials. Long-acting somatostatin analogues are used not only for symptom control but also for their anti-proliferative effect. Targeted agents, such as everolimus and sunitinib, have improved PFS in GEP-NET. The recently presented NETTER-1 trial confirms the place of peptide receptor radionuclide treatment (PRRT) in treating NET. While chemotherapy remained an important option for high grade tumors. Despite promising results from recent trials, challenges include establishing the optimal sequencing of therapies to optimize outcome and preserve the quality of life.

\section{1. Introduction}

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are a diverse group of tumors arising from neuroendocrine cells distributed throughout the body, most commonly arising from the gastrointestinal system. Siegfried Oberndorfer described the term ‘karzinoid’ in 1907 for a small intestinal tumor that was less aggressive in behavior when compared to adenocarcinoma \textsuperscript{[1]}. The incidence of neuroendocrine tumors has increased considerably over the past few decades from 1.09 to 5.25 per 100,000 people from 1973 to 2004 in the United States \textsuperscript{[2]}. Most recently, study from Canada reported a similar increase from 2.48 to 5.86 per 100,000 per year from 1994 to 2009 \textsuperscript{[3]}. However, incidence and prevalence vary with different regions of the world \textsuperscript{[4,5]}. The most common site of primary NET is the gastrointestinal system (60\%) followed by the bronchopulmonary tree (27\%), with the following breakdown: small intestine (34\%), rectum (23\%), colon (19\%), stomach (7.7\%), pancreas (7.5\%), and appendix (6.6\%). Prior classification schemes grouped them by both embryonic origin and aspects of histological differentiation, but these did not carry significant prognostic weight nor explain the observed heterogeneity of the clinical course of different patients with GEP-NET. Subsequently, in 2010, the World Health Organization (WHO) proposed the current classification (Table 1) according to mitotic index and Ki-67 (proliferative rate) \textsuperscript{[6]}. Low-grade tumors display a low level of growth and exhibit an indolent clinical course over many years. On the contrary, poorly differentiated tumors have aggressive behavior with guarded prognosis and are treated similarly to small cell carcinoma of the lung with platinum doublet chemotherapy. This heterogeneity makes optimal management of GEP-NET challenging and, therefore, mandates a multi-disciplinary approach involving surgeons, radiologists, gastroenterologists, oncologists, endocrinologists, and nuclear medicine physicians among others.

We discuss key therapeutic options and management aspects for GEP-NET, a field, which is rapidly evolving.

\section{2. Clinical presentation and investigations}

Most GEP-NET are sporadic, but some may be due to familial syndromes, such as multiple endocrine neoplasias 1 (MEN1), Von Hippel–Lindau syndrome, tuberous sclerosis complex, and neurofibromatosis type 1 \textsuperscript{[7]}. It has been suggested that the occurrence of hereditary NET varies with site of origin of the tumor and associated syndrome, ranging 5\% to 30\% of cases \textsuperscript{[8]}. For example, the frequency of nonfunctioning pancreatic endocrine tumor is 54.9\% in MEN1 patients and 20\% in Von Hippel–Lindau syndrome \textsuperscript{[9,10]}. The clinical presentation of GEP-NET depends on the site of the primary tumor, location of metastasis, and also the tumor’s hormone secretion status (functional or non-functional). Most GEP-NET are non-functioning and...
present late with symptoms arising from mass effect and metastases. Nonfunctional tumors are also increasingly diagnosed incidentally on imaging performed for other reasons, or during surgery. On the other hand, functional tumors may present with symptoms related to the active hormone being secreted, such as serotonin, gastrin, insulin, prosta-
glandins, or histamine [11-13]. Interestingly, symptoms are often nonspecific, and patients may often be misdiagnosed with other conditions, such as anxiety, irritable bowel syndrome or food allergy, leading to delay in diagnosis. The classical carcinoid syndrome – the triad of flushing, diarrhea, and bronchospasm – is present in approximately 9% of patients and associated with liver metastases [14,15]. Occasionally, mesenteric fibrosis associated with small bowel GEP-NET leads to bowel ischemia and malabsorption. The same pathophysiological process may also cause fibrosis of the right-sided heart valves, particularly tricuspid, causing progressive heart failure [16]. Around 20% patients with NET present with a degree of carcinoid heart disease at initial presentation [17].

### 2.1. Biochemical markers

NET synthesize and secrete various peptides and neuroa-
mines, which could be used as biomarkers for NET. Chromogranin A (CgA) is the most established biomarker and is used for diagnosis and monitoring in GEP-NET [18,19]. CgA is an acidic glycoprotein, exclusively present in the dense secretory granules of most neuroendocrine cells and released with peptide hormones upon stimulation [20]. Both functional and non-functional NET secrete CgA and elevation of CgA strongly correlates with tumor burden; thus, it serves as a universal marker for NET. A recent meta-analysis suggests the high sensitivity of 0.73 [95% confidence interval (CI) 0.71–0.76] and specificity of 0.95 (95% CI 0.93–0.96) for diagnosis of NET. However, the specific diagnostic performance of CgA may depend on the assay used [21,22]. Nobels et al. reported elevated CgA in 50% (103/208) patients with neuroendocrine tumors. CgA levels were frequently elevated in subjects with gastrinoma (100%), pheochromocytoma (89%), nonfunctioning tumors of the endocrine pancreas (69%), and carcinoid tumor (80%). In subjects with pituitary adenoma (13%), insulinoma (10%), and paraganglioma (8%), elevated CgA levels were only rarely present [23]. Notably, poorly differentiated grade 3 (G3) neuroendocrine carcinoma (NEC) frequently do not secret CgA [24]. Measurement of CgA may also help to detect tumor recurrence during postoperative surveillance and save patients from multiple regular expensive investigations [25]. In addition, multiple small studies demonstrated the prognostic role of CgA, particularly, in pancreatic NET [26-28]. One drawback of CgA as a biomarker is its elevation in other diseases, including renal failure, cardiac disease, other tumors, and false elevation with proton pump inhibitors [20].

Serotonin and its metabolite 5-hydroxyindole acetic acid (5-HIAA) have been measured in blood and urine samples, respectively, as markers of carcinoid syndrome [29]. Despite its high specificity, it is a less preferred biomarker due to the inconvenience in collection, low sensitivity, and false elevation with certain foods and drugs [30]. There are other biomarkers include pancreastatin, chromogranin B and C and neuron-specific enolase, which are less widely used in clinic [30]. Of note, pancreastatin was noticed to have higher sensitivity and specificity in diagnosing NET and also associated with poor prognosis [31,32]. In addition to the above, specific hormones (such as gastrin, C-peptide, tachykinins, serotonin, and vasoactive peptide) could be measured to further delineate the secretory profile of the tumor [30]. However, diagnosis of NET is based on integration of clinical symptoms, biochemical markers, pathology, and radiological appearance of tumors, rather than any single parameter.

### 2.2. Novel biomarkers

#### 2.2.1. Circulating tumor cells

Novel technology development has enabled isolation of circulat-
ing tumor cells (CTCs) from peripheral blood and gave opportunity to learn more about the biology of tumor. The ‘real-time biopsy’ potential based on CTC has range of utility including prognostic and predictive biomarker [33]. A study by Khan et al. analyzed CTCs by cell search system in 176 patients with measurable metastatic NET. It shows 49% patients had ≥1 CTC and that was associated with increased tumor burden, increased tumor grade, and elevated serum CgA. Moreover, the presence of ≥1 CTC was associated with worse progression-free survival (PFS) and overall survival (OS) [hazard ratio (HR), 6.6 and 8.0, respectively; both \( P < 0.001 \)] [34]. Recently, Childs et al. evaluated expression of CTCs in GEP-NET (\( n = 31 \)) patients where 87% patients had somatostatin receptor (SSTR) positive tumors on functional imaging. CTCs were detected in 68% patients, but SSTR2 and SSTR5 staining was positive in 16% and 6% of cases, respectively [35]. This example highlights challenges in using CTCs as a biomarker and require further validational studies.

#### 2.2.2. NETest (multi-transcript molecular signature)

NETest (Wren Laboratories, Branford, CT, USA) is a novel and commercially available, RT-PCR-based molecular test developed to assess 51 NET specific gene transcripts from
circulating messenger RNA (mRNA) and analyze using a series of mathematical algorithms. Modlin et al. compared it to plasma CgA levels at baseline and following treatment in patients with advance GEP-NET (n = 63; treatment-naive: n = 28) in a training set and validated in an independent set. In the treatment-naive GEP-NET group, the PCR score was significantly elevated (P < 0.0001) compared to the treated group. For detection of GEP-NET, the multi-transcript gene signature demonstrated a high sensitivity (85–98%), specificity (93–97%). In patients with low CgA, 91% exhibited elevated transcript markers. Moreover, in detecting differentiation between stable and progressive disease, the biomarker also exhibited high sensitivity (91%), specificity (91%), positive predictive value (86%), and negative predictive value (95%), significantly better compared with plasma CgA testing (P < 0.005). Subsequently, it has been shown to be accurately predicting response to SSA earlier time point than CGA [36]. Moreover, it also helps to identify residual disease after surgical resection or cytoreduction [37]. Furthermore, it is reproducible and not affected by proton pump inhibitors [38]. Therefore, NETest has a role in the identification of disease progression, defining treatment efficacy, and assessment of completeness of resection [29].

2.2.3. MicroRNAs (miRNAs) in NET

miRNAs are endogenous short non-coding RNAs that down-regulate target gene expressions and serve as regulators in the growth process [39]. miRNAs have important roles in development and progression of cancer. Currently, MiRNAs offer promise as a biomarker for cancer detection, diagnosis, and prognosis assessment in both the tumor tissue and circulation [40]. Rubel and colleagues demonstrated the association of miRNA-133a downregulation with progression from primary to metastatic carcinoid neoplasms out of 95 miRNAs [41]. Most recently, Li et al. investigated miRNA expression in 24 specimens with well-differentiated small intestinal NET. Nine miRNAs were significantly dysregulated: five (miR-96, miR-182, miR-183, miR-196, and miR-200) were upregulated during tumor progression, whereas four (miR-31, miR-129-5p, miR-133a, and miR-215) were significantly downregulated in ileal NET [42]. MiRNAs are a promising avenue for further investigation.

3. Radiological imaging

A vast array of functional and non-functional imaging modalities is used to localize, stage, and establish the biological behavior of GEP-NET. Multiphasic CT is the most common modality of imaging for initial staging purpose. As GEP-NET are highly vascular, the tumors enhance intensely with intravenous contrast during the early arterial phase of CT, with wash out during the delayed venous phase. However, CT is not particularly sensitive in detecting small liver lesions [43]. MRI remains a useful tool in evaluating liver metastases, which are hypointense on T1-weighted images and hyperintense on T2-weighted images [44]. In addition, diffusion-weighted imaging (DWI) in MRI helps to differentiate NET metastases from other hypervascular lesions, such as hemangiomas [45]. In a prospective study involving 64 GEP-NET patients with liver metastasis shows the relative sensitivities of somatostatin receptor scintigraphy (SRS), CT, and MRI were 49.3%, 78.5%, and 95.2%, respectively, to detect liver metastasis [46]. Endoscopic ultrasound is a valuable investigation in localizing pancreatic NET lesions with high sensitivity (87%) and specificity (98%) [47].

Functional nuclear imaging plays a crucial role in the diagnosis, staging, patient selection for peptide receptor radio-nuclide treatment (PRRT) and response assessment. NET express SSTR on the surface of the tumor cells according to the degree of differentiation, and this can be imaged with radioactive somatostatin analogs. The most common radio-pharmaceutical agent used for SRS in past decades has been 111Indium–DTPA–octreotide (Octreoscan™), which has a high affinity for the two most common somatostatin receptors (SSTR2 and SSTR5). However, in recent years, 68gallium-based positive emission tomography (PET) (68Ga-DOTATOC and 68Ga-DOTATATE) scan has become increasingly popular due to its marked superior over Octreoscan™ with regard to better spatial and temporal resolution, rapid clearance, and low antigenicity. A meta-analysis of 68Ga-DOTATATE PET scan in the diagnosis of NET (10 studies, 416 patients) demonstrated high sensitivity of 96% (95% CI, 91–99) and specificity of 100% (95% CI, 82–100) [48]. 18F-Fluorodeoxyglucose (FDG) PET has an important complementary role to 68Ga-DOTATATE PET. The FDG uptake is dependent on tumor’s glycolytic metabolism, which is higher in poorly differentiated GEP-NET [49]. Interestingly, Squires et al. conducted a retrospective review of 153, mainly GEP-NET patients, at a single center and demonstrated a low sensitivity of FDG-PET for grade 1 (52%), which increased significantly with grade 2 (86%) and grade 3 (100%). In addition, they also highlighted that the 5-year OS of patients with FDG-PET positive tumors was significantly worse than those with negative tumors (40% vs. 100%, P = 0.006) irrespective of the grade of tumor [50]. Similarly, Binderup et al. conducted a prospective trial of 98 patients with NET has demonstrated FDG-PET uptake as a strong negative prognostic marker with a higher risk of death (HR, 10.3, 95% CI, 1.3–78.9). Moreover, multivariate analysis confirmed standardized uptake value (SUVmax) of >3 was the only predictor of PFS [51]. Thus, FDG-PET has a role in the identification and characterization of high-grade tumors and also potentially can aid in the prognostication of low-grade tumors. The combination of 68GA-DOTATATE PET and FDG-PET could provide additional information to histopathology by demonstrating tumor heterogeneity, and thereby directing further appropriate therapy [52].

4. Treatment landscape

Treatment for GEP-NET should be tailored according to symptoms, the burden of disease, biology, operability and the general health of the patient. The clinical heterogeneity of GEP-NET has made it difficult to conduct large randomized studies of systemic therapy. Although several large trials have shown benefit for somatostatin analogs and targeted agents, in particular, the correct choice of therapy in a particular scenario and sequencing of therapies remain unresolved questions. Multiple guidelines are available to aid treatment
decisions, but differences exist in these guidelines, mainly due to regional variability in available treatment options [53–55]. Fortunately, the results of recent trials such as NETTER-1 and RADIANT-4 trial have continued to expand the range of proven treatment options. We have summarized all available systematic therapeutic options for GEP-NET (Figures 1 and 2, Table 2).

5. Surgery

Large proportion (60–75%) of GEP-NET present with liver metastasis, which also negatively impact overall prognosis [62]. ENETS guideline acknowledged that interventional strategies alter the prognosis with overall 5-year survival increased from <50% to 60–70% in patient undergoing aggressive treatment including surgery for metastasizes compared with historic control. To achieve goal of improvement in outcome, patient need to be selected on the bases of extent of tumor and tumor biology. The minimal criteria required for liver surgery with ‘curative intent’ are: (1) resectable well-differentiated liver disease with acceptable morbidity and <5% mortality, (2) absence of right heart insufficiency, (3) absence of extra-abdominal metastases (previously assessed by CT scan and SRS), and (4) absence of diffuse peritoneal carcinomatosis. A one-step liver resection is feasible for simple unilobar disease while two step sequential approach is required for a complex pattern. For advanced disease, cytoreductive surgery should be considered in patients in whom 90% of the tumor can be safely removed for palliation of symptoms and potentially increased survival [63–67]. A debulking surgery is an alternative option for patients with uncontrolled functional tumors due to hormone secretions or non-functional tumors with symptoms related to tumor burden [53].

Mayo et al. published a cohort study assessing outcomes of surgical treatment for NET liver metastases in comparison to historic control, involving 339 patients including 40% pancreatic NET (pNET) and 25% small bowel primaries, enrolled across eight major international centers. In total, 78% of patients underwent hepatic resection, 3% hepatic ablation and 19% had hepatic resection combined with ablation. The median survival was 125 months, with overall 5- and 10-year survival of 74%, and 51%, respectively, which was three times more than that of historic control of patients of NET with untreated liver metastases. The authors noted that patients with hormonally functional NET who had R0/R1 resection benefited the most from surgery. On multivariate analysis, synchronous liver metastases, non-functional tumor and extrahepatic disease were associated with decreased survival. Interestingly, patients with non-functional hormonal status and R2 resection still carry an excellent median survival of 84 months [68]. In addition to this study, others have suggested that some patients with a high tumor burden may have a survival benefit from an R2 palliative debulking as long as the majority (>75–80%) of the liver disease can be removed [63,68–70]. Moreover, tumor debulking may also facilitate better symptom control with resultant reduction in the secretion of bioactive substances.

6. Liver directed non-surgical interventions

In addition to surgery, multiple other local interventions are evaluated to manage liver metastases from NET including ablative techniques, such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), drug-eluting bead

Figure 1. Systemic therapies in GEP-NET.
therapy (DEB-TACE) and intra-arterial Yttrium-90. However, the role of locoregional treatment is not well defined in GEP-NET as no randomized data are available to compare these treatments with currently available systemic treatments/resection. However, ablative techniques such as RFA can be used to treat patients with lower metastases either as a sole therapy in a selective non-surgical candidate or in combination with surgery. RFA as a sole therapy not recommended in patients with tumors >5 cm in diameter or tumor near vital structures. TAE and TACE may be used to treat liver metastases in patient

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**Table 2. Phase III trials for targeted treatments.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient number</th>
<th>Arms</th>
<th>PFS in months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIANT-2</td>
<td>Mixed NET (n = 429)</td>
<td>Everolimus + octreotide LAR vs. placebo octreotide LAR</td>
<td>16.4 vs. 11.3</td>
<td>P = 0.0066</td>
</tr>
<tr>
<td>Pavel et al. (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RADIANT-3</td>
<td>PanNET (n = 410)</td>
<td>Everolimus vs. placebo</td>
<td>11 vs. 4.6</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Yao et al. (2011)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RADIANT 4</td>
<td>NET GI or Lung origin (n = 302)</td>
<td>Everolimus vs. placebo</td>
<td>11 vs. 3.9</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Yao et al. (2015)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Raymond et al. (2011)</td>
<td>pNET (n = 171)</td>
<td>Sunitinib vs. placebo</td>
<td>11.4 vs. 5.5</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>[59]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SWOG 50518</td>
<td>NET (n = 427)</td>
<td>Bevacizumab + octreotide LAR vs. INF α-2β + octreotide LAR</td>
<td>16.6 vs. 15.4</td>
<td>P = 0.55</td>
</tr>
<tr>
<td>Yao et al. (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NETTER-1</td>
<td>Midgut NET</td>
<td>PRRT (lutathera) vs. octreotide LAR 60 mg</td>
<td>Median PFS not reached vs. 8.4</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Strosberg et al. (2016)</td>
<td></td>
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</tr>
</tbody>
</table>

*Not statistically significant predefined boundary P ≤ 0.0246.

*Pending overall survival analysis.

*Target sample was of 340 patients but study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group.
when surgery is not feasible. They have shown to be effective in symptoms control and tumor growth control. Major side effects are rare but minor side effects include vomiting, pain, fever, elevated transaminases are common [64]. There is consensus that selective internal radiation therapy is still investigational, and further data required for a long-term safety and superiority to other intervention [53]. These treatments should only be considered in selective patients based on size, distribution, number of liver lesions, vascularization, proliferative index and local physicians’ expertise [71].

7. Somatostatin analog

Roger Guillemin received a Nobel prize in 1977 for the discovery of a peptide hormone, isolated from sheep, which could inhibit the release of growth hormone [72]. It soon became apparent that somatostatin had a broad range of inhibitory effects, mediated through binding to specific G-protein coupled surface receptors exhibiting five distinct sub types (sst1–sst5) [73]. Somatostatins’ inhibitory effects are mediated via its exocrine, endocrine, paracrine and autocrine functions [74,75]. The GEP-NET arising from target tissue of somatostatin, express a high density of these receptors with the predominant subtype of sst2 [76], with well-differentiated tumors expressing higher densities than that of poorly differentiated tumors [77]. Even though SSTs share 40–60% homology, they exert different biological actions [78]. Upon activation, they exert an inhibitory effect through four intracellular pathways including; activation of adenyl cyclase, activation of K+ /Ca2+ channels, activation of protein phosphatases and activation of intracellular tyrosine phosphatase [79,80]. Thus SSA’s may help to control symptoms related to excess hormone secretion, and have an antiproliferative effect by inducing cell cycle arrest and/or apoptosis, with inhibition of tumor angiogenesis and growth factors [80,81]. They can also modify the inflammatory response of the immune system to enhance its antiproliferative effect [82,83].

Native somatostatin has a very short half-life (3 min), and thus requires continuous infusion [84]. It can also cause rebound hypersecretion of hormones, thus limiting its routine clinical application for long-term symptom control. Since the 1980s, three long-acting analogs have been developed including octreotide LAR, lanreotide, and pasireotide, with different binding affinity to a range of receptors subtypes [80,85–87]. Currently, they are available for various indications including treatment of symptoms of hormone excess from NET and also for controlling tumor growth.

7.1. Octreotide

7.1.1. Octreotide for symptom control

Octreotide LAR was the first long-acting synthetic somatostatin analog with demonstrated efficacy in both carcinoid symptom control and anti-proliferative effects in patients with GEP-NET [88]. Kvols et al. evaluated 150 μg three times daily in 25 NET patients with carcinoid syndrome. They achieved palliation of symptoms in 88% of patients and reduction of 5-HIAA level in 72% of patients [89]. Subsequently, a randomized phase III study compared short-acting octreotide with octreotide LAR 10, 20, or 30 mg monthly in 93 patients with NET carcinoid syndrome. This showed a similar outcome in all four arms for complete or partial treatment success (58.3%; 10 mg, 66.7%; 20 mg, 71.4%; 30 mg, 61.9%; P ≥ 0.72 for all pairwise comparisons). However, flushing was better controlled by octreotide LAR 20-mg dose [88,90].

7.1.2. Antiproliferative effects

The anti-proliferative effect of octreotide LAR was examined in PROMID, a randomized, placebo-controlled, double-blind phase IIIb study in treatment naive patients with advanced well-differentiated (95% with grade 1) midgut NET [91]. Total 85 patients were randomized to receive 30-mg octreotide LAR monthly via IM injection versus placebo with the primary end point being time to tumor progression. Octreotide LAR significantly improved time to progression when compared with placebo (14.3 vs. 6 months in the placebo arm; HR, 0.34; 95% CI, 0.20–0.59; P = 0.000072). An updated analysis revealed no difference in median OS between patients assigned to octreotide and placebo (84.7 and 83.7 months, HR, = 0.83 [95% CI: 0.47–1.46]; P = 0.51). Patients on both arms received post-study octreotide LAR which could likely effect overall outcome. On subgroup analysis, median survival was poor in patients with high tumor load (57.5 vs. 107.6 months, HR, 2.49, 95% CI, 1.36–4.55; P = 0.002). There was a trend toward improved OS in patients with low hepatic tumor load receiving octreotide compared to placebo (median not reached and 87.2 months; HR, 0.59, 95% CI, 0.29–1.2; P = 0.142) [92]. While some drug agencies, such as the FDA have not as yet approved octreotide LAR for asymptomatic NET, it is widely used in clinical practice and recommended by international guidelines [93,94].

7.2. Lanreotide

7.2.1. Lanreotide for symptom control

Lanreotide autogel is a long-acting somatostatin analog given deep subcutaneously every 28 days. A recent phase III study investigated efficacy and safety of Lanreotide autogel versus placebo in 115 SSA-naïve patients or those responsive to conventional doses of octreotide; lanreotide reduced the need for short-acting octreotide (49% vs. 34%, absolute difference 15%; P = 0.02). However, the trial did not meet its predefined difference (30%) [95]. Even though no direct head to head studies are available, the effects on carcinoid symptom relief seem comparable to octreotide LAR [96].

7.2.2. Antiproliferative effect

The CLARINET study, a phase III randomized, double-blind trial, examined lanreotide 120 mg every 28 days compared to placebo in patients with advanced, well-differentiated or moderately differentiated, non-functioning, somatostatin receptor-positive NET of grade 1 or 2 (with a Ki-67 of <10%) between 2006 and April 2013. Lanreotide significantly improved PFS compared with placebo (median not reached vs. 18.0 months; HR, 0.47; 95% CI, 0.30–0.73, P < 0.001). The estimated rates of PFS at 24 months were 65.1% in the lanreotide group and 33% in the placebo group. However, there were no significant differences between two groups in quality of life or OS. The
most common adverse event (AE) was diarrhea, which was more prevalent in patients receiving lanreotide (26% in the lanreotide group and 9% in the placebo group) [97]. On the basis of CLARINET finding, lanreotide is approved in the United States and Europe to treat unresectable well-differentiated GEP-NET.

7.2.3. Pasireotide
Pasireotide is a new agent and binds with high affinity to most subtypes and exhibits 30–40-fold higher affinity to SSRT1 and SSRT5 than octreotide or lanreotide [98]. In a randomized, double-blind, phase III study, pasireotide long-acting release (pasireotide LAR) 60 mg every 28 days was compared to octreotide long-acting repeatable (octreotide LAR) 40 mg every 28 days in managing carcinoid symptoms refractory to first-generation somatostatin analogs. Similar efficacy in symptom control was observed in the two arms (pasireotide LAR, 20.9%; n = 45 octreotide LAR, 26.7%; odds ratio, 0.73; 95% CI, 0.27–1.97; P = 0.53). The most frequent drug-related AEs (pasireotide vs. octreotide) include hyperglycemia (28.3% vs. 5.3%), fatigue (11.3% vs. 3.5%), and nausea (9.4% vs. 0%) [87]. Pasireotide may be a potential option for the patient with refractory carcinoid symptoms [53]. However, it has poor toxicity profile and absence of superior efficacy to first-generation SSA.

7.3. Summary of SSA
Even though both somatostatin LAR and Lanreotide have shown antiproliferative actions in phase III RCT, there are differences between the CLARINET and PROMID studies including clinical characteristics of patients, tumor biology and tumor assessment as summarized in Table 3. Despite these differences, they have identical HRs for progression of primary midgut tumors. Therefore, it is hard to establish the superiority of one somatostatin analog over the other from these results. Moreover, results are lacking to establish the clear superiority of early intervention over a ‘wait and see’ approach for slow growing well-differentiated tumors.

Other potential strategies to improve the effect of SSA include potent SSAs, dose escalation of current SSAs and combination treatment with other targeted agents and chemotherapy [99,100]. Dose escalation of SSAs above standard recommended dose was reviewed in a retrospective study including 239 NET patients treatment with octreotide LAR above 30 mg every 28 days due to the suboptimal symptom (68%) control and radiographic progression (28%). Improvement and resolution of symptoms were observed in 80% of patients after dose escalation [101]. This strategy is yet to be examined in a prospective randomized trial.

8. Telotristat etiprate (LX 1606)
Excessive serotonin is the key element in the development of carcinoid syndrome. This biological concept led to the discovery of a novel target to inhibit the tryptophan hydroxylase (TPH) activity, which is involved in serotonin (5HT) release, responsible for the carcinoid syndrome symptoms [102]. Telotristat etiprate is an oral peripheral TPH inhibitor that has been developed to offer an additional symptoms control for patients with carcinoid syndrome and diarrhea related to excess serotonin secretion. The phase III study Telotristat Etiprate for Somatostatin Analog Not Adequately Controlled Carcinoid Syndrome (TELESTAR) enrolled 135 patients with metastatic NET with carcinoid syndrome, which was not adequately controlled on SSA therapy and randomized to receive 250 or 500 mg of telotristat etiprate or placebo in addition to SSAs [103]. The result was presented in abstract form at 2015 Neuroendocrine Tumor Symposium. The primary endpoint analysis shows that patients who added telotristat etiprate to the standard of care at both the 250 and 500 mg doses experienced a statistically significant reduction from baseline compared to placebo in the average number of daily bowel movements over the 12-week study period (P < 0.001). Moreover, the proportion of patients with a durable response (≥30% reduction in bowel movement frequency for ≥50% of study period) was 20% (placebo), 44% (LX 1606: 250), and 42% (LX 1606: 500), (P ≤ 0.040 for both comparisons). It also shows significant reduction of 24-h u5-HIAA at week 12 in 40%
patients (LX 1606: 250), and 58% patients (LX 1606: 500), but increased more than 11% in the placebo group (P < 0.001 for both dosages). Mild to moderate depression was the most noticeable side effect in the treatment arm. However, treatment-emergent AEs, serious AEs and discontinuation due to AEs were similar in all three treatment arms [104]. Subsequently, the result of TELESTAR extension phase was reported in European Neuroendocrine Tumor Society (ENET) annual conference and reported a decrease in bowel movement frequency in the placebo group after cross over to telotristat etiprate [105]. Thus, telotristat etiprate could be an additional option for symptoms management but yet to be approved by regulatory agencies.

9. Chemotherapy

Cytotoxic chemotherapy, an established treatment option for most cancers, has a relatively limited role in NET, and particularly in well-differentiated NET. While platinum-based chemotherapy is standard therapy in poorly differentiated NET as in line with small cell carcinoma of the lung, this treatment has a very low response for the slow growing well-differentiated tumors. Moertel et al. demonstrated objective tumor regression rate of 7% in well-differentiated carcinoid tumors compare with 67% in poorly differentiated NECs when treated with cisplatin with etoposide combination [106]. Several chemotherapeutic agents such as streptozocin, TMZ, 5FU, dacarbazine, doxorubicin, irinotecan, topotecan, and platinum agents have been investigated as single agents, or in combination, for NET [107]. However, many trials have included a heterogeneous group of tumors and did not incorporate the newer tumor classification based on Ki-67; this has made it difficult to reach to the conclusion about first line treatment. Nevertheless, it is essential to identify patients with an aggressive variant, classified as NECs, as median survival is poor in the absence of chemotherapy. In addition, treatment of well-differentiated NET with these agents is usually associated with a modest response rate of only 10–20% [107]. Currently, additional to NEC patients, it is also recommended in the patient with grade-2 pNET with bulky disease, high symptom burden, rapid progression in ≤6–12 months and patients with possible chance of achieving a response to allow for surgery as a neoadjuvant option [53].

9.1. Alkylating agents

The largest study reported by Eastern Cooperative Oncology Group compared the standard combination of 5-FU/doxorubicin versus streptozocin/5-FU in 249 advanced carcinoid tumors with different primary sites (25% small intestine, unknown, lung, and rectum). There was a crossover to dacarbazine (DTIC) after progression. There were no differences in the objective response rates (15.9% vs. 16%) and PFS (4.5 vs. 5.3 months) between the treatment arms. However, median survival was 24.3 months in streptozocin arm versus 15.7 months in DTIC arm (P = 0.267). The response rate to DTIC was modest (8.2%) with a median survival of 11.9 months after crossover [108].

In a single-arm phase II study, single-agent DTIC in patients with progressive pNET demonstrated a response rate of 34% and OS of 19.3 months, but it was associated with significant grade four and five toxicities [109]. This result led to the investigation of TMZ, an oral alkylating agent with less toxicity but having the same metabolites. A retrospective study by Ekeblad et al. involved 36 heavily pretreated patients with metastatic NET (12 patients with pNET) receiving single-agent TMZ at 200 mg/m² for 5 days, every 4 weeks. The response rate was 14% with stable disease by 53% and time to progression was 7 months [110]. Subsequently, in phase II trial, 28 patients with metastatic well-modernately differentiated NET (Ki-67 < 20%), with progression on sandostatin 60 mg, received capecitabine 1500 mg/m²/day (PO divided BID, maximum 2500 mg/day) on day 1–14, and TMZ 150–200 mg/m²/day (PO divided BID, lower dose for patients who had prior chemotherapy or extensive radiation) on day 10–14, with the next 2 weeks off, in a 28-day cycle. Interestingly, overall response rate was 43% (11% complete response), and stable disease rate was 54%, the median PFS was >20 month for all patients, and median OS was >25.3 months. The most common G3/4 toxicities were lymphopenia (32%), hyperglycemia (15%, unlikely related), thrombocytopenia (3%), and diarrhea (3%) [111]. These promising results formed a foundation for future studies of TMZ-containing combination chemotherapy for progressive GEP-NET [112]. Currently, capecitabine and temozolomide combination (CAP/TEM) provides an alternative option to STZ/5FU. In other tumor types, the methyl-guanine methyl transferase (MGMT) expression, is associated with TMZ resistance through its ability to remove methyl/alkyl groups from the O6-position of guanine, thereby preventing TMZ-induced DNA damage. Therefore, loss of MGMT could predict response to TMZ as has been clearly demonstrated in the management of gliomas [113]. However, data is not consistent to show high methyl-guanine–DNA methyltransferase (MGMT) expression is associated with therapeutic resistance to temozolomide in patients with GEP-NET [114,115]. Future prospective studies will help to clarify the potential predictive value of MGMT in GEP-NET.

9.2. Platinum agents

Cisplatin and etoposide-based combinations remain standard treatment for poorly differentiated tumors, with high response rates and median OS of 15–19 months [106,116]. A retrospective review of 252 patients with advanced GEP-NEC treated with carboplatin/etoposide or cisplatin/etoposide, demonstrated response rate of 31% and PFS of 4 months and median OS of 11 months, with no difference observed between the two combinations. Interestingly, multivariate analysis suggested that tumors with Ki-67 < 55% were less responsive to platinum-based chemotherapy. This result provides insight into heterogeneity in tumor interaction with chemotherapy according to biological profile based on Ki-67 [117].

Oxaliplatin is widely used in combination with fluorouracil/midine gastrointestinal malignancy. Multiple studies have shown its activity in GEP-NET in combination with 5FU, capecitzabine or gemcitabine [118–122]. Study by Kunz et al. enrolled 40 patients enrolled with an advanced neuroendocrine tumor to receive bevacizumab 7.5 mg/kg IV and
oxaliplatin 130 mg/m² IV on day 1 and capecitabine 850 mg/m² twice daily on days 1–14 on a 21-day. In regards to results, partial response was observed in 23%, stable disease in 71%, and progressive disease in 6%. Moreover, median PFS was 13.7 months and treatment was well tolerated [122].

9.3. Irinotecan

Irinotecan is another frequently used chemotherapy in gastrointestinal cancers and also has activity in small cell lung cancer [123]. Initial phase II trial enrolling untreated extensive stage extra pulmonary small cell carcinoma and received 60 mg/m² irinotecan on days 1, 8, and 15, and 25 mg of cisplatin on days 1–3 for every 28 days’ cycle. After two cycles, objective responses were observed in 10 patients (66.7%), including three complete responses (20%) and seven partial responses (46.7%). The median time to tumor progression was 4.5 months, the median survival time was 11.4 months, and the 1-year survival rate was 46.7%. Toxicities were relatively mild, and there were no treatment-related deaths [124]. Most recently, a large retrospective analysis of 206 patients with GEP NEC, mixed adenoneuroendocrine carcinoma and rapidly progressive NET was conducted from 23 hospitals in Japan. Out of 206 patients, 160 received cisplatin and irinotecan and 46 cisplatin and etoposide. Results revealed better overall response rate (50% vs. 27%), PFS (5 vs. 4 months) and OS (13 vs. 7 months) in favor of irinotecan arm [125]. Irinotecan in combination with 5-fluorouracil (FOLFIRI regimen) has also shown response rate of 31% as second-line treatment after progression on the etoposide–platinum combination [126]. Currently, Irinotecan-containing regimens provide options for first line and second-line treatment [53,127].

9.4. Topotecan

Topotecan-based chemotherapy has a modest response rate in small cell lung carcinoma up to 20% with median improvement in survival of 3 months compared to best supportive care [128]. In a retrospective analysis of 22 patients with NEC treatment with single agent oral topotecan 2.3 mg/m² shows stable disease in five patients with median PFS of 2.1 months and 18% survival at 1 year. Most common toxicity was hematological including leukopenia (grade 3: 14%, grade 4: 9%) and thrombocytopenia (grade 3: 14%) [129]. Thus, topotecan has modest anti-tumor activity in progressive NECs.

In summary, it is prudent to differentiate patients who are candidates for first-line chemotherapy. Not all high-grade patients, defined by WHO criteria, respond similarly to cisplatin-based treatment. Platinum-based chemotherapy has modest response rate for tumors with Ki-67% of 20–55%. Those patients may derive more clinical benefit with other chemotherapy regimens.

10. Interferon therapy

Interferon receptors are expressed in NET and inhibit cell proliferation via induction of interferon-inducible genes and lead to control of hormone secretion, clinical symptoms, and tumor growth, somewhat similar to that of somatostatin analogs. However, they do not act rapidly and have a less favorable safety profile than somatostatin analogs [130]. Subjective response rate of interferon alpha is about 60%, with biochemical responses in 44% and tumor responses in 11% of patients. The addition of interferon alpha to SSA has been investigated in several trials to improve response rate and overcome resistance, but results are not consistent [130-132]. NCCN and ENETS guidelines advise that interferon can be considered as a treatment option for progressive NET [53,93]. Adverse effects of Interferon are frequent and involve multiple systems. Most common side effects are flu-like syndrome, anemia, leukopenia, liver dysfunction, diarrhea and nausea and depression [133]. Hence, interferon is only used in very selected experienced centers due to its significant adverse effects and greater availability of other agents.

11. Targeted treatment

In recent years, molecular profiling and whole genome sequencing have enabled identification of therapeutic targets for many neoplasia, including NET. The most extensively investigated and targetable pathways in NET include PI3 K-AKT-mTOR pathway and vascular endothelial growth pathway. Moreover, advances in functional imaging and therapeutic radiopharmaceuticals have enabled to target NET with PRRT and changed treatment paradigm for patients with SSTR positive NET (Table 3).

11.1. Everolimus

Everolimus (Afinitor, Novartis) is an oral inhibitor of the mTOR pathway, an intracellular serine/threonine kinase that regulates key cell functions involving cell survival, proliferation, and metabolism; it plays a central role in tumorigenesis in many tumors [134]. Multiple observations support the importance of the mTOR pathway in the pathogenesis of NET. First, NET are related to many familial cancer syndromes, such as neurofibromatosis type 1 and tuberous sclerosis, which are due to mutations in the genes encoding proteins that lie upstream from mTOR [57]. The whole genome sequencing analysis of pancreatic NET observed mutation in genes in the mTOR pathway in 14% of the tumors [58]. While analysis by Shida and colleagues noticed the expression of mTOR in 45% of GEP-NET on immunohistochemistry. It was higher in poorly differentiated compared with well-differentiated tumors (67% vs. 27%) [135].

After positive results from early phase studies, the efficacy and safety of everolimus, alone or in combination with SSA, was evaluated in series of phase III trials (RADIANT-2, RADIANT-3, and RADIANT-4) in NET. In the RADIANT-2 trial, 429 patients with advanced functional NET (Primary: 52% small intestine, 10% lung, 6% colon) were randomized to receive either everolimus 10 mg/day plus octreotide LAR 30 mg every 28 days or placebo and octreotide LAR every 28 days. The result favored the everolimus arm with PFS of 16.4 months vs. 11.3 months (HR, 0.77, 95% CI, 0.59–1.00, P = 0.024) for the control arm, but did not reach levels of prespecified statistical significance (P = 0.018). Heterogeneous
study population and imbalance of prognostic baseline covariates favoring the placebo arm could have contributed to the negative results [136]. A subsequent exploratory multivariate analysis, adjusting for imbalance, confirmed a significant PFS benefit for the everolimus arm (HR, 0.62; 95% CI, 0.51–0.87; \( P = 0.003 \)). Significant prognostic factors included baseline CgA levels, WHO PS, lung as the primary site, and bone involvement [59]. Another post hoc analysis of RADIANT-2 study found patients with colorectal NET, a poor prognostic group, had significant benefit from everolimus with octreotide LAR (PFS 29.9 vs. 6.6 months) [137]. In the phase III RADIANT-3 trial, 410 patients with advanced pNET were randomized to receive either everolimus 10 mg/m² plus best supportive care or placebo plus best supportive care. Everolimus was associated with significant prolongation of PFS (11.4 vs. 4.6 months, \( HR, 0.35 \) 95% CI, 0.27–0.45, \( P < 0.0001 \)) [138]. These results lead to approval of everolimus in pNET in the USA and Europe.

Most recently, the RADIANT-4 trial investigated 302 patients with progressive, well-differentiated, non-functioning lung and gastrointestinal neuroendocrine neoplasms. They were randomized (2:1) to everolimus or placebo, both with supportive care. Patients were stratified by tumor origin, performance status, and previous somatostatin analog treatment. Median progression-free survival was 11.0 vs. 3.9 months (HR, 0.48, 95% CI, 0.35–0.67, \( P < 0.001 \)). Although not statistically significant, the results of the first pre-planned interim OS analysis indicated that everolimus might be associated with a reduction in the risk of death (HR, 0.64 95% CI, 0.40–1.05, \( P = 0.037 \)); the boundary for statistical significance was 0.0002. A subgroup analysis confirmed beneficial effects across subgroups based on the primary tumor origin including unknown primary [60]. Most common side effects were stomatitis, diarrhea, fatigue, hypoglycemia, infections, rash, and peripheral edema. However, grade 3/4 side effects include stomatitis, infection and pneumonitis were less than <10%. This series of RADIANT trials confirmed the anti-tumor effect of everolimus on well-differentiated GEP-NET (G1 and G2) and provided a reasonably well-tolerated option for patients with progressive disease.

11.2. Sunitinib

Angiogenesis plays a central role in NET, as evidenced by the relatively increased vascularity of NET frequently demonstrated on CT imaging. Also, expression of VEGF has been noticed in carcinoid and pancreatic NET compared to other tumor types [81,139]. Therefore, the angiogenesis pathway provides an attractive therapeutic target [140]. Sunitinib is an oral multikinase inhibitor with activity against multiple signaling pathways including VEGFR1 and 2 and PDGFR-a and b. In a phase III trial, 171 patients with advanced progressive well-differentiated pNET were randomized to sunitinib 37.5 mg day orally continuously or placebo. The study was discontinued early due to higher rates of serious AEs and death in the placebo group and greater PFS in the sunitinib group. The median PFS was 11.4 months in patients receiving sunitinib compared to 5.5 months in the placebo arm (HR: 0.418, \( P = 0.0001 \)) [141]. Moreover, sunitinib was beneficial for most sub groups in subgroup analysis. At data cut-off, the hazard ratio for death was 0.41 (95% CI, 0.19–0.89; \( P = 0.02 \)) in favor of sunitinib. Subsequent OS analysis at 5 years of follow-up showed a median OS of 38.6 months for those randomized to Sunitinib and 29.1 months for those randomized to PBO (HR = 0.73, 95% CI, 0.50–1.06; \( P = 0.094 \)). The non-significance of these results could be contributed to by 69% crossover of patients from placebo arm to sunitinib upon progression [142]. The common side effects include leukopenia, hand and foot syndrome, hypertension and neutropenia ranging from 6% to 12% comparable to other trials of sunitinib in GIST and renal cell carcinoma. In addition, quality of life scores did not differ significantly in both groups, although diarrhea and insomnia appeared to be statistically worse in the treatment group. This result led to approval of sunitinib for well-differentiated pNET in USA and Europe. Currently, it is also under investigation in a patient with midgut carcinoid (ClinicalTrials.gov, clinical trial identifier: NCT01731925) [143].

11.3. Bevacizumab

Bevacizumab is a humanized monoclonal antibody which binds to VEGF-1 and 2 and leads to tumor growth inhibition by inducing regression of vascularization. It has been investigated in combination with several other compounds including octreotide, chemotherapy, and other targeted agents but has not yet entered routine clinical use.

Two important trials were presented at America Society of Clinical Oncology (ASCO) meeting in 2015. Yao et al. presented SWOG 0518 in which 402 patients with metastatic or unresectable, well-differentiated, G1/2 NET with progressive disease or other poor prognostic features were randomized (1:1) to receive the combination of octreotide LAR 20 mg every 3 weeks with Bevacizumab 15 mg/kg or the combination of octreotide LAR with interferon α-2b (5 million units three times per week). Poor prognostic features were defined as having progressive disease, refractory carcinoid syndrome, grade 2 disease with at least six lesions, or colorectal or gastric primary tumors. In the primary endpoint analysis, median PFS was not significantly different with bevacizumab versus interferon (16.6 vs. 15.4 months (HR, 0.93; 95% CI, 0.73–1.18; \( P = 0.55 \)). Overall response rates were significantly higher with bevacizumab than interferon (12% vs. 4%; \( P = 0.008 \)). Bevacizumab was also superior to interferon as assessed by the median time to treatment failure (9.9 vs. 5.6 months; HR, 0.72; 95% CI, 0.58–0.89; \( P = .003 \)). As expected; grade 3 side effects were less in the bevacizumab arm including hypertension (32%) and proteinuria (9%) [144]. However, results were difficult to interpret, from this trial, as the comparator arm in this trial was not considered universally standard. In addition, Kulke et al. presented CALGB 80,701 phase II trial, which randomized 150 patients with advanced pancreatic NET to receive everolimus 10 mg daily with or without Bevacizumab (10 mg/kg intravenously every 2 weeks). The addition of bevacizumab to everolimus did not statistically improve median PFS (16.7 vs. 14.0 months, HR, 0.80; 95% CI, 0.55–1.17; \( P =.012 \)) or median OS (36.7 vs. 35.0 months HR, 0.72; 95% CI, 0.4–1.28; \( P = 0.13 \)) at cost of very high grade 3/4 toxicities (81%). However, response rate was higher in
combination arm (31% vs. 12%, \( P = 0.005 \)) [145]. There are several other combinations with Bevacizumab under investigation including TMZ, capecitabine/oxaliplatin and other tyrosine kinase inhibitors with response rates ranging from 10% to 50% and stable disease as observed in 68–85% with favorable PFS of 7–12 months [146–148]. These studies provide proof of concept of activity of various combinations, yet to be tested in phase III trials. Incremental toxicity needs to be balanced against any gain PFS/OS in these new combinations.

Given that both sunitinib and everolimus have shown benefit in pNET, decisions regarding treatment choice should be tailored depending on potential toxicity profile and patient status. For example, Everolimus may be more suitable for cardiovascular patients as sunitinib could cause hypertension and rarely heart failure. On the other hand, sunitinib, may be a preferred option for diabetic patients as everolimus could cause hyperglycemia. The integration of an oncology nurse into the current practice model would be useful to educate patients, monitor toxicity and aid in the acute management of side effects [149].

11.4. Peptide receptor radionuclide treatment (PRRT)

The initial success of SRS with \(^{111}\) In labeled octreotide laid down the foundation and inspired the development of targeted radiopharmaceuticals for the treatment of NET. \(^{68}\) Gallium is a radiometal and positron emitter with a half-life of 68 min used for functional diagnostic imaging with PET/CT imaging. On this background, several radiolabeled somatostatin analogs have been developed including \(^{90}\) Y-DOTATOC with \(^{90}\) Ytrrium as \(\beta\)-emitter and \(^{177}\) Lu-DOTATOC and \(^{177}\) Lu-DOTATATE with \(^{177}\) lutetium as \(\beta\)-emitter [61,150]. Both show vast improvement in their distribution profile tumor scintigraphy quality and affinity for (sst2, the main somatostatin receptor subtype in many NET) compared with \(^{111}\) Indium based treatment [151]. The labelled peptide undergoes receptor-mediated internalization and intracellular retention leading to tumour radiation delivery sufficient to control tumour growth [150]. \(^{177}\) Lu-DOTATATE, a radionuclide with a half-life of 6.7 days, emits both B and Y radiation allowing imaging and dosimetry after therapy. In the first large study, the efficacy of \(^{177}\) Lu-DOTATATE was assessed in 310 patients and the toxicity profile in 504 patients. Results demonstrated complete and partial responses in 30% patients with median time to progression of 40 months and median OS of 46 months. Most common acute or subacute adverse reaction includes nausea (25%) vomiting (10%), temporary hair loss (62%) and abdominal discomfort or pain (10%). Serious delayed toxicities occurred in 9 patients including renal failure, liver failure and myelodysplastic syndrome (MDS) [152]. A recent report from Bodei et al. provides long-term toxicity data from 807 patients who received PRRT with 30 months of median follow-up. Significant side effects included grade 3 + 4 nephrotoxicity (1.5%), myelodysplastic syndrome (2.4%) and acute leukemia (1.1%). Development of MDS or AML is more likely in patients who received extensive pre-treatment with chemotherapy [153]. A recent study was also carried out to evaluate the quality of life (QOL) for GEP-NET patients treated with \(^{177}\) Lu-DOTATATE. Results demonstrated significant improvement in the global health status/QOL scale and symptoms score with \(^{177}\) Lu-DOTATATE [154].

Despite multiple retrospective studies and single arm, prospective studies over two decades, no phase III trial was available until NETTER-1 trial. NETTER-1 was a multicenter, randomized, controlled trial evaluating \(^{177}\) Lu-DOTA\(^{2}\)-Tyr\(^{3}\)-octreotate (lutahera) in 230 patients with inoperable, progressive, grade 1–2, somatostatin receptor positive midgut NET. Two-hundred thirty eligible patients from Europe and the United States were randomized to receive lutahera 7.4 Gbq every 8 weeks (x4 administrations) versus octreotide LAR 60 mg every 4 weeks. In regards to the primary end point, median PFS in the lutahera arm is not yet reached, while the median PFS in the octreotide LAR 60 mg arm was 8.4 months (HR, 0.21, 95% CI, 0.13–0.34; \( P < 0.0001 \)). Moreover, from interim results, 18% patients had complete and partial responses (CR + PR) in the lutahera group versus 3% in the octreotide LAR 60 mg group (\( P = 0.0008 \)). Although the OS data was not mature enough for a definitive analysis, the number of deaths was 13 in the lutahera group and 22 in the octreotide LAR 60 mg group (\( P = 0.0186 \) at interim analysis), which gives a positive signal for an improvement in OS. This result of the NETTER-1 trial has established a role for PRRT in NET and also opens up new avenues for treatment of GEP-NET [155].

PRRT has also been assessed in combination with radiosensitizing chemotherapy (5FU or capecitabine) with encouraging initial results; it is also under evaluation in RCT [156–159]. PRRT has also been used after initial therapy for patients who have progressed following an initial response to PRRT without any increase in short-term toxicity [160].

12. Expert commentary

The management of GEP-NET is challenging due to biological heterogeneity, diverse range of symptoms, variable clinical course and limited high-level evidence from large randomized trials. Therefore, a multidisciplinary team approach is essential and recommended [161–163] Overall goals in the advanced setting should be to halt tumor growth, prevent complications, palliate symptoms with minimal drug-related complications while ensuring quality of life is maintained [164].

Currently, it is challenging to predict therapeutic outcome and recommend treatment based on existing evidence, as it is limited to a handful of trials with small patient numbers and a heterogeneous group of tumors. As reflected, by different survival times for various tumor primary sites irrespective of the disease stage at diagnosis [2]. Accurate pathological, and anatomical staging is the first step toward management as treatment is fundamentally different between low versus high grade and low volume localized versus high volume systemic disease. Functional nuclear imaging is essential, not only for more accurate staging, but also in determining biological aggressiveness [165,166]. Cytoreductive surgery should be considered in a highly selected group of patients, either to prevent complications, such as obstruction or to decrease symptoms and
improve systemic treatment when metastatic disease is thought to be resectable.

There are mainly four types of systemic therapeutic options available including somatostatin analogs, targeted treatment, PRRT, and chemotherapy. For low volume low-grade tumors (grade 1), a trial of ‘wait and watch’ approach is a reasonable option to assess the pace of tumor. For well-differentiated GEP-NET, SSA should be consider first-line treatment for symptom control as well as for tumor growth control as demonstrated in CLARINET and PROMID study. Unfortunately, no data yet exists to support a best optimal sequence of available treatment options after progression on maximal dose SSA therapy. Therefore, it needs to be evaluated by risk versus benefit ratio of individual treatment, patient preferences and availability of treatment. NETTER-1 trial has demonstrated excellent efficacy and safety of PRRT across all well differentiated (Ki-67 ≤ 20%) GEP-NET patients and should be considered as second-line treatment. The efficacy of radiosensitizing chemotherapy with PRRT (as well as the optimal regimen) needs further evaluation.

Everolimus for pNET and other GEP-NET and sunitinib for pNET provide improvement in PFS but not in OS, provide alternate option as a second line treatment. Although associated with substantial toxicity, Interferon is considered as second line treatment in some countries. Chemotherapy remains the backbone of treatment for poorly differentiated GEP-NET and also for 3rd/4th line treatment for well-differentiated GEP-NET. Moreover, it is also an valid option for high volume grade 2 GEP-NET where rapid response is required. TMZ and capecitabine combination is a promising treatment, particularly in high-grade disease with Ki-67 < 55. Other chemotherapeutic agents which have shown moderate response rates include streptozocin, DTIC, irinotecan, and platinum compounds, particularly useful for high-grade tumors and NEC.

13. Five-year view

The landscape of cancer care has entered an era of personalized medicine where treatment selection for each patient is becoming individualized. The future management of GEP-NET will hinge on the development of predictive and prognostic biomarkers through an understanding of tumor biology, molecular, and genetic composition. Advancement in technology to identify predictive biomarkers will help guide clinicians in stratifying and subgrouping patients in this complex disease to offer an optimal sequence of treatment and ultimately improve the quality of clinical care. Prognostic biomarkers will help to identify patients with an excellent prognosis, which could be observed and spare them from potentially toxic treatment; while early identification of aggressive variants could warrant a more aggressive approach. The whole genome sequencing of pNET has identified actionable mutations like BRAF and PTEN. Moreover, as an understanding of the NET genomic landscape increases, this, in turn, could facilitate exploration of novel agents and rationalize combination of agents [167].

In addition, advancement in understanding of biological interactions of radionuclides will also give the opportunity to improve PRRT outcome and also help to develop imaging biomarkers for therapy. The exciting avenue of exploration is immunotherapy which has recently been shown to be a successful treatment option for many cancers but has not yet been fully investigated in NET. (ClinicalTrials.gov Identifier: NCT02628067). In addition, integration of interactive mobile technologies in the current model of care could help to capture and research symptoms, quality of life, and toxicity in real time and apply supportive care to improve the quality of life [168].

Key issues

- GEP-NET are widely variable regarding hormone production, clinical behaviour, prognosis and management options; hence; it is recommended to discuss patient in multidisciplinary tumour board to facilitate personified care.
- Functional imaging like 68 Ga-DOTATATE has additional value to traditional imaging to localise burden and also characterize the biology of disease non-invasively.
- Somatostatin analogues (octreotide and lanreotide) control symptoms arising from hormone excess and exhibit anti-proliferative effects in well differentiated GEP-NET; due to their favorable toxicity profile, they are used as first-line treatment in unresectable patients.
- Surgical resection with acceptable morbidity (<30%) and mortality (0–5%), is the gold standard treatment for treatment of liver metastasis to improve survival. Cytoreductive surgery is appropriate when >90% of tumour volume removal is feasible.
- Sunitinib and everolimus are two targeted therapies approved for progressive pancreatic NET and are reserved for use in tumors that have progressed on somatostatin analogue therapy. Recently, the RADIANT-4 trial demonstrated improvement in PFS in other variety of NET including small bowel origin.
- Peptide receptor radionuclide therapy (PRRT) is a promising treatment modality for inoperable or metastasized somatostatin receptor positive GEP-NET tumors patients after progression from somatostatin analogues.
- Chemotherapy combination based on streptozocin is one the treatment option for progressive G1/G2 GEP-NET. Although temozolomide-based chemotherapy is emerging option for this group of patients, poorly differentiated neuroendocrine carcinomas, which carry a poor prognosis, are treated with platinum-based chemotherapy.

Declaration of interest

N. Pavlakis is an advisor for Amgen, Novartis, Pfizer and Roche Pharma AG. TJ. Price is on the advisory board for Ipsen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
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Papers of special note have been highlighted as:
• of interest
• of considerable interest


• Largest epidemiological study of neuroendocrine tumours.


• It highlights current consensus on biomarker in neuroen-docrine tumours.


11. Most updated ENETS consensus guidelines for GEP-NET.


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