HHS Public Access

Author manuscript

Neuroendocrinology. Author manuscript; available in PMC 2022 June 08.

Published in final edited form as:

Neuroendocrinology. 2020 ; 110(6): 444–476. doi:10.1159/000503721.

Neuroendocrine neoplasms of the small bowel and pancreas

Ashley Kieran Clift[1], **Mark Kidd**[2], **Lisa Bodei**[3], **Christos Toumpanakis**[4], **Richard P. Baum**[5], **Kjell Oberg**[6], **Irvin M. Modlin**[7], **Andrea Frilling**[1]

[1]Department of Surgery & Cancer, Imperial College London, London, UK

[2]Wren Laboratories, Branford, Connecticut, USA

[3]Department of Nuclear Medicine, Memorial Sloan Kettering Cancer Centre, New York, New York, USA

[4]Centre for Gastroenterology/Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK

[5]Theranostics Centre for Molecular Radiotherapy and Precision Oncology, Zentralklinik, Bad Berka, Germany

[6]Department of Endocrine Oncology, Uppsala University, Uppsala, Sweden

[7]Yale University School of Medicine, New Haven, Connecticut, USA

Abstract

The traditionally promulgated perspectives of neuroendocrine neoplasms as rare, indolent tumours are blunt and have been outdated for the last two decades. Clear increments in their incidence over the past decades render them increasingly clinically relevant, and at initial diagnosis many present with nodal and/or distant metastases (notably hepatic). The molecular pathogenesis of these tumours is increasingly yet incompletely understood. Those arising from the small bowel or pancreas typically occur sporadically; the latter may occur within the context of hereditary tumour predisposition syndromes. Neuroendocrine neoplasms can also be associated with endocrinopathy of hormonal hypersecretion. Tangible advances in the development of novel biomarkers, functional imaging modalities and therapy are especially applicable to this sub-set of tumours. The management of small bowel and pancreatic neuroendocrine tumours may be challenging, and often comprises a multidisciplinary approach wherein surgical, medical, interventional radiological and radiotherapeutic modalities are implemented. This review provides a comprehensive overview of the epidemiology, pathophysiology, diagnosis and treatment of small bowel and pancreatic neuroendocrine tumours. Moreover, we provide an outlook of the future in these tumor types which will include the development of precision oncology frameworks for

Corresponding author: Professor Andrea Frilling, Department of Surgery and Cancer, Imperial College London – Hammersmith Hospital Campus Du Cane Road, London, W12 0HS, a.frilling@imperial.ac.uk, Tel: +44-208-3833941.

Author contributions:

All authors contributed to the conception of this paper, literature review, writing and critical review. The focus for each author per each section is as follows: Introduction (A.K.C. and A.F.); Epidemiology and risk factors (I.M.M. and M.K.); Pathophysiology (A.K.C. and C.T.); Diagnosis (I.M.M., M.K., L.B. and R.P.B.); Therapeutic strategies (all authors); Quality of life (K.O.); Clinical Trials (A.K.C.); Future Perspectives (I.M.M.)

Disclosure statement:

M. K. is an employee of Wren Laboratories; I. M. M. is a medical consultant for Wren Laboratories. All other authors declare no competing interests.

individualised therapy, multi-analyte predictive biomarkers, artificial intelligence-derived clinical decision support tools and elucidation of the role of the microbiome in neuroendocrine neoplasm development and clinical behaviour.

Keywords

neuroendocrine tumour; neuroendocrine neoplasm; small intestine; pancreas

Introduction

Neuroendocrine neoplasms (NEN) comprise a heterogeneous collection of tumours derived from widely distributed neuroendocrine cells, most commonly arising from the gastroenteropancreatic and bronchopulmonary tracts [1,2]. NEN can be sub-stratified into neuroendocrine tumours (NET), and the more aggressive neuroendocrine carcinomas (NEC) on the basis of proliferation index and differentiation. They present multiple clinical challenges with regards to their protean clinical manifestations ranging from incidental discovery to florid endocrinopathy, as well as consequences of hormone hyper-secretion such as cardiac valve disease. They also possess a proclivity to distant metastasis, and currently available biomarkers have poor laboratory metrics [3]. Historical perceptions of NEN as indolent rarities are wholly incorrect given that over 50% display at least nodal metastasis at diagnosis [2,4], and several studies have demonstrated an evolving epidemiology with clear increments in their annual incidence [5–7]. Data from the Surveillance, Epidemiology, and End Results Program (SEER) database (version 9, 1973–2004) of the US National Cancer Institute suggested that NEN were more prevalent than hepatobiliary, oesophageal and pancreatic adenocarcinomas combined [8]. A palpable theme in recent years has been a movement away from eminence-based to evidence-based practice, exemplified by the first ever randomised phase III clinical trials in this arena [9–12].

Combined, small bowel (SB) and pancreatic (Pan) NEN may represent almost a half of all NEN, and the majority of patients with these tumours have distant metastases at diagnosis [2,13]. Between 61–91% of SBNEN and 28–77% of PanNEN treated at specialist centres display hepatic metastases [14,15]. These two types are the most prevalent, most studied, and among the most aggressive of the NEN family. Furthermore, many of the recent advances in therapy were studied in these tumour types. The management of SBNEN (jejunal and ileal) and PanNEN is primarily influenced by the disease grade, stage, and underlying pathobiology of the neuroendocrine cell type or their direction of differentiation [16,17]. In this review, we provide a comprehensive overview of the epidemiology, pathophysiology, diagnosis, management and quality of life issues of small bowel and pancreatic NEN. We anticipate future perspectives in the clinical care of patients with these tumours, providing an outlook on current status and future advances.

Methods

The authors undertook a comprehensive review of the literature for the purposes of this review article. The PubMed database was searched by the authorship for their relevant sections, with search terms including ‘neuroendocrine’, ‘carcinoid’,

'pancreatic' and 'small bowel/small intestinal' combined with search terms such as 'epidemiology', 'chromogranin', 'biomarker', 'genetics', 'genomics', 'surgery', 'peptide receptor radiotherapy', 'somatostatin', 'quality of life', and 'imaging'. Recent iterations of guidelines from international societies (such as European Neuroendocrine Tumor Society) were also reviewed.

Epidemiology and risk factors

Epidemiology—In 1973, the annual incidence of NEN in the USA was 1.31/100,000 [18]. In 2003, this figure had risen to 2.47/100,000 [19]. Currently, the incidence of NEN in the US is 6.98/100,000 (Figure 1) [5]. This is a ~5-fold increase since the 1973 initial observations, and occurs across all sites, stages and grades. Increased age-standardised annual incidences in NEN have also been documented in Australian [20] (1.7/100,000 in 1989 vs. 3.3/100,000 in 2006), Norwegian [2] (13.1/100,000 in 1993 vs. 21.3/100,000 in 2010) and Taiwanese [21] (0.3/100,000 in 1996 vs. 1.51/100,000 in 2008) registries. According to SEER v18, SBNEN and PanNEN incidences are currently estimated at 1.2 and 0.7 per 100,000, respectively [5]. The overall 20-year duration prevalence of all NEN is estimated at 171,321; SBNEN constituting 32,122 patients with 3-fold fewer PanNEN (10,707) [5]. Possible attributable factors for this increase evolving epidemiology include increased use of endoscopy, and also improvements in the sensitivity of widely used imaging modalities, leading to increased detection of early-stage, asymptomatic disease [5].

The median overall survival (OS) for NEN (irrespective of site and grade) is 9.3 years [5]. For small bowel (median OS: 14 years), this ranges from 70 months (advanced disease with distant metastases) to 170 months (localized disease) and from 30 months (Grade 3) to 160 months (Grade 1). For pancreas (median OS: 3.6 years): 21 months (advanced) to 235 months (localized disease) and from 15 months (Grade 3) to 140 months (Grade 1) [5].

Multivariable analyses have identified that ethnicity, age, differentiation, stage and site all have statistically significant correlations with survival. In general, Caucasian ethnicity, age (<50 years), and localised, well-differentiated NEN exhibit the best survival. Small bowel tumour patients are approximately 1.5 times more likely to survive longer than those with PanNEN [19]. Many of these correlations are self-evident since they pertain to degree of malignancy, disease duration and patient performance status.

Overall survival (median 5-year) appears to have improved between 2004 and 2012 [5]. The hazard ratio (HR) for all NEN has improved to 0.79 (95% CI: 0.73–0.85) consistent with an increase in survival [5]. Substantial improvements were evident for disseminated disease (HR: 0.71 [95% CI: 0.62–0.81]), with metastatic PanNEN demonstrating the greatest improvement (HR: 0.56 [0.44–0.70]) [5].

A degree of caution should be exercised in the assessment of these apparently rising values of incidence and improvements in outcome. The increase in incidence may represent increased awareness. Improved outcomes may be partly attributable to stage migration (the "Will Rogers effect") predicated by improved imaging technology, and improved systemic therapy, such as use of somatostatin analogues. Thus, detection of earlier stage disease will readjust timing of intervention and be associated with diminished disease burden. While it

is attractive to consider risk factor exposure as relevant, few factors have been identified and none have been corroborated. The mortality decreases noted (e.g., 2012 vs. 2004) integrated with an increasing incidence likely represent a combination of more effective diagnosis, earlier therapeutic intervention, improvement in treatment techniques, novel technologies, the development of cohesive patterns of treatment and the rational usage of therapy based upon effective clinical trials [19].

Risk factors—A meta-analysis of all case-control studies undertaken between 1994–2014 comprising 4,144 cases of combined SBNEN and PanNEN and 108,303 controls identified several candidate risk factors for SBNEN and PanNEN [22]. A family history of any cancer, “ever smoking” (but not specifically heavy smoking) [23] and gall-bladder disease/ cholecystectomy were associated with ~1.5-fold increased risk of developing SBNEN [24]. Alterations in bile homeostasis are known to modify bile-salt catabolite production, alter the gut microbiota and modify the mucosal immune environment. These catabolites, which include known tumour promoters (such as deoxycholic acid), are primarily absorbed in the terminal ileum (and neuroendocrine cells) which therefore has a prolonged exposure to these agents [25]. Furthermore, a master regulator analysis has been recently performed - in this case, upregulation of immune markers (such as CD19) had been identified as a critical feature of tumor progression in SBNEN and PanNEN [26]. These are hypothesized to play a role in host tolerance and immune suppression with reprogramming to a more malignant phenotype [26]. Such observations, however, have no current practical clinical application.

Defined risk factors for the NEN of pancreas include a family history. Multiple endocrine neoplasia type 1 (MEN 1) confers a 30–80% life-time risk for developing PanNEN [27]. Other factors include, ever smoking, drinking and diabetes mellitus. Alcohol is a known pancreatic carcinogen while diabetes constitutes aspects that reflect an immune-pancreatic neuroendocrine cell dysfunction. It is relevant that germline single nucleotide polymorphisms in immune-function genes (*TNF* and *IL1B*) are associated with an increased risk of PanNEN [28–30], possibly through their role in inflammation which may increase susceptibility to tumorigenesis. Unlike pancreatic adenocarcinoma, ABO blood type is not associated with an elevated risk of PanNEN [31]. More recent discussions of the role of master regulators and the immune system in the pathogenesis of PanNEN require further rigorous investigation [26].

Pathophysiology

Neuroendocrine cells are those which release hormones subsequent to stimulation from the nervous system, and are distributed throughout the body in many organs, including the pituitary gland, lungs, thymus, thyroid, skin, gonadal tissues, pancreas, adrenal glands, and are scattered throughout the gastrointestinal tract. They are derived from neuroendocrine precursor cells during development, and the functionality of secreted hormones may be diverse. Accordingly, neuroendocrine neoplasms are tumours which arise from these ubiquitously situated cells. In keeping with their protean organs of origin, they are a highly heterogeneous class of tumours in terms of clinical behaviour, their association with endocrine syndromes predicated by hormonal secretion, and proclivity to metastasis.

NEN-related clinical syndromes—Most gastroenteropancreatic (GEP) NEN are sporadic, but approximately 5% arise in the context of caner predisposition syndromes. Some, especially PanNEN may be associated with several familial (inherited) syndromes, the commonest being MEN 1, which results from inactivating mutations of the putative tumour-suppressor *MEN1* gene located on chromosome 11q13.1 [32]. The three main clinical manifestations of MEN 1 include primary hyperparathyroidism (>95% of cases) due to parathyroid hyperplasia or adenomas, PanNEN (25–75%, almost invariably multifocal) and pituitary tumours (20–40%). Such patients can also develop bronchial, thymic and gastric NEN, as well as adrenocortical proliferation, lipomas and ependymomas [33]. Once a MEN 1 diagnosis is established, a *MEN1* germline mutation DNA test should be performed in all patients' kindreds, and *MEN1* mutation carriers should be included in a screening programme for MEN 1-associated tumours, which may begin at age 5 with blood testing for insulinoma, for example [33]. Von-Hippel Lindau syndrome (VHL) is another rare, multi-organ genetic disorder associated with pancreatic lesions, commonly non-secreting PanNEN [34]; it also includes cerebral hemangioblastomas, clear cell renal carcinomas, phaeochromocytomas and cystic pancreatic tumours. Finally, neurofibromatosis type-1 [35,36] and tuberous sclerosis [37] are very rare inherited disorders that can also be associated with PanNEN. Distinct hereditary forms of SBNEN have also been described and their genetic underpinnings are increasingly being elucidated [38–40], such as mutations in *MUTYH,* which encodes MYH glycosylase, involved in base excision repair of DNA. These tend to present as isolated endocrinopathies, as opposed to constellations as seen in MEN1.

GEP NEN can be secretory (i.e. "functional") in up to 30–40% of cases, producing symptoms associated with the predominant hormone/peptide secreted (Table 1). These may comprise the archetypal "carcinoid syndrome" and "carcinoid heart disease". The latter represents the development of cardiac valve fibrosis (mainly tricuspid and pulmonary valves) [41].

There is also the possibility of 'secondary' hormone secretion syndromes in both SBNEN and PanNEN [42]. For example, in the experience of the Uppsala group, 6% of PanNEN patients demonstrated multiple hormone secretions, and 4% had secondary changes of the secreted hormone profiles during follow-up.

Genetic and epigenetic landscape of small bowel NET—Comprehensive exome and whole-genome sequencing efforts have identified SBNET as mutationally 'quiet' compared to other solid neoplasms with 0.1 variants per 10^6 nucleotides, which are mostly transitions (a point mutation in which a purine is changed to the other purine or a pyrimidine to the another)[43]. For comparison, in small bowel adenocarcinoma the median mutational burden is approximately 3.96 mutations per 10^6 nucleotides [44], comparable to colorectal and gastric carcinoma [45,46]. Sequencing of tumours from 50 individuals with SBNET identified 1230 genes with somatic mutations, however 90% were only present in single individuals. The single gene in which a consistent rate of mutation was observed was *CDKN1B* (encodes p27, a cyclin-dependent kinase inhibitor) in 10% of cases, which was confirmed in an extension set of 180 SBNEN (rate 8%) but without a mutational 'hotspot' [47]. These mutations are typically loss-of-function, truncating mutations. The heterozygous frameshift-inducing, loss-of-function mutations observed suggest that *CDKN1B* functions as

a haploinsufficient tumour suppressor gene, however no clear distinction has been observed between *CDKN1B* mutated and *CDKN1B* wild-type SBNET in terms of p27 expression nor clinical behaviour [48]. Whether or not this is a 'druggable' target is yet to be elucidated. Mutations identified in other genes include *APC* (7.7%), *CDKN2C* (7.7%), *BRAF, KRAS, PIK3CA* and *TP53* (3.8% each) [49].

Whilst somatic copy number variations, specifically segmental losses of chromosome 18 have been appreciated to occur in up to 78% of SBNET for several years [47,50,51], identification of mutations in associated candidate tumour suppressor genes has remained somewhat elusive [52], although *LAMA3* (encodes laminin – involved in basement membrane, regulate cell migration and mechanical signal transduction), *SERPINB5* (tumour suppressor) and *RANK/TNFRSF11A* (TNF receptor family, involved in osteoclast biology and lymph node development) show epigenetic changes associated with reduced expression in the setting of chromosome 18 loss, i.e. an epigenetic 'second-hit' after loss of heterozygosity [53]. Recent high-coverage target sequencing of 52 sporadic SBNET identified allelic loss of *BCL2, CDH19, DCC* and *SMAD4* in 44% of cases, all located on chromosome 18 [49]. Chromosomal losses involving 3p, 9, 11q, 13 and 16 have also been demonstrated, as have chromosomal gains on chromosomes 4, 5, 7, 14 and 20, although in a reduced frequency [50,51,54,55]. These chromosomal aberrations appear to coalesce into two distinct progression models: one in which loss of chromosome 18 is followed by further chromosomal attritions (e.g. in 3p, 11q, and 13), and another in which chromosome 18 remains its integrity but tumour genomes display gains on chromosomes 4, 5, 7, 14 or 20 [56].

Despite a paucity of clear driver mutations, integrative genomic analyses have shown profound epigenetic changes relevant to tumorigenesis and metastasis development. Differential promoter methylation of *RASSF1A* and *CTNNB1* has been observed in metastatic versus primary 'midgut' (i.e. GI tract from duodenum to transverse colon) NEN generally (*RASSF1A:* 61% vs. 85%, and *CTNNB1:* 57.6% vs. 27.3%)[57]. In SBNET specifically, increased methylation of *TP73, CHFR* and *RUNX3* is observed [53,58]. Comprehensive molecular profiling of 97 SBNET samples delineated SBNET into three distinct molecular sub-types on copy number variance analysis: group A demonstrated chromosome 18 loss only (55%, including all samples with *CDKN1B* mutations [10%]), group B showed no large copy number variations (19%) and group C was typified by multiple copy-number variations (26%, included chromosomal gain on 4, 5 and 20) [53]. There was significant divergence in DNA methylation profiles between these 3 groups, notably in VEGF, EGFR and mTOR pathways, suggesting clear variation in epigenetic pathogenic mechanisms and possibly molecularly-based treatment stratification, but crucially, significant differences in progression-free survival were observed in a sub-set of 32 sample from patients followed-up after resection of the primary tumour: progression-free survival (PFS) in group A, B and C was: not reached, 56months and 21months, respectively (p=0.02) [53]. Epigenome aberrances may not only unveil putative drivers of tumorigenesis, but also harbingers of a metastatic phenotype – hypermethylation of gastric inhibitory polypeptide receptor gene (*GIPR*) may be seen in 74% of SBNET, and promoter/gene body hypermethylation as well as increased *GIPR* expression associate with the presence of hepatic metastases [53]. Integrative analysis specifically in liver metastases

from SBNET display similar loss of chromosome 18 compared to primary tumours, but increased rates of chromosome 20 gain, deletion of chromosome 19, and gain on 17q, the latter of which has only been seen in metastases (21% thereof) and contains the HER2/neu(17q11–21) proto-oncogene [59]. Global hypomethylation is exaggerated in liver metastases vs. primary SBNET (methylation rates 0.572, 0.515, $p<0.001$), and the liver metastases epigenome is enriched with increased expression of PI3K, ERBB1, PDGFRβ and mTOR signalling pathway components [59].

The microRNA (miRNA) landscape in GEP NEN may bear relevance to novel biomarkers [60–62]. Expression of miRNA in SBNEN tissue is deranged compared to normal small bowel [63], with 39 miRNAs showing significant deregulation (38 upregulated), miR-204–5p, miR-7–5p and miR-375 the most up-regulated, and a 29 miRNA 'signature' evident in SBNEN [64]. Divergences in the 'miRNomes' of localised, locally metastatic and distantly disseminated SBNEN manifest as the downregulation of miR-1 and miR-143–3p in the latter two (most floridly in hepatic metastases), which may in turn bear impact on the expression of FOSB and NUAK2 oncogenes [64].

Genomic landscape of pancreatic NET—In contrast to the presently rather opaque genomic landscape of SBNET, some recurrent mutations in PanNET have been recognised for some time. Early genomic analyses identified that approximately 35% of PanNET harboured *MEN1* mutations [65,66]. In MEN 1, *MEN1* mutations may occur throughout coding regions, commonly with truncating mutations [67]. Physiological menin exerts influence on cell cycle regulation via increasing expression of *CDKN2C/CDKN1B* (suppresses cell cycle), suppressing the function of PI3K/mTOR pathway signalling, and promoting homologous DNA repair which targets double-strand breaks [68].

Exome sequencing of 10 sporadic PanNET with screening of commonly mutated genes in a further sample of 58 PanNET[65] showed that 44% of tumours demonstrated mutations in *MEN1*, and 43% had mutations in *DAXX* (encoding the death-domain-associated protein (DAXX)) or *ATRX* (encoding transcriptional regulator ATRX; mutations in ATRX cause X-linked alpha-thalassaemia/mental retardation syndrome). Mutations in *DAXX* or *ATRX* appeared mutually exclusive. DAXX functions as an apoptotic regulator and influences the intracellular distribution of the known tumour suppressor PTEN [69], whilst ATRX functions include chromatin remodelling. These mutations may promote chromosomal instability, and alternative telomere maintenance (i.e. via telomerase-independent mechanisms) compliant with later observations that 61% of PanNET display abnormal telomeres, all of which had *DAXX* or *ATRX* mutation [70]. Clinical relevance of *DAXX* or *ATRX* loss was shown in a cohort of 321 individuals undergoing PanNET resection: alternative lengthening of telomeres and *DAXX* or *ATRX* loss was significantly associated with higher tumour grade, increased rate of lymph node metastases and distant metastases. Five-year disease free survival and 10-year disease-specific survival was 40% and 50% for patients with DAXX/ATRX negative PanNET, vs. 96% and 89%, respectively, for patients with DAXX/ATRX wild-type PanNET[71].

The most profound characterisation of the genomic landscape of PanNET was that performed by the International Cancer Genome Consortium of 98 PanNET [72]. A lower

mutational load compared to pancreatic adenocarcinoma was observed: 0.82 mutations per megabase DNA (range 0.04–4.56) vs. mean 2.62 (range 0.65 to 28.2) [73]. Five forms of mutational signatures were identified: deamination (spontaneous removal of amine groups from nucleotides, particularly cytosine which predicates GC to AT transitions), APOBEC/AID (enzymatic deamination of cytosine), BRCA (failure of double-strand break repair by homologous recombination), cosmic signature 5 (transcriptional strand bias for T>C substitutions, unknown aetiology) [74] and a hitherto undescribed signature of G:C>T:A transversions driven by germline inactivating mutations in the base-excision repair gene *MUTYH* in conjunction with somatic loss of heterozygosity; this leads to bi-allelic inactivation of *MUTYH*. Evidence of chromothripsis, the occurrence of complex chromosomal rearrangements during a single 'catastrophic' genomic event, was seen in 9% of PanNET, although atypically, *TP53* mutations were absent in such cases. The burden of germline mutations was higher than expected for PanNET, including 4% of cases harbouring deleterious germline variations in *CHEK2,* a tumour-suppressor DNA damage repair gene. Alongside the 41% mutation rate in *MEN1* seen, four core pathways in PanNET pathogenesis were elucidated. First, DNA damage repair deficiencies were observed in 11% of patients; these manifested as mutations in *MUTYH,* as well as *CHEK2* and *BRCA2* (both involved in homologous recombination). Second, in addition to the aforementioned mutations in *MEN1*, genes implicated in altered chromatin modification comprised inactivation of *SETD2* and *MLL3* (mutation 5% and 5%). Third, alterations in telomere length were again confirmed as a major aspect of PanNET pathogenesis, with inactivating mutations in *DAXX* and *ATRX* observed in 22% and 10% of patients, respectively. Lastly, activation of the mTOR signalling pathway is driven by the inactivating mutations of negative regulators of this pathway in 12% of PanNET, such as in *PTEN* (7% mutation rate), *DEPDC5* (2% mutation rate), *TSC1* (2% mutation rate) and *TSC2* (2% mutation rate). *EWSR1* gene fusion events were observed in 3% of cases which appeared to be activating for mTOR, as did amplification of *PSPN*, which functions as a RET receptor ligand [72].

The International Cancer Genome Consortium analysis also identified evidence of somatic copy number variation of the genes which are recurrent mutation targets as aforementioned. Copy number variation was seen in *MEN1* (70%), *MUTYH* (47%), *CHEK2* (49%), *BRCA2* (9%), *SETD2* (51%), *MLL3* (10%), *DAXX* (53%), *ATRX* (19%), *PTEN* (40%), *DEPDC5* (49%), *TSC1* (17%) and *TSC2* (43%).

Chromosomal alterations have been documented in other studies, including: frequent loss of 1q, 3p (including *VHL* gene locus) and 11q (*MEN1* and *ATM* gene loci); inconsistently demonstrated (that is, not observed in every study) and less frequent loss of 6q, 10q (*PTEN* locus) and 11p; and finally recurrent gains on 7q and 9q [75]. Genome methylation studies have demonstrated hyper-methylation of *RASSF1A, CDKN2A* and *VHL* genes and/or their promoter regions, as well as hypomethylation of *ALU* and *LINE1* [68,76]. Notably, PanNET with *DAXX/ATRX* loss and PanNET with chromosomal instability show DNA hypomethylation, suggesting that the latter acts as the conduit through which chromosomal instability is predicated in this tumour sub-set [76].

Global microRNA expression in 44 pancreatic tumours (of which 40 were PanNET) identified a distinctive common signature of pancreatic tumours, comprising expression of miR-103 and miR-2017 alongside lack of miR-155 [77]. PanNET were distinguishable from acinar carcinomas on the basis of 10 microRNAs, and notably miR-21 expression correlated with increased tumour grade (Ki67) and the existence of hepatic metastases. The microRNA landscape of PanNEN has been extensively reviewed elsewhere [63].

The tumour microenvironment—Discrepancies in the apparent activity of anti-tumour agents *in vitro* compared to *in vivo* may be attributable to the effects of the 'tumour micro-environment'. This concept eschews a neoplastic cell-only view of solid tumours, and instead considers the nebular accompanying non-neoplastic network (inflammatory cells, endothelial-related cells, fibroblasts/myofibroblasts, and extracellular matrix) within the cancer niche. Such factors are increasingly appreciated to be implicated in pharmacological treatment efficacy/resistance, tumour aggressiveness, proclivity to metastasis and tumour growth. These have been extensively reviewed elsewhere [78,79].

By virtue of their expression of pro-angiogenic factors, including but not limited to vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and angiopoietin-2 (more so in PanNEN) [78], neuroendocrine tumours are highly vascularised, with a microvasculature network up to an order of magnitude denser than that observed in epithelial neoplasms. The 'neoangiogenic switch' may be related to tumour-infiltrating immune cells, but this requires further investigation. Perturbed angiogenesis is relevant to targeted therapy such as sunitinib and mTOR inhibitors (and resistance thereto), but whilst it is clearly fundamental to tumorigenesis, its role in metastasis in NEN is not yet fully clear.

Fibrosis is an appreciated phenomenon in NEN, which may cause extracellular matrix remodelling (an arbiter of tumour development), but also distant fibrotic complications such as cardiac valve disease ('carcinoid heart') or mesenteric desmoplasia, which are sources of significant morbidity in NEN patients [80]. It is believed that these fibrotic complications are mediated via a serotonin-related mechanism: serotonin receptors are recognised to be implicated as the target of several pharmacological agents that predicate drug-induced fibrosis, and the receptors themselves can mediate proliferation of interstitial cells and fibroblasts in models (reviewed extensively in [79]).

Knowledge of the immune landscape in NEN is in relative infancy. PanNEN have a relatively 'cold' immune environment compared to pancreatic adenocarcinoma carcinoma with few tumour infiltrating lymphocytes [81]. In SB NET, this landscape is heterogeneous and the prognostic effects are unclear [79]. Program death 1 (PD-1) and related ligands within the PD-L1 and PD-L2 pathway have generated much excitement as targets in other malignancies for immunotherapy: expression of PD-L1 is seen in approximately 22% of NET generally, with the highest expression in G3 tumours [82]. Trials are ongoing to assess the role of PD-1 inhibitors in GEP NET. Results from the KEYNOTE-028 trial (pembrolizumab) relevant to NEN have been published in abstract form, wherein it has been demonstrated that 1 and 14 of a total 16 PanNEN patients showed objective response and stable disease, respectively [83].

Diagnosis

As relatively rare neoplasms, NEN are not currently the subject of screening or preventative initiatives. The only exception is surveillance for the development of PanNEN in certain hereditary tumour predisposition syndromes with clinical/biochemical/radiological means [84,85]. Mostly sporadic, the clinical features of SBNEN and PanNEN have diverse symptomatology (Table 1).

Tumour grading is based on the Ki67 index or number of mitoses per 10 high-powered fields (HPF) [16]. NEN may be classified as neuroendocrine tumours (NET) or neuroendocrine carcinoma (NEC). Grade 1 (NET) have a Ki67 of <2% or <2 mitoses per 10 HPF. Grade 2 (NET) have a Ki67 index of between 3–20%, or between 2–20 mitoses per 10 HPF. Grade 3 NEN have a Ki67 index of >20%, or >20 mitoses per 10 HPF, and can be sub-classified into G3 NET and G3 NEC – this is on the basis of their differentiation. Grade 3 NET are well-differentiated, and G3 NEC are poorly differentiated.

Tumour staging is detailed in Table 2 (for SBNET) and Table 3 (for PanNET).

Biochemical investigations—NEN produce bioactive agents which may be measurable analytes specific to an individual cell/tumour type. In addition, many NEN co-secrete chemicals associated with granule exocytosis or maturation e.g., chromogranin A (CgA) or neuron-specific enolase (NSE) (Table 4) [86–88].

The most frequently used biomarkers (i.e. plasma or serum CgA) are non-specific and have significant shortcomings such as limited sensitivity and specificity, and scope for drug interference (e.g. proton pump inhibitors) or false positives in renal insufficiency or dialysis. As a consequence, their clinical utility is limited [89]. While measurements of individual hormone markers like insulin or VIP can help rule-in a diagnosis of a specific PanNEN e.g., insulinoma or VIPoma, they have no widespread use because they do not function as “pan”-NEN markers. As a consequence of laboratory limitations and inadequate clinical utility, the development of informative molecular tool (a “pan”-NEN marker) is an unmet need. To resolve this, evaluations of circulating tumour cells (CTCs) or multianalyte biomarkers (e.g., miRNA, mRNA and metabolomics-based markers) have been undertaken.

miRNA biomarkers [63] either derived from tumour cells or from the local microenvironment have passed the early developmental stages and are now undergoing investigation [90]. Recent longitudinal assessment of miRNA profiling in SBNEN undergoing resection demonstrated an ability to discriminate between SBNEN patients and healthy controls with an area under the curve (AUC) of 0.951, with capabilities in identifying residual and recurrent disease [91]. CTCs, though intuitively attractive as a direct measurement of tumour cell-related events [92,93] have, to date, failed to provide evidence of broad clinical utility [89]. This reflects the inability to capture all tumour cells, the heterogeneity of captured cells and the limitations in the molecular assessment of a single cell. Currently, technological inadequacies in the “capture and count” strategy, as well as the complexity of single cell analysis remain limitations [89,94]. As a diagnostic test, CTC measurement is only accurate in ~50% of NEN [95] (that is, CTC can be detected in only half of the cases of confirmed metastatic NEN).

The role of metabolomic profiling in NEN is an encouraging novel approach in the field. Briefly, this technique involves the assessment of metabolites and their interactions in biological tissue/biofluids. Therefore, it is multiparametric and transcends measurement of single metabolites such as urinary 5-HIAA. Metabolic phenotyping of urine has been shown to differentiate between healthy controls and NEN patients (AUC 0.9), distinguish SBNEN and PanNEN, and has power of class separation between functional and non-functional NEN, although with much lower accuracy and possibly low clinical utility (AUC=0.6). Importantly, this approach has capability of delineating those with and without metastases on the basis of class-specific variation in hippurate metabolism (AUC 0.86) [96]. Hippurate is associated with the microbial degradation of certain dietary components, so it is possible that this suggests a link between gut microbiome and NEN (especially SBNEN). Further work is underway to ascertain the diagnostic, prognostic and predictive capabilities of this approach.

The 'NETest' is a multigene expression-based (mRNA) assay developed from transcriptomic analysis of GEP NEN [97,98]. Measurements appear robust and exhibit a consistent and reliable high degree of sensitivity and specificity (both >95%) [97]. The values are standardised, reproducible, and are not influenced by age, gender, ethnicity, fasting, or acid suppressive medication [99,100]. The assay has been independently validated [101]. Since the multi-gene assay captures diverse functional "omic" components of each tumour, the assay provides a broad molecular biological characterisation of tumour behaviour. In several studies comparing the NETest with single analyte measurements for diagnosis, the NETest is superior [102–104] (Figure 2). One prospective study compared the NETest to CgA, pancreastatin (a post-translational derivative of CgA) and neurokinin A, a neurologically active peptide sometimes produced by SBNEN. Using age-matched and gender-matched GEP NEN (n=41) and controls, the area under the curve (AUC) for the NETest was 0.93 compared to ~0.6 for the others [102]. The NETest was 93% positive whereas single analytes were positive in ~40%. In two other independent studies, a daily clinical practice registry audit (NCT02270567) of NEN [103] and a prospective, university-based study [105] the diagnostic accuracy of the NETest was confirmed to be 95–100%. Physician confidence in using monoanalytes like CgA or pancreastatin was low (accuracy 25–50%).

Prognostic and predictive biomarkers—Alterations in biomarker levels can define prognosis and provide information about outcome irrespective of intervention. In this respect, a NEN-relevant example is high grade (G3) lesions, which have a significantly worse prognosis than G1/ G2 neoplasia [106]. A highly elevated CgA (>6× upper limit of normal) has been associated with a poorer prognosis for SBNEN but not PanNEN [107] which reflects the low diagnostic accuracy of CgA for PanNEN [108]. High NETest lssevels (≥80), in contrast, has been demonstrated in three separate studies to be an effective (accurate in ≥95% of patients) prognostic marker [103,109,110]. Moreover, a positive NETest score after "complete resection" in lung and GEP-NEN is associated with disease recurrence [111,112]. Overall, elevated NETest levels are >80% more accurate than CgA as a prognostic marker [111,113].

Predictive biomarkers provide information regarding the effect of a therapeutic intervention. The majority of NEN biomarker studies do not differentiate between a predictive and

prognostic function, despite the fact that biomarkers can exhibit both features. Current investigations indicate that CgA, urinary 5-hydroxy-indole acetic acid (5-HIAA, a catabolic product of serotonin excreted from NEN), and tumour grade have prognostic utility [89]. However, they do not have predictive utility. In peptide receptor radionuclide therapy (PRRT) however, prediction of efficacy has been demonstrated using a multigene test in an individual patient. The measurement of the expression of 8 genes combined with tumour grade (positive predictor quotient [PPQ]) was demonstrated to be ~95% accurate as a predictive tool in a developmental cohort [114]. Accuracies in subsequent independent prospective validation in two PRRT studies were 93–97%, versus 0% in two cohorts either receiving somatostatin analogues or no treatment. Thus, a specific multianalyte test can function as a predictive biomarker for a specific treatment modality [115].

A further possible example of a predictive biomarker is the use of MGMT promoter methylation status in the use of the alkylating chemotherapeutic agent temozolomide for PanNET – lower expression of MGMT is correlated with favourable progression-free survival, treatment response and overall survival in a retrospective study [116], but the statistical significance of this is unclear, with clarity on the matter pending results from an ongoing trial (NCT03217097).

Molecular imaging, radiological and endoscopic investigations—Imaging plays a fundamental role in diagnosis, staging, treatment selection and follow-up. Current modalities (Table 5) include radiological techniques (multiphasic multidetector computed tomography [CT] and magnetic resonance imaging [MRI]), endoscopic techniques (endoscopic ultrasound [EUS], enteroscopy, video capsule endoscopy), and molecular functional imaging (hybrid tomographic positron emission tomography [PET]/CT and single positron emission CT [SPECT] techniques). Scintigraphy with ^{111}In-pentetreotide (or 99mTc-EDDA-HYNIC-TOC) has almost universally been replaced by PET with ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA)[117]. Other PET techniques include ^{18}FDG, ^{18}F-DOPA, ^{11}C-5-HTP, GLP-1, ^{64}Cu-SSA and ^{68}Ga-labeled somatostatin receptor antagonists [117–119]. No modality, however, is entirely effective, and the overall sensitivity and specificity is ~80–90%[120]. Typically, sensitivity and specificity can be optimized by integrating anatomic and molecular imaging (Figure 3)[121,122]. Despite substantial advances, a number of critical unmet needs remain. These include more accurate delineation of therapeutic responses, integration of molecular imaging into response criteria, and systematic integration of novel molecular genomic, biologic and image feature information with imaging[123,124].

Morphologic Imaging—Small bowel neuroendocrine primaries are rarely visualised on CT. They are typically small (mm) and up to 30% may be multifocal. Their mesenteric lymph node metastases, however, frequently appear as contrast-enhancing, spiculated masses on CT, sometimes containing calcifications and surrounded by striae of desmoplastic reaction (fibrosis) [125]. Vascular involvement can be assessed by CT-angiogram. Contrast intestinal radiography, video capsule endoscopy and double-balloon enteroscopy can provide information on the location of the primary within the intestinal tract (i.e. if not seen on CT) [126,127]. CT enteroclysis is inferior to video capsule enteroscopy (sensitivity and

specificity: 50% and 25% vs. 38% and 100%, respectively) [128]. Morphologic imaging in general understages disease significantly [129].

PanNEN are highly vascularised and enhance during the arterial and venous phases on CT. Heterogeneous enhancement may occur in larger necrotic lesions [130]. On MRI, they are hypointense on fat-suppressed T1-weighted sequences, hyperintense on fat-suppressed T2, and hyperintense on diffusion images. They enhance after gadolinium, becoming hypointense to isointense [131]. An overview of 11 studies (343 pancreatic NEN) reported CT to have a mean sensitivity and detection rate of 73%, with a 96% specificity. Mean sensitivity and specificity for MRI were 93% and 88%. EUS could detect 45–60% of duodenal lesions and 90–100% of pancreatic lesions [118]. A combination of CT and EUS may reach 100% sensitivity for the localization of a primary pancreatic lesion [132].

The most common site of distant NEN metastasis is the liver and lesions are often hypervascular like the primary. They are hypodense on CT, with rich enhancement during the arterial phase, and during the portal phase [133]. Larger necrotic metastases may enhance heterogeneously. Likewise, on MRI, liver metastases are usually hypointense on T1, hyperintense on T2, and show restricted diffusion on diffusion-weighted (DW) images. After gadolinium, they demonstrate arterial enhancement and washout[134]. Hepatic arterial phase and fast spin-echo T2-weighted sequences are the most sensitive[135]. The introduction of liver-specific contrast gadoxetate allows for greater detection sensitivity (anatomic detail, spatial/contrast resolution) [134]. Overall, MR has a higher sensitivity than CT [136]. The per-lesion sensitivities are 37.5–80% for CT, 32.6–100% for MRI; per-patient specificities are 100% for CT and 88.9% for MRI [137]. However, none of these studies referenced histopathology, which demonstrates that ~50% of lesions are not detected by imaging [129].

Molecular imaging—Functional imaging using PET/CT is essential for detecting small lymph node metastases (<10 mm in size), tiny primary tumours in the small bowel (especially ileum), for detection of initial bone and bone marrow metastases, for excluding extra-abdominal disease and for a more accurate assessment of occult liver metastases not seen at high-quality imaging techniques. Most well-differentiated (i.e. most G1 and G2) SBNEN and PanNEN are characterized by high expression of somatostatin receptors (SSTRs), which enable receptor mediated PET/CT imaging, such as PET/CT using ^{68}Ga-SSAs (DOTATATE, DOTATOC, DOTANOC, NODAGA-JR11, etc.) or the less effective somatostatin receptor scintigraphy (SRS) using the γ-emitters Indium-111 (^{111}In) or Technetium-99 (^{99m}Tc) [138]. Numerous advantages including easy synthesis (with a ^{68}Ge/Ga generator), high spatial resolution (~4–5 mm), simple image quantification, favorable dosimetry and the possibility of modifying clinical management in 44% of patients has made ^{68}Ga-SSA PET/CT the technique of choice [139–141].

The sensitivity of ^{68}Ga-SSA PET/CT for NEN is >90%, with specificity ranging between 92–98% [142–145]. It is essential for the detection of the primary tumor and identification of mesenteric lymph nodes and/or local tumor extension to determine the most appropriate surgical resection for SBNEN. In PanNEN, with an accurate delineation of primaries as well as identification of peripancreatic vascular involvement for evaluation for possible surgery, ^{68}Ga-SSA PET/CT has a significant impact on the surgical treatment decision.

^{68}Ga-SSA PET/CT is more sensitive than DW-MRI in the detection of pancreatic NEN in a direct head-to-head comparative study [146]. ^{68}Ga-SSA PET/CT, if available, should be considered as the first-line diagnostic imaging method for staging in patients with PanNEN [147]. ^{68}Ga-SSA PET/CT has a pivotal role in evaluation for surgical treatment and should be performed prior to any treatment decision for SBNEN or PanNEN. In a series of 52 patients with neuroendocrine liver metastases, results of ^{68}Ga-DOTATOC PET/CT altered the initial treatment decisions based on CT and/or MRI alone in nearly 60 % of patients [148].

Establishing the extent and progression of NEN are necessary to decide which treatment option to choose. The uptake in the tumor lesions as shown by ^{68}Ga-SSA PET/CT, tumor dynamics (doubling time, new lesions after previous treatments), extra-hepatic tumor burden, functional activity of primary tumor and the metastasis, as well as tumor size, location with/without liver metastasis are important factors to select targeted therapies and to optimize individualized treatment planning. Following the determination of high expression of SSTRs of the tumors using receptor mediated imaging, PRRT is then instituted using therapeutic pairs (e.g. beta- or alpha-emitting radioisotopes) labeled with the same probe, as a “THERANOSTICS” strategy for personalized treatment, i.e. using targeted therapies based on specific targeted diagnostic tests.

NEN can also be imaged with ^{18}F-DOPA PET (6-L-^{18}F-dihydroxyphenylalanine) and ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP), which accumulate within cells due to the high activity of L-DOPA decarboxylase. The availability of ^{68}Ga-SSA peptides and their superior sensitivity as compared to ^{18}F-DOPA [149,150] has diminished enthusiasm for the latter technique which does not possess a therapeutic counterpart.

Targeting increased glycolytic metabolism, ^{18}F-FDG is the archetypal oncological radiotracer, yet it is not a primary diagnostic tool in well-differentiated NEN. It is generally recommended for poorly-differentiated NEN, although it has been reported as positive in 57% of G1 and 66% of G2 NEN [151]. Its optimal application, however, may be G2 NEN with Ki67 >15–20% for which ^{68}Ga-SSA PET/CT is less reliable[152]. Increased metabolic uptake can provide predictive information regarding survival [153]. NEN with increased metabolic activity have a significantly lower disease control rate (76% vs. 100%) and PFS (20 vs. 32 months) after PRRT, compared to ^{18}F FDG-negative tumors [151]. It has recently been proposed that FDG may be an independent prognostic marker using a three-tier metabolic grading system based on the tumor to background ratio of uptake [154].

^{64}Cu-SSA-PET/CT may improve the resolution of liver lesions[155]. Radiolabeled SSTR antagonists, characterized by a lack of internalisation were recently introduced into clinical trials. These antagonists, such as ^{68}Ga-NODAGA-JR11 or -LM3 exhibited a higher detection rate for liver metastases and had a significantly higher lesion-based overall sensitivity compared to ^{68}Ga-DOTATOC [119,156]. Other receptor targeted imaging, for example, the chemokine receptor CXCR4 appear promising in higher-grade tumors and glucagon like peptide-1 receptor PET/CT in benign insulinomas which are usually characterized by a low expression of SSTRs [157]. Finally, GLP1 receptor peptides for

imaging of well-differentiated insulinomas (exendin analogs labeled with ^{68}Ga) have shown encouraging results [158] but have limited availability outside of select centres.

Therapeutic strategies

Management strategies for SBNEN (Figure 4) and PanNEN (Figure 5) encompass treatment of the primary tumour, locoregional lymph node and distant metastases (particularly those in the liver), tumour-related symptoms/syndromes, and carcinoid heart disease if present. In non-distantly disseminated disease, resection of the primary tumour and locoregional lymph nodes may be curative. Locoregional and distant disease is commonly encountered and may be amenable to several therapeutic strategies within a multimodal treatment concept.

Consideration of multiple clinico-pathological features is relevant not only to treatment selection, but also prognostication in terms of overall survival. This is self-evident given the interplay between disease characteristics, tumour behaviour/status and therapy selection. The presence of carcinoid heart disease, mesenteric lymph node metastases, distant abdominal lymph node metastases, liver metastatic burden, extra-abdominal metastases, skeletal involvement and peritoneal carcinomatosis are independent prognostic factors for overall survival in SBNEN [159]. Bone metastases have a distinct prognostic impact to that of other distant metastases (inferior overall survival with the former) [160], and although occurring only in approximately 5% of metastatic GEP NEN, lung metastases have significant detriment to overall survival which is in addition to that presented by distant metastases at other sites [161]. Multivariate prognostic scores have been developed for both SBNEN and PanNEN in terms of overall survival or recurrence post-surgery [162–165].

Surgical intervention for primary tumours - SBNEN—Several options exist for the surgical treatment of the primary tumour. All patients with localised SBNEN with or without regional metastases in the mesenterium should be considered for curative resection [166,167]. As part of the surgical approach, meticulous intra-operative exploration of the abdomen and small bowel palpation is advised [168]; this is superior to all currently available gold-standard imaging modalities in terms of lesion detection, as up to 70% of patients' disease is understaged by preoperative imaging [169]. This is particularly important as approximately 30–54% of SBNEN are multifocal [170] and often only a few millimetres in size, which is rarely appreciated on imaging [169]. A laparoscopic approach is therefore not advisable.

A key issue in resection of SBNEN is not necessarily the primary tumour *per se*, but the focus on preserving bowel function whilst selectively resecting mesenteric lymph nodes. Extensive en-bloc small bowel resections should be avoided as these may predicate short bowel syndrome. The length of resected bowel does not correlate with the number of excised lymph nodes [171], and skip metastases (i.e, those outside the 'expected' lymph node region) may occur in up to two-thirds of patients, which may mandate extensive lymphadenectomy to prevent unresectable locoregional recurrence[172]. An examination of 1,925 SBNEN patients from the SEER database without distant metastases found that the number of resected then histopathologically examined lymph nodes and lymph node ratios

(involved nodes:total nodes) were prognostic for overall survival – patients with 12 or more resected and examined lymph nodes had the best survival outcomes [173].

In asymptomatic patients with stage IV SBNEN, prophylactic ‘up-front’ locoregional surgery is discussed controversially, although it appeared to not be associated with favourable survival outcomes compared to delayed locoregional surgery [174]. Up to 30% of SBNEN are associated with peritoneal carcinomatosis (PC) [175], which is infiltration of the peritoneum with tumour deposits and an independent negative prognosticator [159]. As PC may cause intestinal obstruction and cause death in 40% of SBNEN if not treated [175], resection of peritoneal lesions should be part of locoregional surgery [176].

Resecting the primary tumour in the setting of unresectable liver metastases from SBNEN may avert ileus, gut obstruction and desmoplastic reaction, and it may be associated with prolonged survival [177–179], which in a retrospective study was irrespective of tumour grade [180]. However, such studies have a bias towards an aggressive approach in patients with a better baseline performance status, thus the relative attribution of benefit to the procedure versus the underlying characteristics of individuals is unclear.

There is also some experience with intestinal transplantation for highly selected patients with SBNEN with mesenteric lymph node metastases not amenable to standard surgical techniques of resection [181].

Surgical intervention for primary tumours – PanNEN—Patients with functional PanNEN irrespective of size, and those with non-functional and, therefore, asymptomatic Pan NEN >2cm should be evaluated for surgery [182]. However, the relatively arbitrary 2cm cut-off may not be valid as a standalone arbiter of potential for malignant behaviour in non-secretory PanNEN, as 38% of these tumours ≤2cm display malignant features (i.e. metastasis to nodes) and a 2 cm cut-off for surgery has an 84% sensitivity for malignancy [183]. Typical resections (pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy) or atypical parenchyma-sparing resections may be used. Atypical resections may have lesser long-term endocrine/exocrine sequelae but there are risks of pancreatic fistulae (abnormal connections between pancreas and other organs/structures) [184]. Post-operative complications with pancreatic surgery do not appear to associate with the risk of recurrence of PanNEN [185].

Surgical exploration is advised for MEN1-associated gastrinomas as they are frequently metastatic, necessitating aggressive surgery [186]. There is lack of consensus regarding appropriate aggressiveness in MEN1- associated insulinomas [187]. Conservative management of MEN1-associated non-functioning PanNEN ≤2cm may be associated with low disease-specific mortality [188], whereas this is inappropriate in tumours 3cm or larger [189].

Endoscopic ablative technologies may also be utilised in PanNEN patients that would be poor candidates for surgery, or where extensive resection is not desired [190].

In line with the specific considerations for MEN1-associasted PanNEN, PanNEN arising in the context of von Hippel Lindau disease (VHL) are also subject to focussed strategies. In

a multinational registry of over 2000 patients, it was identified via multivariate prediction modelling that VHL-PanNEN should be considered for operated if their size approaches 2.8cm in diameter [191]. A genotype-guided approach integrating genetic sequencing and tumour dimeter data has been advocated for directing risk stratification – in a study of 229 patients with pancreatic lesions in VHL, those with a missense mutation in *VHL* developed metastatic disease significantly more frequently and required surgical intervention more so than others, especially those with mutations in exon 3 [192].

Surgical management of neuroendocrine liver metastases (NELM)—Surgery is an integral component of multimodal strategies for NEN: 67–91% of small bowel NEN and 28.3–77% of pancreatic NEN treated at specialist centres display metastasis to the liver [193], and surgery is associated with the most favourable outcomes [3,194] but also constitutes an important palliative option [195]. These decisions are guided by tumour grade and morphologic growth patterns of NELM – type I corresponds to single metastasis, type II denotes isolated metastatic bulk with accompanying smaller deposits, and type III refers to disseminated metastatic spread; unfortunately, only up to 20% of patients may be candidates for surgery [196]. Radical resection of disease with curative intent, i.e. partial hepatectomy, is associated with median 5-year and 10-year overall survivals 70.5% (range 31–100%) and 42% (range 0–100%), respectively [197], and is suitable in patients with G1/G2 NEN with type I disease burden, or selected patients with type II liver deposits. Despite the role of surgery in G3 neoplasms usually being restricted to rare cases of localised disease, there is fledgling evidence that resection/ablation of LM from G3 neuroendocrine carcinoma improves overall survival (median OS 35.9months vs. 8.4months without) [198]. Advanced surgical procedures such as two-step resections may be considered [199]. Cytoreductive resection has a purely palliative intent, and can be considered in patients with G1/G2 liver metastases too extensive for curative resection, and/or causing excessive hormone-related symptoms. The classically promulgated target of 90% extirpation may not be necessary, with a 70% target possibly beneficial without significant detriment to outcomes [195,200]. Regardless of the resection margin attained, NELM almost invariably recur – median 5-year and 10-year disease-free survival after surgery with curative intent is only 29% and 1%, respectively [197]. Accordingly, resection should be regarded as an ultimately palliative strategy offering longer term control. This is predicated by even gold standard imaging significantly understaging disease, specifically hepatic micrometastases [129,201].

Patients with traditionally non-resectable liver metastases due to small-for-size liver remnant may be considered for two-stage hepatectomy with portal vein ligation/separation or associated liver partitioning and portal vein ligation for staged hepatectomy (ALPPS).

Patients with unresectable disease may be considered for orthotopic liver transplantation, and a recent systematic review has detailed median 5-year overall survival of 63%, comparable to hepatocellular carcinoma [202]. Essentially all published studies have been retrospective in nature, and the selection criteria for transplantation are typically poorly described in many series, if at all [203]. Therefore, it is difficult to identify clear consensus on the optimal selection tools to identify patients most likely to benefit from this radical approach to guide organ allocation. Generally, patients have G1/2 disease, a primary tumour drained by the portal venous tract which is itself resectable. The ‘Milan NET’

criteria diverge from this insofar as they are clearly documented and have been utilised in a prospective series. The ‘Milan NET’ criteria for patient selection for orthotopic liver transplantation in neuroendocrine liver metastases[204], in the context of completely resected primary tumour are as follows:

- Age <60
- G1/G2 tumour grade
- Primary tumour drained by the portal venous system
- Metastatic involvement limited to the liver
- Hepatic tumour burden not >50%
- Six months of no tumour progression

Excellent outcomes have been attained with these criteria, i.e. 10-year overall and disease-free survivals of 88.8% and 86.9%, respectively [204]. As aforementioned, other institutional protocols for patient selection are poorly described in the literature, yet there appears to be some agreement regarding contraindications in such reports, such as high grade disease (G3) and non-resectable extra-hepatic metastases [179]. Living donor liver transplantation is uncommon but represents another possible avenue in the context of shortages of deceased-donor organs. It is important however, to rigorously consider these highly favourable results with liver transplantation executed to highly selective criteria in the context of scope for significant bias. Narrow selection criteria by definition introduces bias and may optimise overall survival regardless of the true treatment effect.

Multivisceral transplantation has been used in a very small number of cases [205,206]. Novel concepts include neoadjuvant PRRT [181,207,208], or adjuvant somatostatin analogue therapy post-transplant to reduce the risk of recurrence.

Non-surgical therapeutic strategies for liver metastases—Alternatives in the armamentarium for neuroendocrine liver metastases include locally ablative techniques (i.e. radiofrequency, microwave, laser or ‘cryo’ ablation) and percutaneous interventional procedures (i.e. transarterial embolization (TAE), transarterial chemoembolisation [TACE] and selective internal radiotherapy with yttrium-90 particles [SIRT]). Some studies have also detailed selective hepatic artery infusion of peptide receptor radionuclide therapeutics [209].

Ablation may be used as a repeatable, stand-alone modality for incompletely resectable liver metastases, or as a surgical adjunct, and may offer rapid symptom alleviation in metastases refractory to pharmacological therapy. The ablative modalities are associated with 5-year overall survival rates of 37–57%, with the best results obtained in liver metastases smaller than 5cm in size and ablation margins >1cm [210,211].

The percutaneous angiographic techniques seek to exploit the observation that hepatic metastases obtain the majority of their oxygenation from the hepatic artery, and they are especially helpful in liver-predominant disease (metastatic NEN in which metastases are located exclusively or predominantly in the liver) of grade 1 or 2. Briefly, the hepatic artery may be blandly embolised, or infused with embolic beads/microspheres which may secrete

chemotherapeutic agents or emit radiation. Clear comparison of the differing modalities may be complex due to the divergent response assessment criteria used in retrospective case series. For TACE, the median objective response rate is 58.4%, and median overall survival from first procedure is 34.9months [212]. The average objective response rate for SIRT is 51% (95% CI: 47 to 54%), the average disease control rate is 88% (95% CI: 85 to 90%) [213], and the response rates may correlate with survival [214]. One-, 2- and 3-year survival post-SIRT is 72.5%, 57% and 45%, respectively [215]. The degree of hepatopulmonary shunting must be evaluated prior to SIRT to avoid deposition of radioactive embolospheres in the pulmonary circulation. The best outcomes are observed in patients with <50% hepatic tumour burden and no extra-hepatic disease [3,216].

Treatment with TAE, TACE and SIRT may be associated with the post-embolisation syndrome, comprising a constellation of fatigue, fever, deranged liver function and abdominal pain. A recent systematic review of percutaneous angiographic techniques identified grade 3 toxicities occurring in up to 25% of those receiving TACE, and up to 13% of those undergoing SIRT [212].

Future randomised controlled trials are required to identify if any of these angiographic techniques is superior to the other, superior to non-interventional modalities, or if specific tumour types respond better to one variation.

Somatostatin analogues—Octreotide and Lanreotide are cyclic peptide somatostatin analogs (SSAs) which bind with high affinity to SSTR2, and also moderately to SSTR3 and SSTR5, which are expressed on many several types, but particularly neuroendocrine cells. Somatostatin's physiological functions include regulation of hormone secretion (including suppressing release of serotonin, insulin and growth hormone). SSAs have been the cornerstone of treatment of the carcinoid syndrome, attaining significant symptomatic relief in up to 80% of patients.

Octreotide was the first analog developed in 1982, first in a short acting form [217]. Long-acting SSA formulations have been developed, such as octreotide LAR [218]. Lanreotide has similar efficacy as octreotide in reducing flushes and diarrhoea in patients with carcinoid symptoms, and exists as a long-term formulation administered subcutaneously [219]. Data on symptomatic responses (diarrhea and flushing) to octreotide LAR and long-acting Lanreotide have been reported to be 74.2% and 67% respectively [220]. Side effects of somatostatin analogs are in generally mild and include nausea, bloating and diarrhoea that resolve over time. There is a long-term risk of developing gallstones. In addition to symptomatic relief, SSAs may exert an anti-proliferative activity as SSTRs may be implicated in cellular pathways involved in proliferation and apoptosis [219]. A review of trials conducted between 1987 and 2011 [221] and randomized controlled trials (RCTs) revealed that octreotide and Lanreotide can contribute to achieving stable disease and tumour reduction and increase median time to progression [222] [10]. Whilst the anti-proliferative effect has manifested as prolonged progression-free survival, their effect on overall survival has not yet been demonstrated. For example, long-term follow-up of the PROMID trial demonstrated that the OS in treatment and placebo arms were 84.7 months and 83.7 months (HR = 0.83, 95% CI: 0.47 to 1.46, p=0.51). Pasireotide LAR binds to

4 out of 5 SSTRs, and demonstrated symptom control (reduced diarrhea and flushing) in patients with SBNETs in a phase II multicenter study [223]. Additionally, pasireotide LAR and octreotide had a similar effect on symptom control patients with advanced GEP-NETs whose disease related symptoms were un-controlled by first generation somatostatin analogs [224]. However, further development of pasireotide LAR in GEP NEN is currently on hold. Tryptophan hydroxylase (TPH), rate limiting enzyme in serotonin synthesis, converts tryptophan to 5-Hydroxytryptophan which is subsequently converted to serotonin. Telotristat ethyl is a novel, oral small molecule and TPH-inhibitor that can reduce bowel movement frequency in patients with the carcinoid syndrome [225].

Interferon therapy—Interferon Alpha is considered to be a second line therapy in neuroendocrine tumors that are functionally active with low proliferation capacity, such as G1/G2 SB NEN and well-differentiated PanNEN [226]. It may be suitable to use interferon alpha as an add-on therapy to somatostatin analogs in functioning tumours. An alternative treatment is Pegylated interferon alpha. Interferon alpha has an anti-proliferative activity and may be considered for anti-proliferative purposes if other approved drugs are unavailable, especially in small intestinal NEN, advanced gastrointestinal NEN, G1 with progressive disease or with other poor prognostic features[227].

Interferon Alpha therapy appears to be associated with a more considerable side effect/ toxicity profiles as compared to SSAs. Possible side-effects include flu-like symptoms, fatigue and neuropsychiatric derangements. Hepatotoxicity occurs in up to 30% of patients, and haematotoxicities including anaemia, thrombvocytopaenia and leukocytopaenia may occur in 25%, 10–20% and 40–60% of patients, respectively [228].

Peptide receptor radionuclide therapy—Patients with G1/G2 disease with non-resectable metastases may be suitable for Peptide receptor radionuclide therapy (PRRT); this utilises radiolabeled octreotide derivatives, such as ^{90}Y-octreotide (^{90}Y-DOTA-Tyr^{3} -octreotide) and ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC (^{177}Lu-DOTA-Tyr^{3},Thr^{8}-octreotide) for NEN treatment [229]. This is widely used in Europe and has been introduced into the USA recently. Wider international implementation is anticipated. Non-controlled studies in PanNEN and SBNEN have demonstrated its effectiveness: objective responses (Figures 6, 7) occur in 28–39% [230,231], symptomatic improvements have been noted, and a positive impact on survival parameters is documented [154,231,232]. A recent phase III, randomised, controlled trial of midgut NEN, progressive on standard-dose octreotide LAR (NETTER-1), demonstrated ^{177}Lu-DOTATATE to be more effective than high-dose octreotide LAR (median PFS 28.4 months versus 8.4 months), resulting in a 79% reduction of the risk of progression and a significant symptomatic improvement (e.g. fatigue, diarrhea, pain) [9,233]. ^{177}Lu-DOTATATE has been approved by the EMA (September 2017) and by the FDA (February 2018).

PRRT with either ^{90}Y-octreotide or ^{177}Lu-DOTATATE or -DOTATOC is generally well-tolerated, with modest toxicity to the kidneys and bone marrow. Acute side effects include mild nausea (25% of patients), and vomiting, related to the co-administered nephro-protective amino acid infusion (in up to 10%) [234]. Subacute effects include mild to moderate fatigue, mild alopecia, and mild hematologic toxicity (WHO grades 1 or 2)

transiently in 85–90% of patients [235]. Severe (grades 3 and 4) toxicity occurs in 10–15% irrespective of the type of radiopeptide used; this is usually reversible and very rarely requires transfusion or granulocyte support [234]. The spectrum of permanent myelotoxicity ranges from reduction of bone marrow reserve to secondary myeloproliferative diseases (myelodysplastic syndrome and leukemia) but these are rare (approx. 2%). They do not occur more frequently than with other myelotoxic treatments [235–237].

Strategies to stratify patients and identify those that will benefit are a key unmet need. Currently, the intensity of SSTR overexpression (assessed on molecular imaging) is used but has low sensitivity (<60%) [238]. As an alternative, measurements of the expression of specific NEN transcripts in blood integrated with the tumor grade provide a PRRT predictive quotient (PPQ) which stratifies PRRT “responders” from “non-responders” and may become an additional important option. This quotient exhibited a 95% accuracy in three independent cohorts demonstrating patients can be effectively identified prior to PRRT [115].

Chemotherapy and targeted agents—Prior to the realisation of biologic or molecularly-targeted agents, systemic chemotherapy was the only option within the armamentarium for advanced GEP NEN. Initial reports with streptozocin (STZ)-based regimens demonstrated impressive response rates (69%) especially in PanNEN, however no objective radiological criteria were utilized, whilst the overall impact on survival was rather low [239]. Thereafter, several typically retrospective series have demonstrated a role of systemic chemotherapy in G3 NEN (either poorly differentiated neuroendocrine carcinomas, or well differentiated tumours) and in PanNEN, whilst its role in small intestinal NEN remains doubtful [240]. The chemotherapy regimens used in G3 NEN are platinum-based, in particular cisplatin or carboplatin in combination with etoposide, whilst in PanNEN, the combination of 5-FU and STZ has been most commonly used [241]. Recently, oral temozolomide (TMZ) plus capecitabine has become more popular, demonstrating better response rates in PanNEN based on retrospective series, however, there is no directly comparative trial to date comparing STZ with TMZ-based regimens [242]. TMZ-regimens may have a role even in G3 NEN with Ki67<55% and especially well-differentiated morphology, in whom the response rate of platinum-based regimens seems to be lower, based on the results of the large retrospective NORDIC study [243]. In clinical practice, systemic chemotherapy is the first choice in patients with advanced G3 NEN and in advanced symptomatic G1/G2 PanNEN with high tumour volume, whilst it is considered as second line treatment in G1/G2 PanNEN with signs of substantial clinical or radiological progression [193]. More studies are needed to identify: a) the role of chemotherapy as neo-adjuvant or adjuvant treatment, b) factors predictive of response and c) the optimal second-line chemotherapy regimen upon progression following first-line therapy, especially when other systemic treatments are considered inappropriate.

Advances in understanding of molecular pathways implicated in angiogenesis, proliferation and overall tumour growth have resulted in the introduction of molecular targeted agents, such as mTOR inhibitors and tyrosine kinase inhibitors (TKI). Oral everolimus, an mTOR inhibitor has demonstrated substantial effect on median PFS in large randomized phase III trials, which included patients with advanced and progressive PanNEN (11 months vs 4.6 months of placebo) and non-functional gastrointestinal NEN (11 months vs 3.9 months of

placebo) [244]. Similar results were noted with oral sunitinib, a TKI, in a randomized phase III trial with progressive PanNEN, where the median PFS was 11.4 months vs 5.5 months with placebo [245]. Although the objective response rates have not been impressive (≤5%) with these agents, there is a trend towards prolonging overall survival (sunitinib) [246]. In clinical practice, everolimus and sunitinib are considered as first line options in advanced PanNEN with reduced somatostatin receptor expression, and as second-line options in progressive G1/G2 Pan NEN. Everolimus can be also used a second-line treatment in progressive, non-functioning, G1 NEN [193]. Recently, bevacizumab, a monoclonal anti-VEGF antibody and pazopanib, a multi-TKI have been evaluated in phase II trials, however, more data are needed to establish their beneficial role [247].

Whilst there are no extant trials in which direct comparisons are made between molecular/targeted therapies in NEN, one important recent study was the systematic review and network meta-analysis of trial data by Kaderli, et al [248]. The study authors identified randomised controlled trials in the NEN field in which 2 or more therapies were used. Thirty randomised controlled trials were identified, and patients were assigned to 22 different therapies in total. The network meta-analysis comprised 16 trials, and multiple therapy combinations were projected to have significant effects on disease progression compared to placebo. For example, in panNEN: everolimus plus SSA (hazard ratio and 95% confidence interval, HR=0.35 [0.25 to 0.51]), interferon plus SSA (HR=0.31 [0.13 to 0.71]), and everolimus plus bevacizumab plus SSA (HR=0.44 [0.26 to 0.75]). In gastrointestinal NEN, effective combinations included: everolimus plus SSA (HR=0.31 [0.11 to 0.90]), PRRT plus SSA (HR=0.08 [0.03 to 0.26]), and bevacizumab plus SSA (HR=0.22 [0.11 to 0.90]). Overall, the trend appeared that combination therapies are appropriate for NEN patients and possible superior to single-modality treatment.

Quality of life

There are manifold treatment-related effects on quality of life in GEP NEN, for example, the risks of post-pancreatic surgery complications (exocrine failure, endocrine failure leading to diabetes, and also pancreatic fistulae), the risks of short gut syndrome in SBNEN (avoidable by adhering to surgical principles as detailed earlier), and also risks of medical therapies (diabetes with everolimus therapy, and gallstones with SSAs). However, the impacts of NEN on quality of life transcend therapy-related complications.

Health related quality of life (HRQoL) expresses the objective impact of health status on an individual's wellbeing and has become an important endpoint in NEN research, as individual objective (that is, measurable) clinical parameters are not necessarily reasonable proxies of HRQoL. Over 20 questionnaires have been developed to assess this[249], and the most widely used is the cancer-specific EORTC QLQ-C30, which has been psychometrically validated for most common tumours. However, EORTC QLQ-C30 may not be sensitive enough to detect small changes in HRQoL in NEN patients during treatment. The EORTC QLQ-C30-GINET21 [250] may be more sensitive to aspects of treatments such as toxicity, symptoms and tumor progression. The Norfolk QOL-NET questionnaire represents an alternative to the EORTC QLQ-C30 GINET21 with certain added advantages[251] as

Norfolk QOL NET captures more aspects of flushing, respiratory and cardiovascular impact in carcinoid syndrome than the EORTC QLQ GINET21.

Psychological morbidity may also be relevant to NEN patients, and may be assessed with several different scales[249].

A systematic review showed that symptoms and quality of life issues in pancreatic NEN differ in the various subtypes,[252]; this emphasises the need to develop subtype-specific HRQoL measures for PanNEN.

Quality of life impact with specific treatments have been addressed in several recent studies; for example, in patients with advanced, non-functioning, well-differentiated gastrointestinal/pulmonary NEN, everolimus delays disease progression while preserving overall HRQoL [253]. The HRQoL of patients with progressive mid-gut NEN treated with Lutetium-177-DOTATATE PRRT or high-dose Octroetide LAR (control arm) has also been evaluated in the phase III NETTER-1 trial [233]. Median time to HRQoL deterioration was significantly longer in the 177Lu -DOTATATE arm versus the control arm for the following domains: global health status (28.8 months vs 6.1 months), physical functioning (25.2 months vs 11.5 months), as well as fatigue, pain, diarrhoea and disease-related worries and body image. Clearly, the significant impact of PRRT on progression-free survival in NETTER-1 was accompanied by significant HRQoL benefit.

One must consider the oft relatively protracted life expectancy of patients with NEN, and also that multimodal therapies may be implemented. Thus, HRQoL analysis may be useful in appropriate treatment selection and monitoring patients holistically as opposed to a focus on tumour response. Future development in the tailoring of subtype-targeted HRQoL tools will be essential in the care of NEN patients.

Clinical trials in neuroendocrine neoplasms – progress and limitations

Typically heralded as the apotheosis of assessment for novel therapies, the randomised clinical trial presents the most seductive paradigm in evidence-based experimental oncology for many cancer types. However, there are manifold challenges and limitations to this approach, specifically with regards to the increasing focus on tumour-specific care and precision oncology, with NEN presenting a pertinent example.

Currently available trial data in NEN have only clearly demonstrated prolongation of progression-free survival with medical therapies in advanced NEN; this is certainly a function of inadequate follow-up time to as yet rigorously evaluate effects on overall survival. Preliminary data suggested a favourable overall survival effect in one trial as of yet [9]. Trials have only examined treatments in the palliative setting.

The lengthy nature of NEN clinical trials pose logistical challenges and therefore sluggish propagation of new standards in clinical care, and the relative rarity of NEN necessitates multi-centric collaboration to ensure adequate recruitment. The latter is especially relevant to the concept of surgical trials in metastatic NEN, given that less than a quarter of patients may be surgical candidates.

However, the foremost issue is that of disease heterogeneity, which the standard two-to-three arm trial abjectly lacks an appreciation for. Even NEN of the same histological grade and origin can display wholly divergent clinical behaviours, and this is ignored in randomisation of a group of NEN defined purely by two histological/radiological parameters. Accordingly, results from any NEN RCT will be blunt in terms of ramifications on clinical practice improvement.

A precision oncology approach endeavours to meticulously identify critical therapeutic targets of an individual's disease, and appreciates the florid inherent heterogeneity in a cohort that is falsely perceived to be/referred to as homogeneous. Drivers of an individual neuroendocrine tumour's phenotype, susceptibility to agents targeting master genetic or protein regulators, and critical tumour dependencies can be assessed, with tumour-guided design of therapeutic strategies therefrom. Such approaches are under development and may well in future supplant the lengthy classical trial model in identifying optimal treatments for NEN patients.

Future perspectives

In order to expedite meaningful advances in the management of SBNEN and PanNEN, focus on a series of areas is required as opposed to further permutations and commutations regarding what is known and currently used. A critical issue in a field in which few resources are invested, owing to the low incidence of the disease, is to advance novel concepts with the likelihood of clinically meaningful applications as opposed to repetitive studies of areas that are "well" understood or whose further exploration are likely to yield little more than drug prescription information:

1. **Define the mechanistic basis of tumour biology.—**The use of systems biology and algorithm-based analysis to define and delineate both *in vivo* and *in silico* the critical dependencies of individual tumours. Current random or empiric-based therapy requires critical evaluation by scientists knowledgeable in the field of precise cancer cell targeting as opposed to clinicians. Recent work on the concept of candidate drivers, master regulators, and critical dependencies using sophisticated mathematical analyses to define the regulatory network of cancer gene expression is likely to define rational intervention. System biology tools need to replace clinical intuition, expensive trials and archaic experience as objective components of the therapeutic decision making process.

2. **The development of precision oncology frameworks.—**This will facilitate the systematic prioritisation of drugs targeting mechanistic tumour dependencies in individual patients. In place of lengthy clinical trials confounded by heterogeneity, kappa value errors and subjective assessments, compounds can be prioritized on the basis of their capacity to invert the concerted activity of master regulator proteins that mechanistically regulate tumour cell state. Analysis of a patient-specific tumour allows identification of master regulator genes and proteins, including key regulators of neuroendocrine lineage progenitor states and immune-evasion. Their specific role as critical tumour dependencies can be confirmed *in silico* prior to random treatment with a "selected" agent. Scientific strategies such as these are likely to supplement clinical efforts to empower precision oncology.

3. **Assessment of the role of the immune system in tumor evolution.—**The development of neoplasia implies both an *a priori* tumour cell role and a modulatory process by immune regulation in the tumour microenvironment. Tools to explore this interaction and elucidate the interactive role of the tumour biome with the immune mechanisms responsible for surveillance are likely to provide information of biological relevance as well as therapeutic application.

4. **The development of imaging modalities and strategies that better define tumor biology.—**Anatomical tumour imaging defines spatial location but provides little information relevant to the biology and behaviour of a tumour. Functional imaging is limited to identification of a small number of membrane receptors and the assessment of the glycolytic pathway. The use of different radiopharmaceuticals to assess metabolic or proliferative tumour elements as well as the integration of such information to blood-based molecular information would provide a multidimensional molecular/metabolic assessment of an individual tumour in real-time

5. **Development of predictive therapeutic biomarkers.—**There is a critical need to specifically and objectively identify the sensitivity of a tumour to a therapeutic agent rather than empirical usage as adjudicated by a scientific advisory board or multi-disciplinary group. Identification of a target alone (e.g. somatostatin receptor) does not adequately and objectively predict the response of the tumour cell to a therapy completely. Specific deficiencies in individual NEN such as homologous recombination aberrances (targetable with PARP inhibitors) may influence targeted treatment selection in PanNEN, and genomic insights into common dysregulation of mTOR pathway constituents in PanNEN may yield new markers to predict responses to mTOR inhibitor therapy. Similarly, blood based genomic assessment of the likelihood of tumour cell responses to PRRT are effective strategies in predicting efficacy when expensive and potentially toxic isotopic therapy is delivered.

6. **Artificial intelligence tools to facilitate diagnosis and management.—**The development of clinical decision support tools based on the concept of individualised risk prediction. Databases that utilise multi-parametric patient information including symptomatology and risk factors (known or to be determined) for tumour types, as a basis for screening tools for general practitioners. The combination of this with point-of-care fingerprick molecular genomic diagnosis as has been described for the NETest should serve as a model.

7. **Implementation of multianalyte genomic biomarkers in blood.—**These should define the molecular biology of the tumour and capture the clinical status of a lesion by providing real-time information as to the status of the patient. Tissue biomarkers are of value in initial characterisation, but their relevance decreases with time and clonal evolution of a tumour. Repetitive assessment is not clinically feasible hence blood-based information remains the new frontier of management. Chromogranin and other mono-analyte markers are widely acknowledged to be of limited value and should be regarded as having been part of the early evolution of the subject. The development of multi-analyte type genomic assays

in blood for predicting treatment response, monitoring treatment efficacy and assessing the different “omic” elements that define the progress of a tumour in real time are a critical requirement.

8. Development of outcome surrogates to facilitate objective assessment of clinical efficacy.—This requires a mathematical integration of tissue-based and blood-based molecular information and more specific metabolic-focused isotopes that amplify functional imaging. Follow-up of phase III clinical trials; data thus far have demonstrated that medical therapies prolong progression-free survival only. The determination of progression is, however, deeply flawed since imaging modalities lack adequate discriminant indices to identify micro-progression. Whilst PFS is a useful surrogate measure (in the absence of an alternative), a valid multidimensional assessment of the indices that constitute prolongation of life needs development and study.

9. Investigation of the role of the microbiome in NEN.—It is likely that gut-derived neuroendocrine neoplasia may have a links to the gut microbiome given the physical and chemical relationship of the two cell systems. For example, gut microbiota is considered a virtual endocrine organ that has metabolic implications. It produces and regulate multiple compounds, like butyrate or propionate that directly regulates the host digestive system [254]. Manipulating the microbial composition of the GIT is known to modulate tryptophan, a precursor to serotonin, both required for neuroendocrine cell biology and a key neurotransmitter within both the enteric and central nervous systems. Moreover, the microbiome has been implicated in the pathogenesis (largely via obesity and immune dysregulation [255]) and treatment responses for example to anti-PD-1 therapies (largely through immune regulation) [256]. The study of effects of microbiome constitution and/or perturbation on the development and clinical behaviour of NEN should be considered in conjunction with the gut immune system since it may provide the scientific basis to better understand pathogenic mechanisms and their drug dependencies.

Conclusions

Neuroendocrine neoplasms of the small bowel and pancreas represent tumours of increasing clinical relevance, but also increasing clinical challenge. Previously they were considered to be abstruse clinical entities representing arcane aspects of endocrine oncology, but a more sophisticated understanding of their clinical complexity, pathophysiology, biology and molecular genomic background have facilitated advances in standardisation of diagnosis, classification and therapy. What is critically required is to establish optimal treatment selection criteria, utilize molecular genomic disease biomarkers and establish systems biology strategies to identify optimal patient specific therapy combination/sequences. While clinical trials have obvious relevance, the information derived from them will be amplified by utilizing specialised treatment and research networks that integrate objective strategies to predict or assess treatment efficacy. In this respect three key areas need to be developed and applied. Firstly, the development of increasingly informative functional imaging using artificial intelligence and metabolic tracers. Secondly the integration with imaging of real time multianalyte genomic analysis of individual tumours (liquid biopsy). Thirdly the application of system biology strategies to a multidimensional assessment of the relationship

of the metabolome, the microbiome and the proliferome to neuroendocrine neoplasia and the delineation of disease progression. A successful future requires a paradigm shift from group pathological classification to an exploration of the molecular matrix of an individual tumour using mathematically based assessments of cTDNA and mRNA-based delineations of disease status.

Funding sources:

There is no specific funding to report for this manuscript

References

1. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM: The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 2011 Mar;40:1–18, vii. [PubMed: 21349409]
2. Boyar Cetinkaya R, Aagnes B, Thiis-Evensen E, Tretli S, Bergestuen DS, Hansen S: Trends in Incidence of Neuroendocrine Neoplasms in Norway: A Report of 16,075 Cases from 1993 through 2010. Neuroendocrinology 2017;104:1–10. [PubMed: 26562558]
3. Frilling A, Clift AK: Therapeutic strategies for neuroendocrine liver metastases. Cancer 2015 Apr 15;121:1172–86. [PubMed: 25274401]
4. Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AKC, et al. : Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 2008 Nov 15;113:2655–64. [PubMed: 18853416]
5. 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 Oncol 2017 Oct 1;3:1335. [PubMed: 28448665]
6. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, Knowledge NETwork O behalf of the K: Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer 2014 Jun 1;21:R153–63. [PubMed: 24322304]
7. Ellis L, Shale MJ, Coleman MP: Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. Am J Gastroenterol 2010 Dec;105:2563–9. [PubMed: 20823835]
8. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. : One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008 Jun 20;26:3063–72. [PubMed: 18565894]
9. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. : Phase 3 Trial of177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017 Jan 12;376:125–135. [PubMed: 28076709]
10. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. : Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014 Jul 17;371:224–33. [PubMed: 25014687]
11. 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 on Long Term Survival. Neuroendocrinology 2016 Jan 6; DOI: 10.1159/000443612
12. 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 Mar;387:968–977. [PubMed: 26703889]
13. Miller HC, Drymousis P, Flora R, Goldin R, Spalding D, Frilling A: Role of Ki-67 proliferation index in the assessment of patients with neuroendocrine neoplasias regarding the stage of disease. World J Surg 2014 Jun;38:1353–61. [PubMed: 24493070]

14. Panzuto F, Boninsegna L, Fazio N, Campana D, Pia Brizzi M, Capurso G, et al. : Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. J Clin Oncol 2011 Jul 10;29:2372–7. [PubMed: 21555696]
15. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. : ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016;103:172–185. [PubMed: 26731013]
16. Lloyd RV, Osamura RY, Klöppel G, Rosai J, World Health Organization., International Agency for Research on Cancer: WHO classification of tumours of endocrine organs
17. Amin M, Edge S, Greene F: AJCC Cancer Staging Manual 8th Edition. ed 8 2018.
18. Godwin JD: Carcinoid tumors. An analysis of 2,837 cases. Cancer 1975 Aug;36:560–9. [PubMed: 1157019]
19. Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003 Feb 15;97:934–959. [PubMed: 12569593]
20. Luke C, Price T, Townsend A, Karapetis C, Kotasek D, Singhal N, et al. : Epidemiology of neuroendocrine cancers in an Australian population. Cancer Causes Control 2010 Jun 24;21:931–938. [PubMed: 20419344]
21. Tsai H-J, Wu C-C, Tsai C-R, Lin S-F, Chen L-T, Chang JS: The Epidemiology of Neuroendocrine Tumors in Taiwan: A Nation-Wide Cancer Registry-Based Study. PLoS One 2013 Apr 22;8:e62487. [PubMed: 23614051]
22. Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G: Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Ann Oncol 2016 Jan;27:68–81. [PubMed: 26487581]
23. Rinzivillo M, Capurso G, Campana D, Fazio N, Panzuto F, Spada F, et al. : Risk and Protective Factors for Small Intestine Neuroendocrine Tumors: A Prospective Case-Control Study. Neuroendocrinology 2016;103:531–7. [PubMed: 26356731]
24. Nogueira L, Freedman ND, Engels EA, Warren JL, Castro F, Koshiol J: Gallstones, Cholecystectomy, and Risk of Digestive System Cancers. Am J Epidemiol 2014 Mar 15;179:731–739. [PubMed: 24470530]
25. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD: The Epidemiology and Pathogenesis of Neoplasia in the Small Intestine. Ann Epidemiol 2009 Jan;19:58–69. [PubMed: 19064190]
26. Alvarez MJ, Subramaniam PS, Tang LH, Grunn A, Aburi M, Rieckhof G, et al. : A precision oncology approach to the pharmacological targeting of mechanistic dependencies in neuroendocrine tumors. Nat Genet 2018 Jul 18;50:979–989. [PubMed: 29915428]
27. de Laat JM, Tham E, Pieterman CRC, Vriens MR, Dorresteijn JAN, Bots ML, et al. : Predicting the risk of multiple endocrine neoplasia type 1 for patients with commonly occurring endocrine tumors. Eur J Endocrinol 2012 Aug;167:181–187. [PubMed: 22581216]
28. Cigrovski Berković M, Catela Ivković T, Marout J, Zjačić-Rotkvić V, Kapitanović S: Interleukin 1β gene single-nucleotide polymorphisms and susceptibility to pancreatic neuroendocrine tumors. DNA Cell Biol 2012 Apr;31:531–6. [PubMed: 21988351]
29. Karakaxas D, Sioziou A, Aravantinos G, Coker A, Papanikolaou IS, Liakakos T, et al. : Genetic polymorphisms of *interleukin 1β* gene and sporadic pancreatic neuroendocrine tumors susceptibility. World J Gastrointest Oncol 2016;8:520. [PubMed: 27326321]
30. Karakaxas D, Gazouli M, Coker A, Agalianos C, Papanikolaou IS, Patapis P, et al. : Genetic polymorphisms of inflammatory response gene TNF-α and its influence on sporadic pancreatic neuroendocrine tumors predisposition risk. Med Oncol 2014 Oct 12;31:241. [PubMed: 25213764]
31. Nell S, van Leeuwaarde RS, Pieterman CRC, de Laat JM, Hermus AR, Dekkers OM, et al. : No Association of Blood Type O With Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1. J Clin Endocrinol Metab 2015 Oct;100:3850–5. [PubMed: 26247473]
32. Frost M, Lines KE, Thakker RV: Current and emerging therapies for PNETs in patients with or without MEN1. Nat Rev Endocrinol 2018 Apr 16;14:216–227. [PubMed: 29449689]
33. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. : Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1). J Clin Endocrinol Metab 2012 Sep;97:2990–3011. [PubMed: 22723327]

34. Keutgen XM, Hammel P, Choyke PL, Libutti SK, Jonasch E, Kebebew E: Evaluation and management of pancreatic lesions in patients with von Hippel–Lindau disease. Nat Rev Clin Oncol 2016 Sep 31;13:537–549. [PubMed: 27030075]
35. Rogers A, Wang LM, Karavitaki N, Grossman AB: Neurofibromatosis Type 1 and pancreatic islet cell tumours: an association which should be recognized. QJM 2015 Jul 1;108:573–576. [PubMed: 23173186]
36. Agaimy A, Vassos N, Croner RS: Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. Int J Clin Exp Pathol 2012;5:852–62. [PubMed: 23119102]
37. Larson A, Hedgire S, Deshpande V, Stemmer-Rachamimov A, Harisinghani M, Ferrone C, et al. : Pancreatic neuroendocrine tumors in patients with tuberous sclerosis complex. Clin Genet 2012 Dec;82:558–563. [PubMed: 22035404]
38. Dumanski JP, Rasi C, Björklund P, Davies H, Ali AS, Grönberg M, et al. : A MUTYH germline mutation is associated with small intestinal neuroendocrine tumors. Endocr Relat Cancer 2017 Aug;24:427–443. [PubMed: 28634180]
39. Sei Y, Zhao X, Forbes J, Szymczak S, Li Q, Trivedi A, et al. : A Hereditary Form of Small Intestinal Carcinoid Associated With a Germline Mutation in Inositol Polyphosphate Multikinase. Gastroenterology 2015 Jul;149:67–78. [PubMed: 25865046]
40. Järhult J, Landerholm K, Falkmer S, Nordenskjöld M, Sundler F, Wierup N: First Report on Metastasizing Small Bowel Carcinoids in First-Degree Relatives in Three Generations. Neuroendocrinology 2010;91:318–323. [PubMed: 20460879]
41. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. : Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors. J Am Coll Cardiol 2017 Mar 14;69:1288–1304. [PubMed: 28279296]
42. Crona J, Norlén O, Antonodimitrakis P, Welin S, Stålberg P, Eriksson B: Multiple and Secondary Hormone Secretion in Patients With Metastatic Pancreatic Neuroendocrine Tumours. J Clin Endocrinol Metab 2016 Feb;101:445–452. [PubMed: 26672633]
43. Banck MS, Kanwar R, Kulkarni AA, Boora GK, Metge F, Kipp BR, et al. : The genomic landscape of small intestine neuroendocrine tumors. J Clin Invest 2013 Jun;123:2502–8. [PubMed: 23676460]
44. Hänninen UA, Katainen R, Tanskanen T, Plaketti R-M, Laine R, Hamberg J, et al. : Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLOS Genet 2018 Mar 9;14:e1007200. [PubMed: 29522538]
45. Schrock AB, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, et al. : Genomic Profiling of Small-Bowel Adenocarcinoma. JAMA Oncol 2017 Nov 1;3:1546. [PubMed: 28617917]
46. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. : Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013 Jul 16;499:214–218. [PubMed: 23770567]
47. Francis JM, Kiezun A, Ramos AH, Serra S, Pedamallu CS, Qian ZR, et al. : Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. Nat Genet 2013 Dec;45:1483–6. [PubMed: 24185511]
48. Crona J, Gustavsson T, Norlén O, Edfeldt K, Åkerström T, Westin G, et al. : Somatic Mutations and Genetic Heterogeneity at the CDKN1B Locus in Small Intestinal Neuroendocrine Tumors. Ann Surg Oncol 2015 Dec 14;22 Suppl 3:S1428–35. [PubMed: 25586243]
49. Simbolo M, Vicentini C, Mafficini A, Fassan M, Pedron S, Corbo V, et al. : Mutational and copy number asset of primary sporadic neuroendocrine tumors of the small intestine. Virchows Arch 2018 Sep 16; DOI: 10.1007/s00428-018-2450-x
50. Andersson E, Sward C, Stenman G, Ahlman H, Nilsson O: High-resolution genomic profiling reveals gain of chromosome 14 as a predictor of poor outcome in ileal carcinoids. Endocr Relat Cancer 2009 Sep 1;16:953–966. [PubMed: 19458023]
51. Wang GG, Yao JC, Worah S, White JA, Luna R, Wu T-T, et al. : Comparison of genetic alterations in neuroendocrine tumors: frequent loss of chromosome 18 in ileal carcinoid tumors. Mod Pathol 2005 Aug 6;18:1079–87. [PubMed: 15920555]

52. Cunningham JL, Díaz de Ståhl T, Sjöblom T, Westin G, Dumanski JP, Janson ET: Common pathogenetic mechanism involving human chromosome 18 in familial and sporadic ileal carcinoid tumors. Genes, Chromosom Cancer 2011 Feb;50:82–94.
53. Karpathakis A, Dibra H, Pipinikas C, Feber A, Morris T, Francis J, et al. : Prognostic Impact of Novel Molecular Subtypes of Small Intestinal Neuroendocrine Tumor. Clin Cancer Res 2016 Jan 1;22:250–8. [PubMed: 26169971]
54. Kim DH, Nagano Y, Choi I-S, White JA, Yao JC, Rashid A: Allelic alterations in well-differentiated neuroendocrine tumors (carcinoid tumors) identified by genome-wide single nucleotide polymorphism analysis and comparison with pancreatic endocrine tumors. Genes Chromosomes Cancer 2008 Jan;47:84–92. [PubMed: 17943967]
55. Kulke MH, Freed E, Chiang DY, Philips J, Zahrieh D, Glickman JN, et al. : High-resolution analysis of genetic alterations in small bowel carcinoid tumors reveals areas of recurrent amplification and loss. Genes, Chromosom Cancer 2008 Jul;47:591–603.
56. Stålberg P, Westin G, Thirlwell C: Genetics and epigenetics in small intestinal neuroendocrine tumours. J Intern Med 2016 Dec;280:584–594. [PubMed: 27306880]
57. Zhang H-Y, Rumilla KM, Jin L, Nakamura N, Stilling GA, Ruebel KH, et al. : Association of DNA methylation and epigenetic inactivation of RASSF1A and beta-catenin with metastasis in small bowel carcinoid tumors. Endocrine 2006 Dec;30:299–306. [PubMed: 17526942]
58. Verdugo AD, Crona J, Starker L, Stalberg P, Akerstrom G, Westin G, et al. : Global DNA methylation patterns through an array-based approach in small intestinal neuroendocrine tumors. Endocr Relat Cancer 2014 Jan 21;21:L5–L7. [PubMed: 24192231]
59. Karpathakis A, Dibra H, Pipinikas C, Feber A, Morris T, Francis J, et al. : Progressive epigenetic dysregulation in neuroendocrine tumour liver metastases. Endocr Relat Cancer 2017 Feb;24:L21–L25. [PubMed: 28049633]
60. Mandal R, Hardin H, Baus R, Rehrauer W, Lloyd RV.: Analysis of miR-96 and miR-133a Expression in Gastrointestinal Neuroendocrine Neoplasms. Endocr Pathol 2017 Dec 14;28:345–350. [PubMed: 29032398]
61. Panarelli N, Tyryshkin K, Wong J, Majewski A, Yang X, Scognamiglio T, et al. : Evaluating gastroenteropancreatic neuroendocrine tumors through microRNA sequencing. Endocr Relat Cancer 2018 Aug 18; DOI: 10.1530/ERC-18-0244
62. Zimmermann N, Knief J, Kacprowski T, Lazar-Karsten P, Keck T, Billmann F, et al. : MicroRNA analysis of gastroenteropancreatic neuroendocrine tumors and metastases. Oncotarget 2018 Jun 18;9:28379–28390. [PubMed: 29983867]
63. Finnerty BM, Gray KD, Moore MD, Zarnegar R, Fahey TJ Iii: Epigenetics of gastroenteropancreatic neuroendocrine tumors: A clinicopathologic perspective. World J Gastrointest Oncol 2017 Sep 15;9:341–353. [PubMed: 28979716]
64. Miller HC, Frampton AE, Malczewska A, Ottaviani S, Stronach EA, Flora R, et al. : MicroRNAs associated with small bowel neuroendocrine tumours and their metastases. Endocr Relat Cancer 2016 Sep;23:711–26. [PubMed: 27353039]
65. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, et al. : DAXX/ATRX, MEN1, and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors. Science (80-) 2011 Mar 4;331:1199–1203.
66. Corbo V, Dalai I, Scardoni M, Barbi S, Beghelli S, Bersani S, et al. : MEN1 in pancreatic endocrine tumors: analysis of gene and protein status in 169 sporadic neoplasms reveals alterations in the vast majority of cases. Endocr Relat Cancer 2010 Sep;17:771–783. [PubMed: 20566584]
67. Marini F, Giusti F, Fossi C, Cioppi F, Cianferotti L, Masi L, et al. : Multiple endocrine neoplasia type 1: analysis of germline MEN1 mutations in the Italian multicenter MEN1 patient database. Endocrine 2018 Oct 1;62:215–233. [PubMed: 29497973]
68. Mafficini A, Scarpa A: Genomic landscape of pancreatic neuroendocrine tumours: the International Cancer Genome Consortium. J Endocrinol 2018 Mar;236:R161–R167. [PubMed: 29321190]
69. Song MS, Salmena L, Carracedo A, Egia A, Lo-Coco F, Teruya-Feldstein J, et al. : The deubiquitinylation and localization of PTEN are regulated by a HAUSP-PML network. Nature 2008 Oct 9;455:813–7. [PubMed: 18716620]

70. Heaphy CM, de Wilde RF, Jiao Y, Klein AP, Edil BH, Shi C, et al. : Altered Telomeres in Tumors with ATRX and DAXX Mutations. Science (80-) 2011 Jul 22;333:425–425.
71. Singhi AD, Liu T-C, Roncaioli JL, Cao D, Zeh HJ, Zureikat AH, et al. : Alternative Lengthening of Telomeres and Loss of DAXX/ATRX Expression Predicts Metastatic Disease and Poor Survival in Patients with Pancreatic Neuroendocrine Tumors. Clin Cancer Res 2017 Jan 15;23:600–609. [PubMed: 27407094]
72. Scarpa A, Chang DK, Nones K, Corbo V, Patch A-M, Bailey P, et al. : Whole-genome landscape of pancreatic neuroendocrine tumours. Nature 2017 Mar 15;543:65–71. [PubMed: 28199314]
73. Waddell N, Pajic M, Patch A-M, Chang DK, Kassahn KS, Bailey P, et al. : Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015 Feb 26;518:495–501. [PubMed: 25719666]
74. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. : Signatures of mutational processes in human cancer. Nature 2013 Aug 14;500:415–421. [PubMed: 23945592]
75. Capurso G, Festa S, Valente R, Piciucchi M, Panzuto F, Jensen RT, et al. : Molecular pathology and genetics of pancreatic endocrine tumours. J Mol Endocrinol 2012 Aug;49:R37–50. [PubMed: 22586144]
76. Marinoni I, Wiederkeher A, Wiedmer T, Pantasis S, Di Domenico A, Frank R, et al. : Hypo-methylation mediates chromosomal instability in pancreatic NET. Endocr Relat Cancer 2017 Mar;24:137–146. [PubMed: 28115389]
77. Roldo C, Missiaglia E, Hagan JP, Falconi M, Capelli P, Bersani S, et al. : MicroRNA Expression Abnormalities in Pancreatic Endocrine and Acinar Tumors Are Associated With Distinctive Pathologic Features and Clinical Behavior. J Clin Oncol 2006 Oct 10;24:4677–4684. [PubMed: 16966691]
78. Cuny T, de Herder W, Barlier A, Hofland LJ: Role of the tumor microenvironment in digestive neuroendocrine tumors. Endocr Relat Cancer 2018 Nov 1;25:R519–R544. [PubMed: 30306777]
79. Cives M, Strosberg J, Al Diffalha S, Coppola D: Analysis of the immune landscape of small bowel neuroendocrine tumors. Endocr Relat Cancer 2019 Jan 1;26:119–130. [PubMed: 30400003]
80. Laskaratos F-M, Rombouts K, Caplin M, Toumpanakis C, Thirlwell C, Mandair D: Neuroendocrine tumors and fibrosis: An unsolved mystery? Cancer 2017 Dec 15;123:4770–4790. [PubMed: 29112233]
81. Takahashi D, Kojima M, Suzuki T, Sugimoto M, Kobayashi S, Takahashi S, et al. : Profiling the Tumour Immune Microenvironment in Pancreatic Neuroendocrine Neoplasms with Multispectral Imaging Indicates Distinct Subpopulation Characteristics Concordant with WHO 2017 Classification. Sci Rep 2018 Dec 3;8:13166. [PubMed: 30177687]
82. Kim ST, Ha SY, Lee S, Ahn S, Lee J, Park SH, et al. : The Impact of PD-L1 Expression in Patients with Metastatic GEP-NETs. J Cancer 2016;7:484–489. [PubMed: 26958083]
83. Mehnert JM, Rugo HS, O'Neil BH, Santoro A, Schellens JHM, Cohen RB, et al. : 427OPembrolizumab for patients with PD-L1–positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. Ann Oncol 2017 Sep 1;28. DOI: 10.1093/annonc/mdx368
84. Daskalakis K, Tsoli M, Alexandraki KI, Angelousi A, Chatzellis E, Tsolakis AV, et al. : Magnetic Resonance Imaging or Endoscopic Ultrasonography for Detection and Surveillance of Pancreatic Neuroendocrine Neoplasms in Patients with Multiple Endocrine Neoplasia Type 1? Horm Metab Res 2019 Sep 11;51:580–585. [PubMed: 31295747]
85. Casey RT, Saunders D, Challis BG, Pitfield D, Cheow H, Shaw A, et al. : Radiological surveillance in multiple endocrine neoplasia type 1: a double-edged sword? Endocr Connect 2017 Apr;6:151–158. [PubMed: 28298337]
86. Baudin E, Gigliotti A, Ducreux M, Ropers J, Comoy E, Sabourin JC, et al. : Neuron-specific enolase and chromogranin A as markers of neuroendocrine tumours. Br J Cancer 1998 Oct;78:1102–7. [PubMed: 9792158]
87. Oberg K, Krenning E, Sundin A, Bodei L, Kidd M, Tesselaar M, et al. : A Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management. Endocr Connect 2016 Sep;5:174–87. [PubMed: 27582247]

88. van Adrichem RCS, Kamp K, Vandamme T, Peeters M, Feelders RA, de Herder WW: Serum neuron-specific enolase level is an independent predictor of overall survival in patients with gastroenteropancreatic neuroendocrine tumors. Ann Oncol 2016 Apr;27:746–747. [PubMed: 26712902]

89. Oberg K, Modlin IM, De Herder W, Pavel M, Klimstra D, Frilling A, et al. : Consensus on biomarkers for neuroendocrine tumour disease. Lancet Oncol 2015 Sep;16:e435–46. [PubMed: 26370353]

90. Malczewska A, Kidd M, Matar S, Kos-Kudla B, Modlin IM: A Comprehensive Assessment of the Role of miRNAs as Biomarkers in Gastroenteropancreatic Neuroendocrine Tumors. Neuroendocrinology 2018;107:73–90. [PubMed: 29566385]

91. Malczewska A, Frampton AE, Mato Prado M, Ameri S, Dabrowska AF, Zagorac S, et al. : Circulating MicroRNAs in Small-bowel Neuroendocrine Tumors. Ann Surg 2019 Aug 1;1.

92. Khan MS, Kirkwood AA, Tsigani T, Lowe H, Goldstein R, Hartley JA, et al. : Early Changes in Circulating Tumor Cells Are Associated with Response and Survival Following Treatment of Metastatic Neuroendocrine Neoplasms. Clin Cancer Res 2016 Jan 1;22:79–85. [PubMed: 26199388]

93. Khan MS, Tsigani T, Rashid M, Rabouhans JS, Yu D, Luong TV, et al. : Circulating tumor cells and EpCAM expression in neuroendocrine tumors. Clin Cancer Res 2011 Jan 15;17:337–45. [PubMed: 21224371]

94. Schreier S, Sawaisorn P, Udomsangpetch R, Triampo W: Advances in rare cell isolation: an optimization and evaluation study. J Transl Med 2017 Dec 5;15:6. [PubMed: 28057026]

95. Khan MS, Tsigani T, Rashid M, Rabouhans JS, Yu D, Luong TV, et al. : Circulating tumor cells and EpCAM expression in neuroendocrine tumors. Clin Cancer Res 2011 Jan 15;17:337–45. [PubMed: 21224371]

96. Kinross JM, Drymousis P, Jiménez B, Frilling A: Metabonomic profiling: a novel approach in neuroendocrine neoplasias. Surgery 2013 Dec;154:1185–92; discussion 1192–3. [PubMed: 24383116]

97. Modlin IM, Drozdov I, Kidd M: The Identification of Gut Neuroendocrine Tumor Disease by Multiple Synchronous Transcript Analysis in Blood. PLoS One 2013 May 15;8:e63364. [PubMed: 23691035]

98. Kidd M, Drozdov I, Modlin I: Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status. Endocr Relat Cancer 2015 Aug;22:561–575. [PubMed: 26037279]

99. Modlin IM, Drozdov I, Kidd M: Gut neuroendocrine tumor blood qPCR fingerprint assay: characteristics and reproducibility. Clin Chem Lab Med 2014 Mar 1;52:419–29. [PubMed: 24127543]

100. Modlin IM, Aslanian H, Bodei L, Drozdov I, Kidd M: A PCR blood test outperforms chromogranin A in carcinoid detection and is unaffected by proton pump inhibitors. Endocr Connect 2014 Dec;3:215–23. [PubMed: 25316294]

101. van Triejen M: Blood Transcript Profiling for the Detection of Neuroendocrine Tumors: Results of a Large Independent Prospective Blinded Validation Study. Eur J Neuroendocrinol 2018;In Press.

102. Modlin IM, Drozdov I, Alaimo D, Callahan S, Teixiera N, Bodei L, et al. : A multianalyte PCR blood test outperforms single analyte ELISAs (chromogranin A, pancreastatin, neurokinin A) for neuroendocrine tumor detection. Endocr Relat Cancer 2014 Aug;21:615–28. [PubMed: 25015994]

103. Liu E, Paulson S, Gulati A, Freudman J, Grosh W, Kafer S, et al. : Assessment of NETest Clinical Utility in a U.S. Registry-Based Study. Oncologist 2018 Aug 29;theoncologist.2017–0623.

104. Modlin IM, Kidd M, Bodei L, Drozdov I, Aslanian H: The Clinical Utility of a Novel Blood-Based Multi-Transcriptome Assay for the Diagnosis of Neuroendocrine Tumors of the Gastrointestinal Tract. Am J Gastroenterol 2015 Aug 2;110:1223–1232. [PubMed: 26032155]

105. van Treijen MJC, Korse CM, van Leeuwaarde RS, Saveur LJ, Vriens MR, Verbeek WHM, et al. : Blood Transcript Profiling for the Detection of Neuroendocrine Tumors: Results of a

Large Independent Validation Study. Front Endocrinol (Lausanne) 2018 Dec 4;9:740. [PubMed: 30564197]

106. Pape U, Jann H, Müller-Nordhorn J, Bockelbrink A, Berndt U, Willich SN, et al. : Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer 2008 Jul 15;113:256–265. [PubMed: 18506737]
107. Fuksiewicz M, Kowalska M, Kolasińska-Ćwikła A, Ćwikła JB, Sawicki Ł, Roszkowska-Purska K, et al. : Prognostic value of chromogranin A in patients with GET/NEN in the pancreas and the small intestine. Endocr Connect 2018 Jun;7:803–810. [PubMed: 29724794]
108. Jilesen APJ, Busch ORC, van Gulik TM, Gouma DJ, Nieveen van Dijkum EJM: Standard pre- and postoperative determination of chromogranin a in resectable non-functioning pancreatic neuroendocrine tumors--diagnostic accuracy: NF-pNET and low tumor burden. Dig Surg 2014;31:407–14. [PubMed: 25572908]
109. Ćwikła JB, Bodei L, Kolasinska-Ćwikła A, Sankowski A, Modlin IM, Kidd M: Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. J Clin Endocrinol Metab 2015 Nov;100:E1437–45. [PubMed: 26348352]
110. Pavel M, Jann H, Prasad V, Drozdov I, Modlin IM, Kidd M: NET Blood Transcript Analysis Defines the Crossing of the Clinical Rubicon: When Stable Disease Becomes Progressive. Neuroendocrinology 2017;104:170–182. [PubMed: 27078712]
111. Modlin IM, Frilling A, Salem RR, Alaimo D, Drymousis P, Wasan HS, et al. : Blood measurement of neuroendocrine gene transcripts defines the effectiveness of operative resection and ablation strategies. Surgery 2016 Jan;159:336–47. [PubMed: 26456125]
112. Filosso PL, Kidd M, Roffinella M, Lewczuk A, Chung K-M, Kolasinska-Cwikla A, et al. : The utility of blood neuroendocrine gene transcript measurement in the diagnosis of bronchopulmonary neuroendocrine tumours and as a tool to evaluate surgical resection and disease progression†. Eur J Cardio-Thoracic Surg 2018 Mar 1;53:631–639.
113. Genç CG, Jilesen APJ, Nieveen van Dijkum EJM, Klümpen H-J, van Eijck CHJ, Drozdov I, et al. : Measurement of circulating transcript levels (NETest) to detect disease recurrence and improve follow-up after curative surgical resection of well-differentiated pancreatic neuroendocrine tumors. J Surg Oncol 2018 Jul;118:37–48. [PubMed: 30114319]
114. Bodei L, Kidd M, Modlin IM, Severi S, Drozdov I, Nicolini S, et al. : Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2015 Nov 23; DOI: 10.1007/s00259-015-3250-z
115. Bodei L, Kidd MS, Singh A, van der Zwan WA, Severi S, Drozdov IA, et al. : PRRT genomic signature in blood for prediction of 177Lu-octreotate efficacy. Eur J Nucl Med Mol Imaging 2018 Jul 26;45:1155–1169. [PubMed: 29484451]
116. Campana D, Walter T, Pusceddu S, Gelsomino F, Graillot E, Prinzi N, et al. : Correlation between MGMT promoter methylation and response to temozolomide-based therapy in neuroendocrine neoplasms: an observational retrospective multicenter study. Endocrine 2018 Jun 17;60:490–498. [PubMed: 29150792]
117. 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 and Hybrid Imaging. Neuroendocrinology 2017;105:212–244. [PubMed: 28355596]
118. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. : Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008 Jan;9:61–72. [PubMed: 18177818]
119. Nicolas GP, Schreiter N, Kaul F, Uiters J, Bouterfa H, Kaufmann J, et al. : Sensitivity Comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase II Imaging Study. J Nucl Med 2018 Jun;59:915–921. [PubMed: 29191855]
120. Modlin IM, Latich I, Zikusoka M, Kidd M, Eick G, Chan AKC: Gastrointestinal carcinoids: the evolution of diagnostic strategies. J Clin Gastroenterol 2006 Aug;40:572–82. [PubMed: 16917396]

121. Gotthardt M, Dirkmorfeld LM, Wied MU, Rinke A, Béhé MP, Schlieck A, et al. : Influence of Somatostatin Receptor Scintigraphy and CT/MRI on the Clinical Management of Patients with Gastrointestinal Neuroendocrine Tumors: An Analysis in 188 Patients. Digestion 2003;68:80–85. [PubMed: 14581764]
122. Oberg K: Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. Clinics (Sao Paulo) 2012;67 Suppl 1:109–12. [PubMed: 22584714]
123. Sundin A: Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol 2012 Dec;26:803–818. [PubMed: 23582920]
124. Bodei L, Sundin A, Kidd M, Prasad V, Modlin IM: The status of neuroendocrine tumor imaging: from darkness to light? Neuroendocrinology 2015 Jan;101:1–17. [PubMed: 25228173]
125. Buckley JA, Jones B, Fishman EK: Small bowel cancer. Imaging features and staging. Radiol Clin North Am 1997 Mar;35:381–402. [PubMed: 9087210]
126. Gustafsson BI, Kidd M, Modlin IM: Neuroendocrine tumors of the diffuse neuroendocrine system. Curr Opin Oncol 2008 Jan;20:1–12. [PubMed: 18043250]
127. Frilling A, Smith G, Clift AK, Martin J: Capsule endoscopy to detect primary tumour site in metastatic neuroendocrine tumours. Dig Liver Dis 2014;46. DOI: 10.1016/j.dld.2014.07.004
128. Johanssen S, Boivin M, Lochs H, Voderholzer W: The yield of wireless capsule endoscopy in the detection of neuroendocrine tumors in comparison with CT enteroclysis. Gastrointest Endosc 2006 Apr;63:660–5. [PubMed: 16564869]
129. Elias D, Lefevre JH, Duvillard P, Goéré D, Dromain C, Dumont F, et al. : Hepatic metastases from neuroendocrine tumors with a “thin slice” pathological examination: they are many more than you think... Ann Surg 2010 Feb;251:307–10. [PubMed: 20010089]
130. Sheth S, Hruban RK, Fishman EK: Helical CT of Islet Cell Tumors of the Pancreas: Typical and Atypical Manifestations. Am J Roentgenol 2002 Sep;179:725–730. [PubMed: 12185053]
131. Owen NJ, Sohaib SA, Peppercorn PD, Monson JP, Grossman AB, Besser GM, et al. : MRI of pancreatic neuroendocrine tumours. Br J Radiol 2001 Oct;74:968–73. [PubMed: 11675319]
132. Gouya H, Vignaux O, Augui J, Dousset B, Palazzo L, Louvel A, et al. : CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. AJR Am J Roentgenol 2003 Oct;181:987–92. [PubMed: 14500214]
133. Paulson EK, Fisher AJ, DeLong DM, Parker DD, Nelson RC: Helical liver CT with computer-assisted bolus-tracking technology: is it possible to predict which patients will not achieve a threshold of enhancement? Radiology 1998 Dec;209:787–792. [PubMed: 9844675]
134. Luersen GF, Wei W, Tamm EP, Bhosale PR, Szklaruk J: Evaluation of Magnetic Resonance (MR) Biomarkers for Assessment of Response With Response Evaluation Criteria in Solid Tumors. J Comput Assist Tomogr 2016;40:717–722. [PubMed: 27636124]
135. Dromain C, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, et al. : Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol 2005 Jan 1;23:70–8. [PubMed: 15625361]
136. Ronot M, Clift AK, Baum RP, Singh A, Kulkarni HR, Frilling A, et al. : Morphological and Functional Imaging for Detecting and Assessing the Resectability of Neuroendocrine Liver Metastases. Neuroendocrinology 2017; DOI: 10.1159/000479293
137. Ronot M, Cuccioli F, Dioguardi Burgio M, Vullierme M-P, Hentic O, Ruszniewski P, et al. : Neuroendocrine liver metastases: Vascular patterns on triple-phase MDCT are indicative of primary tumour location. Eur J Radiol 2017 Apr;89:156–162. [PubMed: 28267533]
138. Deppen SA, Liu E, Blume JD, Clanton J, Shi C, Jones-Jackson LB, et al. : Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. J Nucl Med 2016 May 1;57:708–714. [PubMed: 26769865]
139. Deppen SA, Blume J, Bobbey AJ, Shah C, Graham MM, Lee P, et al. : 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Nucl Med 2016 Jun 1;57:872–878. [PubMed: 26769864]

140. Ambrosini V, Campana D, Bodei L, Nanni C, Castellucci P, Allegri V, et al. : 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010 May;51:669–73. [PubMed: 20395323]

141. Barrio M, Czernin J, Fanti S, Ambrosini V, Binse I, Du L, et al. : The Impact of Somatostatin Receptor–Directed PET/CT on the Management of Patients with Neuroendocrine Tumor: A Systematic Review and Meta-Analysis. J Nucl Med 2017 May;58:756–761. [PubMed: 28082438]

142. Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, et al. : 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007 May;48:508–18. [PubMed: 17401086]

143. Ambrosini V, Campana D, Tomassetti P, Fanti S: 68Ga-labelled peptides for diagnosis of gastroenteropancreatic NET. Eur J Nucl Med Mol Imaging 2012 Feb 3;39:52–60.

144. Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J: The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. J Nucl Med 2010 Jun;51:875–82. [PubMed: 20484441]

145. Skoura E, Michopoulou S, Mohmaduvesh M, Panagiotidis E, Al Harbi M, Toumpanakis C, et al. : The Impact of 68Ga-DOTATATE PET/CT Imaging on Management of Patients with Neuroendocrine Tumors: Experience from a National Referral Center in the United Kingdom. J Nucl Med 2016 Jan 1;57:34–40. [PubMed: 26471695]

146. Schmid-Tannwald C, Schmid-Tannwald CM, Morelli JN, Neumann R, Haug AR, Jansen N, et al. : Comparison of abdominal MRI with diffusion-weighted imaging to 68Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. Eur J Nucl Med Mol Imaging 2013 Jun 5;40:897–907. [PubMed: 23460395]

147. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. : ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology 2016;103:153–171. [PubMed: 26742109]

148. Frilling A, Sotiropoulos GC, Radtke A, Malago M, Bockisch A, Kuehl H, et al. : The impact of 68Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors. Ann Surg 2010 Nov;252:850–6. [PubMed: 21037441]

149. Ambrosini V, Tomassetti P, Castellucci P, Campana D, Montini G, Rubello D, et al. : Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. Eur J Nucl Med Mol Imaging 2008 Aug;35:1431–8. [PubMed: 18418596]

150. Haug A, Auernhammer CJ, Wängler B, Tiling R, Schmidt G, Göke B, et al. : Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2009 May;36:765–70. [PubMed: 19137293]

151. Severi S, Nanni O, Bodei L, Sansovini M, Ianniello A, Nicoletti S, et al. : Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013 Jun 27;40:881–888. [PubMed: 23443937]

152. Binderup T, Knigge U, Loft A, Mortensen J, Pfeifer A, Federspiel B, et al. : Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med 2010 May;51:704–12. [PubMed: 20395333]

153. 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 Feb 1;16:978–85. [PubMed: 20103666]

154. Ezziddin S, Adler L, Sabet A, Poppel TD, Grabellus F, Yuce A, et al. : Prognostic Stratification of Metastatic Gastroenteropancreatic Neuroendocrine Neoplasms by 18F-FDG PET: Feasibility of a Metabolic Grading System. J Nucl Med 2014 Aug 1;55:1260–1266. [PubMed: 24876204]

155. Pfeifer A, Knigge U, Binderup T, Mortensen J, Oturai P, Loft A, et al. : 64Cu-DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with 111In-DTPA-Octreotide in 112 Patients. J Nucl Med 2015 Jun 1;56:847–854. [PubMed: 25952736]

156. Baumann T, Rottenburger C, Nicolas G, Wild D: Gastroenteropancreatic neuroendocrine tumours (GEP-NET) – Imaging and staging. Best Pract Res Clin Endocrinol Metab 2016 Jan;30:45–57. [PubMed: 26971843]

157. Kulkarni HR, Singh A, Baum RP: Advances in the Diagnosis of Neuroendocrine Neoplasms. Semin Nucl Med 2016 Sep;46:395–404. [PubMed: 27553465]

158. Antwi K, Fani M, Nicolas G, Rottenburger C, Heye T, Reubi JC, et al. : Localization of Hidden Insulinomas with 68Ga-DOTA-Exendin-4 PET/CT: A Pilot Study. J Nucl Med 2015 Jul 1;56:1075–1078. [PubMed: 25999434]

159. Norlén O, Stålberg P, Öberg K, Eriksson J, Hedberg J, Hessman O, et al. : Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. World J Surg 2012 Jun;36:1419–31. [PubMed: 21984144]

160. Scharf M, Petry V, Daniel H, Rinke A, Gress TM: Bone Metastases in Patients with Neuroendocrine Neoplasm: Frequency and Clinical, Therapeutic, and Prognostic Relevance. Neuroendocrinology 2018;106:30–37. [PubMed: 28152537]

161. Daskalakis K, Tsoli M, Srirajaskanthan R, Chatzellis E, Alexandraki K, Angelousi A, et al. : Lung Metastases in Patients with Well-Differentiated Gastroenteropancreatic Neuroendocrine Neoplasms: An Appraisal of the Validity of Thoracic Imaging Surveillance. Neuroendocrinology 2019;108:308–316. [PubMed: 30673674]

162. Modlin IM, Gustafsson BI, Pavel M, Svejda B, Lawrence B, Kidd M: A nomogram to assess small-intestinal neuroendocrine tumor (‘carcinoid’) survival. Neuroendocrinology 2010 Jan;92:143–57. [PubMed: 20733279]

163. Clift AK, Faiz O, Goldin R, Martin J, Wasan H, Liedke M-O, et al. : Predicting the survival of patients with small bowel neuroendocrine tumours: comparison of 3 systems. Endocr Connect 2017 Feb;6:71–81. [PubMed: 28104724]

164. Genç CG, Jilesen AP, Partelli S, Falconi M, Muffatti F, van Kemenade FJ, et al. : A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Nonfunctional Pancreatic Neuroendocrine Tumors. Ann Surg 2018 Jun;267:1148–1154. [PubMed: 28594340]

165. Pusceddu S, Barretta F, Trama A, Botta L, Milione M, Buzzoni R, et al. : A classification prognostic score to predict OS in stage IV well-differentiated neuroendocrine tumors. Endocr Relat Cancer 2018 Jun;25:607–618. [PubMed: 29559553]

166. Hansen CP, Olsen IH, Knigge U: Gastrointestinal Surgery of Neuroendocrine Neoplasms. Front Horm Res 2015;44:149–63. [PubMed: 26303710]

167. Moris D, Ntanasis-Stathopoulos I, Tsilimigras DI, Vagios S, Karamitros A, Karaolanis G, et al. : Update on Surgical Management of Small Bowel Neuroendocrine Tumors. Anticancer Res 2018 Mar 1;38:1267–1278. [PubMed: 29491050]

168. Pasquer A, Walter T, Hervieu V, Forestier J, Scoazec J-Y, Lombard-Bohas C, et al. : Surgical Management of Small Bowel Neuroendocrine Tumors: Specific Requirements and Their Impact on Staging and Prognosis. Ann Surg Oncol 2015 Dec 27;22:742–749.

169. Clift AK, Faiz O, Al-Nahhas A, Bockisch A, Liedke MO, Schloericke E, et al. : Role of Staging in Patients with Small Intestinal Neuroendocrine Tumours. J Gastrointest Surg 2015 Sep 22; DOI: 10.1007/s11605-015-2953-6

170. Gangi A, Siegel E, Barmparas G, Lo S, Jamil LH, Hendifar A, et al. : Multifocality in Small Bowel Neuroendocrine Tumors. J Gastrointest Surg 2018 Feb 8;22:303–309. [PubMed: 29119527]

171. Lardière-Deguelte S, de Mestier L, Appéré F, Vullierme M-P, Zappa M, Hoeffel C, et al. : Toward a Preoperative Classification of Lymph Node Metastases in Patients with Small Intestinal Neuroendocrine Tumors in the Era of Intestinal-Sparing Surgery. Neuroendocrinology 2016;103:552–559. [PubMed: 26445315]

172. Pasquer A, Walter T, Rousset P, Hervieu V, Forestier J, Lombard-Bohas C, et al. : Lymphadenectomy during Small Bowel Neuroendocrine Tumor Surgery: The Concept of Skip Metastases. Ann Surg Oncol 2016 Dec 9;23:804–808. [PubMed: 27613554]

173. Chen L, Song Y, Zhang Y, Chen M, Chen J: Exploration of the Exact Prognostic Significance of Lymphatic Metastasis in Jejunoileal Neuroendocrine Tumors. Ann Surg Oncol 2018 Jul 10;25:2067–2074. [PubMed: 29748891]

174. Daskalakis K, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, et al. : Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. JAMA Oncol 2018 Feb 1;4:183. [PubMed: 29049611]

175. de Mestier L, Lardière-Deguelte S, Brixi H, O'Toole D, Ruszniewski P, Cadiot G, et al. : Updating the Surgical Management of Peritoneal Carcinomatosis in Patients with Neuroendocrine Tumors. Neuroendocrinology 2015 Jan 9;101:105–111. [PubMed: 25592061]

176. Hellman P, Lundström T, Ohrvall U, Eriksson B, Skogseid B, Oberg K, et al. : Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002 Aug;26:991–7. [PubMed: 12016480]

177. Citterio D, Pusceddu S, Facciorusso A, Coppa J, Milione M, Buzzoni R, et al. : Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. Eur J Surg Oncol 2017 Feb;43:380–387. [PubMed: 27956320]

178. Partelli S, Cirocchi R, Rancoita PMV, Muffatti F, Andreasi V, Crippa S, et al. : A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. HPB 2018 Mar;20:197–203. [PubMed: 29196022]

179. Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M: Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. Br J Surg 2012 Nov;99:1480–6. [PubMed: 22972490]

180. Lewis A, Raoof M, Ituarte PHG, Williams J, Melstrom L, Li D, et al. : Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival with or without Liver Treatment. Ann Surg 2018 May;1.

181. Frilling A, Giele H, Vrakas G, Reddy S, Macedo R, Al-Nahhas A, et al. : Modified Liver-free Multivisceral Transplantation for a Metastatic Small Bowel Neuroendocrine Tumor: A Case Report. Transplant Proc 2015 Apr;47:858–62. [PubMed: 25689880]

182. Maurizi A, Partelli S, Falconi M: Pancreatic Surgerypp 139–148.

183. Mills L, Drymousis P, Vashist Y, Burdelski C, Prachalias A, Srinivasan P, et al. : Tumour diameter is not reliable for management of non-secreting pancreatic neuroendocrine tumours. Endocr Connect 2017 Nov 17;6:876–885. [PubMed: 29150545]

184. Partelli S, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A, et al. : Pattern and Clinical Predictors of Lymph Node Involvement in Nonfunctioning Pancreatic Neuroendocrine Tumors (NF-PanNETs). JAMA Surg 2013 Oct 1;148:932. [PubMed: 23986355]

185. Valente R, Lykoudis P, Tamburrino D, Inama M, Passas I, Toumpanakis C, et al. : Major postoperative complications after pancreatic resection for P-NETS are not associated to earlier recurrence. Eur J Surg Oncol 2017 Nov;43:2119–2128. [PubMed: 28821361]

186. Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, et al. : Surgery increases survival in patients with gastrinoma. Ann Surg 2006 Sep;244:410–9. [PubMed: 16926567]

187. Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, et al. : A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas 2014 Jul;43:675–86. [PubMed: 24921202]

188. Triponez F, Sadowski SM, Pattou F, Cardot-Bauters C, Mirallié E, Le Bras M, et al. : Long-term Follow-up of MEN1 Patients Who Do Not Have Initial Surgery for Small ≤2 cm Nonfunctioning Pancreatic Neuroendocrine Tumors, an AFCE and GTE Study: Association Francophone de Chirurgie Endocrinienne & Groupe d'Etude des Tumeurs Endocrines. Ann Surg 2018 Jul;268:158–164. [PubMed: 28263205]

189. Nell S, Verkooijen HM, Pieterman CRC, de Herder WW, Hermus AR, Dekkers OM, et al. : Management of MEN1 Related Nonfunctioning Pancreatic NETs. Ann Surg 2018 Jun;267:1155–1160. [PubMed: 28257328]

190. Barthet M, Giovannini M, Lesavre N, Boustiere C, Napoleon B, Koch S, et al. : Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. Endoscopy 2019 Jan 22; DOI: 10.1055/a-0824-7067

191. Krauss T, Ferrara AM, Links TP, Wellner U, Bancos I, Kvachenyuk A, et al. : Preventive medicine of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors. Endocr Relat Cancer 2018 Sep;25:783–793. [PubMed: 29748190]

192. Tirosh A, Sadowski SM, Linehan WM, Libutti SK, Patel D, Nilubol N, et al. : Association of VHL Genotype With Pancreatic Neuroendocrine Tumor Phenotype in Patients With von Hippel-Lindau Disease. JAMA Oncol 2018 Jan 1;4:124–126. [PubMed: 29075773]

193. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. : ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016 Jan 5;103:172–85. [PubMed: 26731013]

194. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. : Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol 2014 Jan;15:e8–21. [PubMed: 24384494]

195. Frilling A, Clift AK: Surgical approaches to the management of neuroendocrine liver metastases. Endocr Metab Clin North Am 2017;Forthcomin.

196. Frilling A, Li J, Malamutmann E, Schmid K-W, Bockisch A, Broelsch CE: Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 2009 Feb;96:175–84. [PubMed: 19160361]

197. Saxena A, Chua TC, Perera M, Chu F, Morris DL: Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. Surg Oncol 2012 Sep;21:e131–41. [PubMed: 22658833]

198. Galleberg RB, Knigge U, Tiensuu Janson E, Vestermark LW, Haugvik S-P, Ladekarl M, et al. : Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. Eur J Surg Oncol 2017 Sep;43:1682–1689. [PubMed: 28522174]

199. Kianmanesh R, Sauvanet A, Hentic O, Couvelard A, Lévy P, Vilgrain V, et al. : Two-step Surgery for Synchronous Bilobar Liver Metastases From Digestive Endocrine Tumors: A Safe Approach for Radical Resection. Ann Surg 2008 Apr;247:659–665. [PubMed: 18362629]

200. Morgan RE, Pommier SJ, Pommier RF: Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. Surgery 2018 Jan;163:218–225. [PubMed: 29103583]

201. Gibson WE, Gonzalez RS, Cates JMM, Liu E, Shi C: Hepatic micrometastases are associated with poor prognosis in patients with liver metastases from neuroendocrine tumors of the digestive tract. Hum Pathol 2018 Sep;79:109–115. [PubMed: 29763717]

202. 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 Sep;162:525–536. [PubMed: 28624178]

203. Clift AK, Frilling A: Liver transplantation and multivisceral transplantation in the management of patients with advanced neuroendocrine tumours. World J Gastroenterol 2018 May 28;24:2152–2162. [PubMed: 29853733]

204. Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, et al. : The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. Am J Transplant 2016 Oct;16:2892–2902. [PubMed: 27134017]

205. Varkey J, Simrén M, Bosaeus I, Krantz M, Gäbel M, Herlenius G: Survival of patients evaluated for intestinal and multivisceral transplantation - the Scandinavian experience. Scand J Gastroenterol 2013 Jun;48:702–11. [PubMed: 23544434]

206. Mangus RS, Tector AJ, Kubal CA, Fridell JA, Vianna RM: Multivisceral transplantation: expanding indications and improving outcomes. J Gastrointest Surg 2013 Jan;17:179–86; discussion p.186–7. [PubMed: 23070622]

207. Kaemmerer D, Prasad V, Daffner W, Hörsch D, Klöppel G, Hommann M, et al. : Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor. World J Gastroenterol 2009 Dec 14;15:5867–70. [PubMed: 19998512]

208. Baum RP, Kulkarni HR, Singh A, Kaemmerer D, Mueller D, Prasad V, et al. : Results and adverse events of personalized peptide receptor radionuclide therapy with 90Yttrium and 177Lutetium

in 1048 patients with neuroendocrine neoplasms. Oncotarget 2018 Mar 30;9:16932–16950. [PubMed: 29682195]

209. Kratochwil C, López-Benítez R, Mier W, Haufe S, Isermann B, Kauczor H-U, et al. : Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer 2011 Oct 20;18:595–602. [PubMed: 21791571]
210. Groeschl RT, Pilgrim CHC, Hanna EM, Simo KA, Swan RZ, Sindram D, et al. : Microwave ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg 2014 Jun;259:1195–200. [PubMed: 24096760]
211. Akyildiz HY, Mitchell J, Milas M, Siperstein A, Berber E: Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. Surgery 2010 Dec;148:1288–93; discussion 1293. [PubMed: 21134563]
212. Yang TX, Chua TC, Morris DL: Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases - a systematic review. Surg Oncol 2012 Dec;21:299–308. [PubMed: 22846894]
213. Frilling A, Clift AK, Braat AJA, Alsafi A, Wasan HS, Al-Nahhas A, et al.: Radioembolisation with 90Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis. HPB 2018;In Press.
214. Devcic Z, Rosenberg J, Braat AJA, Techasith T, Banerjee A, Sze DY, et al. : The Efficacy of Hepatic 90Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis. J Nucl Med 2014 Sep 1;55:1404–1410. [PubMed: 25012459]
215. Jia Z, Wang W: Yttrium-90 radioembolization for unresectable metastatic neuroendocrine liver tumor: A systematic review. Eur J Radiol 2018 Mar;100:23–29. [PubMed: 29496075]
216. Braat AJAT, Kappadath SC, Ahmadzadehfar H, Stothers CL, Frilling A, Deroose CM, et al. : Radioembolization with 90Y Resin Microspheres of Neuroendocrine Liver Metastases: International Multicenter Study on Efficacy and Toxicity. Cardiovasc Intervent Radiol 2019 Mar 2;42:413–425. [PubMed: 30603975]
217. Bauer W, Briner U, Doepfner W, Haller R, Huguenin R, Marbach P, et al. : SMS 201–995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982 Sep 13;31:1133–40. [PubMed: 6128648]
218. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, et al. : ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary. Neuroendocrinology 2012;95:157–176. [PubMed: 22262022]
219. Pyronnet S, Bousquet C, Najib S, Azar R, Laklai H, Susini C: Antitumor effects of somatostatin. Mol Cell Endocrinol 2008 May;286:230–237. [PubMed: 18359151]
220. Modlin IM, Pavel M, Kidd M, Gustafsson BI: Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010 Jan 15;31:169–88. [PubMed: 19845567]
221. Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB: Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer 2008 May 22;15:701–720. [PubMed: 18524947]
222. Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, 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: a report from the PROMID Study Group. J Clin Oncol 2009 Oct 1;27:4656–63. [PubMed: 19704057]
223. Kvols LK, Oberg KE, O'Dorisio TM, Mohideen P, de Herder WW, Arnold R, et al. : Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. Endocr Relat Cancer 2012 Oct;19:657–66. [PubMed: 22807497]
224. Wolin E, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, et al. : Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther 2015 Sep;9:5075.

225. Kulke MH, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, et al. : Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol 2017 Jan;35:14–23. [PubMed: 27918724]

226. Oberg K: Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion 2000;62 Suppl 1:92–7. [PubMed: 10940694]

227. Yao JC, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. : Phase III Prospective Randomized Comparison Trial of Depot Octreotide Plus Interferon Alfa-2b Versus Depot Octreotide Plus Bevacizumab in Patients With Advanced Carcinoid Tumors: SWOG S0518. J Clin Oncol 2017 May 20;35:1695–1703. [PubMed: 28384065]

228. Cuyle P-J, Prenen H: Practical management of toxicities associated with targeted therapies for advanced gastroenteropancreatic neuroendocrine tumors. Ann Gastroenterol 2018;31:140–150. [PubMed: 29507461]

229. Bodei L, Kwekkeboom DJ, Kidd M, Modlin IM, Krenning EP: Radiolabeled Somatostatin Analogue Therapy Of Gastroenteropancreatic Cancer. Semin Nucl Med 2016 May;46:225–238. [PubMed: 27067503]

230. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. : Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging 2011 Dec;38:2125–35. [PubMed: 21892623]

231. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. : Long-Term Efficacy, Survival, and Safety of [^{177} Lu-DOTA ^{0},Tyr ^{3}]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res 2017 Aug 15;23:4617–4624. [PubMed: 28428192]

232. Mariniello A, Bodei L, Tinelli C, Baio SM, Gilardi L, Colandrea M, et al. : Long-term results of PRRT in advanced bronchopulmonary carcinoid. Eur J Nucl Med Mol Imaging 2016 Mar 21;43:441–452. [PubMed: 26392198]

233. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. : Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ^{177} Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol 2018 Sep 1;36:2578–2584. [PubMed: 29878866]

234. Kwekkeboom DJ, Krenning EP: Peptide Receptor Radionuclide Therapy in the Treatment of Neuroendocrine Tumors. Hematol Oncol Clin North Am 2016 Feb;30:179–191. [PubMed: 26614376]

235. Bodei L, Modlin IM, Luster M, Forrer F, Cremonesi M, Hicks RJ, et al. : Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer 2016 Aug;23:C1–C7. [PubMed: 27353035]

236. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. : Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging 2015 Jan 2;42:5–19. [PubMed: 25273832]

237. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. : Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011 Jun 10;29:2416–23. [PubMed: 21555692]

238. Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJM, van Eijck CHJ, Valkema R, et al. : Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer 2010 Mar;17:R53–73. [PubMed: 19995807]

239. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D: Streptozocin–Doxorubicin, Streptozocin–Fluorouracil, or Chlorozotocin in the Treatment of Advanced Islet-Cell Carcinoma. N Engl J Med 1992 Feb 20;326:519–523. [PubMed: 1310159]

240. Krug S, Gress TM, Michl P, Rinke A: The Role of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors. Digestion 2017;96:67–75. [PubMed: 28728148]

241. Angelousi A, Kaltsas G, Koumarianou A, Weickert MO, Grossman A: Chemotherapy in NETs: When and how. Rev Endocr Metab Disord 2017 Dec 11;18:485–497. [PubMed: 28890993]

242. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen D-T, et al. : First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011 Jan 15;117:268–275. [PubMed: 20824724]

243. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. : Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol 2013 Jan;24:152–160. [PubMed: 22967994]

244. 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 (London, England) 2016 Mar 5;387:968–77.

245. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. : Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011 Feb 10;364:501–13. [PubMed: 21306237]

246. Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. : Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. J Clin Oncol 2016 Nov 10;34:3906–3913. [PubMed: 27621394]

247. Auernhammer CJ, Spitzweg C, Angele MK, Boeck S, Grossman A, Nölting S, et al. : Advanced neuroendocrine tumours of the small intestine and pancreas: clinical developments, controversies, and future strategies. lancet Diabetes Endocrinol 2018 May;6:404–415. [PubMed: 29229497]

248. Kaderli RM, Spanjol M, Kollár A, Bütikofer L, Gloy V, Dumont RA, et al. : Therapeutic Options for Neuroendocrine Tumors: A Systematic Review and Network Meta-analysis. JAMA Oncol 2019 Apr 1;5:480–489. [PubMed: 30763436]

249. Jiménez-Fonseca P, Carmona-Bayonas A, Martín-Pérez E, Crespo G, Serrano R, Llanos M, et al. : Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. Cancer Metastasis Rev 2015 Sep 6;34:381–400. [PubMed: 26245646]

250. Yadegarfar G, Friend L, Jones L, Plum LM, Ardill J, Taal B, et al. : Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. Br J Cancer 2013 Feb 15;108:301–310. [PubMed: 23322194]

251. Vinik E, Carlton CA, Silva MP, Vinik AI: Development of the Norfolk Quality of Life Tool for Assessing Patients With Neuroendocrine Tumors. Pancreas 2009 Apr;38:e87–e95. [PubMed: 19276865]

252. Topping M, Gray D, Friend E, Davies A, Ramage J: A Systematic Review of Symptoms and Quality of Life Issues in Pancreatic Neuroendocrine Tumours. Neuroendocrinology 2017;105:320–330. [PubMed: 28423380]

253. Pavel ME, Singh S, Strosberg JR, Bubuteishvili-Pacaud L, Degtyarev E, Neary MP, et al. : Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017 Oct;18:1411–1422. [PubMed: 28838862]

254. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG: Minireview: Gut Microbiota: The Neglected Endocrine Organ. Mol Endocrinol 2014 Aug;28:1221–1238. [PubMed: 24892638]

255. Russell WR, Duncan SH, Flint HJ: The gut microbial metabolome: modulation of cancer risk in obese individuals. Proc Nutr Soc 2013 Feb 23;72:178–188. [PubMed: 23174203]

256. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. : Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018 Jan 5;359:91–97. [PubMed: 29097494]

257. Modlin IM, Sandor A: An analysis of 8305 cases of carcinoid tumors. Cancer 1997 Feb 15;79:813–29. [PubMed: 9024720]

258. Zhang J, Kulkarni HR, Singh A, Niepsch K, Müller D, Baum RP: Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. J Nucl Med 2019 Mar;60:377–385. [PubMed: 30115686]

259. Rindi G, Kloppel G, Ahlman H, Caplin M, Couvelard A, de Herder WW, et al. : TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006 449(4): 395–401. [PubMed: 16967267]

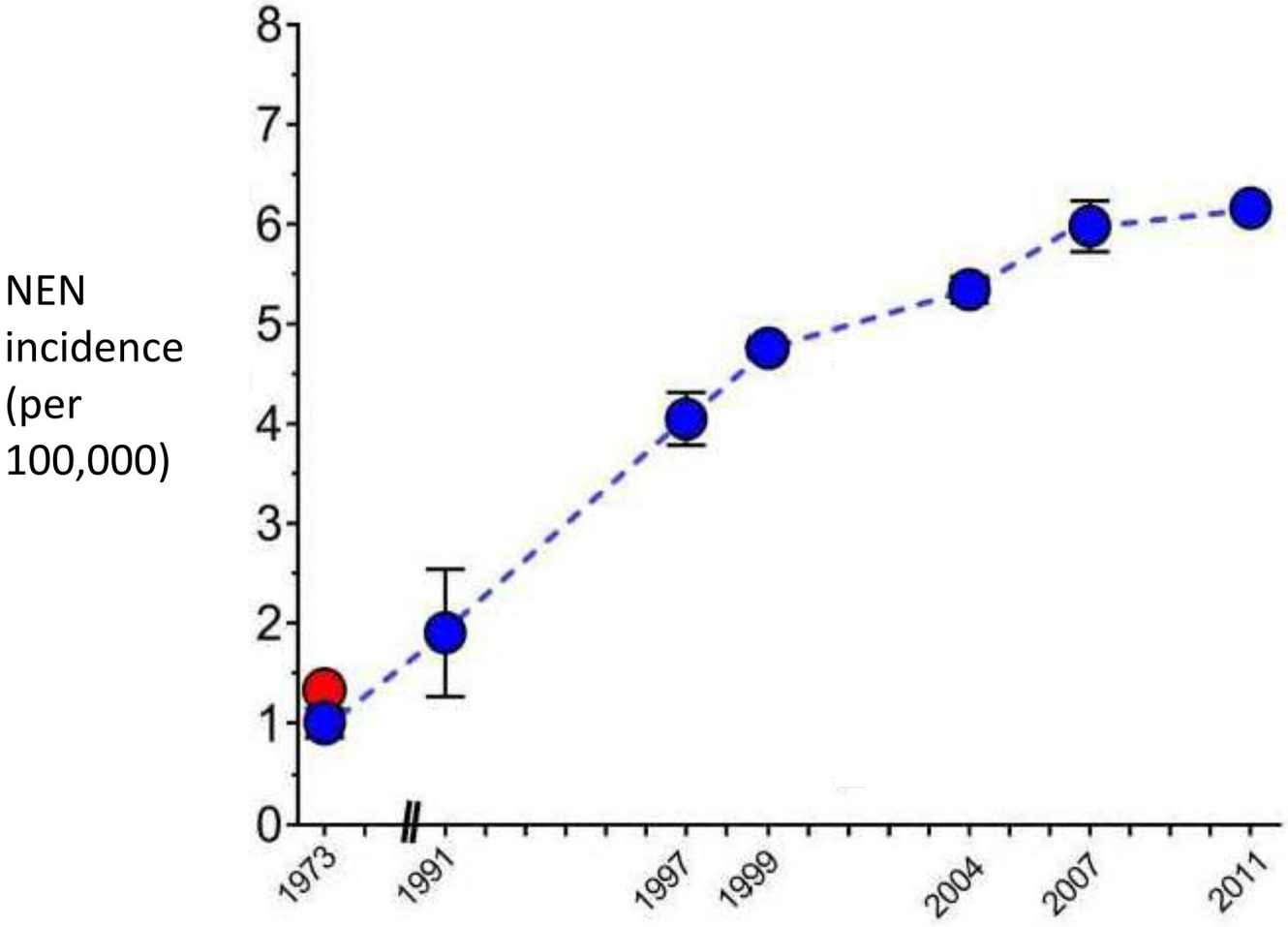

Figure 1. Changes over time in NET incidence in the SEER database.

Godwin identified the incidence of NETs to be ~1.3/100,000 (red dot - 1973) in the ERG-TNCS database (pre-SEER). A retrospective analysis from the SEER database is represented as blue dots. Solid dots are mean incidence, error bars correspond to 95% confidence interval. The SEER analysis of 1997 [257] first identified an increased incidence. Thereafter, all subsequent evaluations have demonstrated a steadily increasing incidence (blue dots). This increase is exponential (logarithmic analysis of years: linear regression >0.96) and is consistent with a continuous state-wide assimilation of advances in histopathology, imaging and awareness (HIA). The continued increase in "incidence" suggests that maximal detection levels of NET disease have not been reached. This reflects the failure of HIA advances to have fully permeated the US health care environment. Given the linear slope of the analysis it seems that a likely "real" incidence may not be reached for decades. The disproportionate effect of endoscopic surveillance of the colon and upper GI for cancer and GERD needs to be considered in defining the incidence of life risk significant neoplasia. Data is derived from [5,8,19]

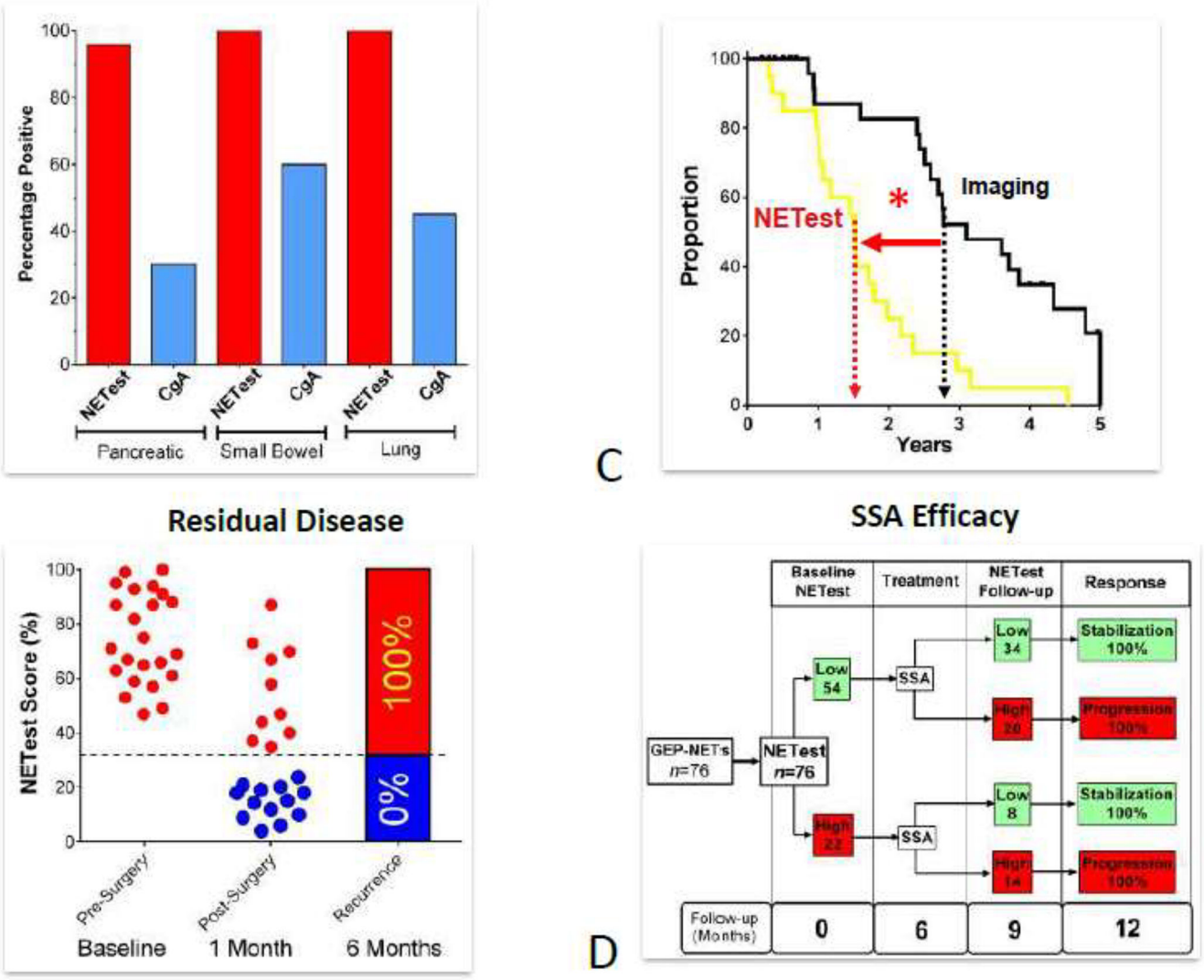

Figure 2. Clinical utility of the NETest.

As a diagnostic test (A) for small bowel or pancreatic NET disease, the percentage positive score is 95–100% (n=212) (top left). For lung NETs (n=207), the accuracy is similar (95%). CgA, in comparison is positive in ~30% pancreas, 75% of SI and 45% lung of NETs. Surgical resection (B) reduces the NETest consistent with the tumour removal being the source of the circulating genes. An elevated score (red circles) one month after surgery identifies residual disease and predicts recurrence. Low scores (blue circles) at 6 months indicates complete resection. Elevated NETest scores (C) have a prognostic implication. In a monitored cohort (n=34) over 5 years an elevated NETest occurs 12 months (*) before CT or MRI image-confirmation of disease progression. Monitoring the efficacy of somatostatin analogue (SSA) (D) demonstrates that SSA therapy with disease stabilization exhibits a low NETest. A high NETest on an SSA indicates disease progression. Thus, NETest has utility as a monitoring tool.

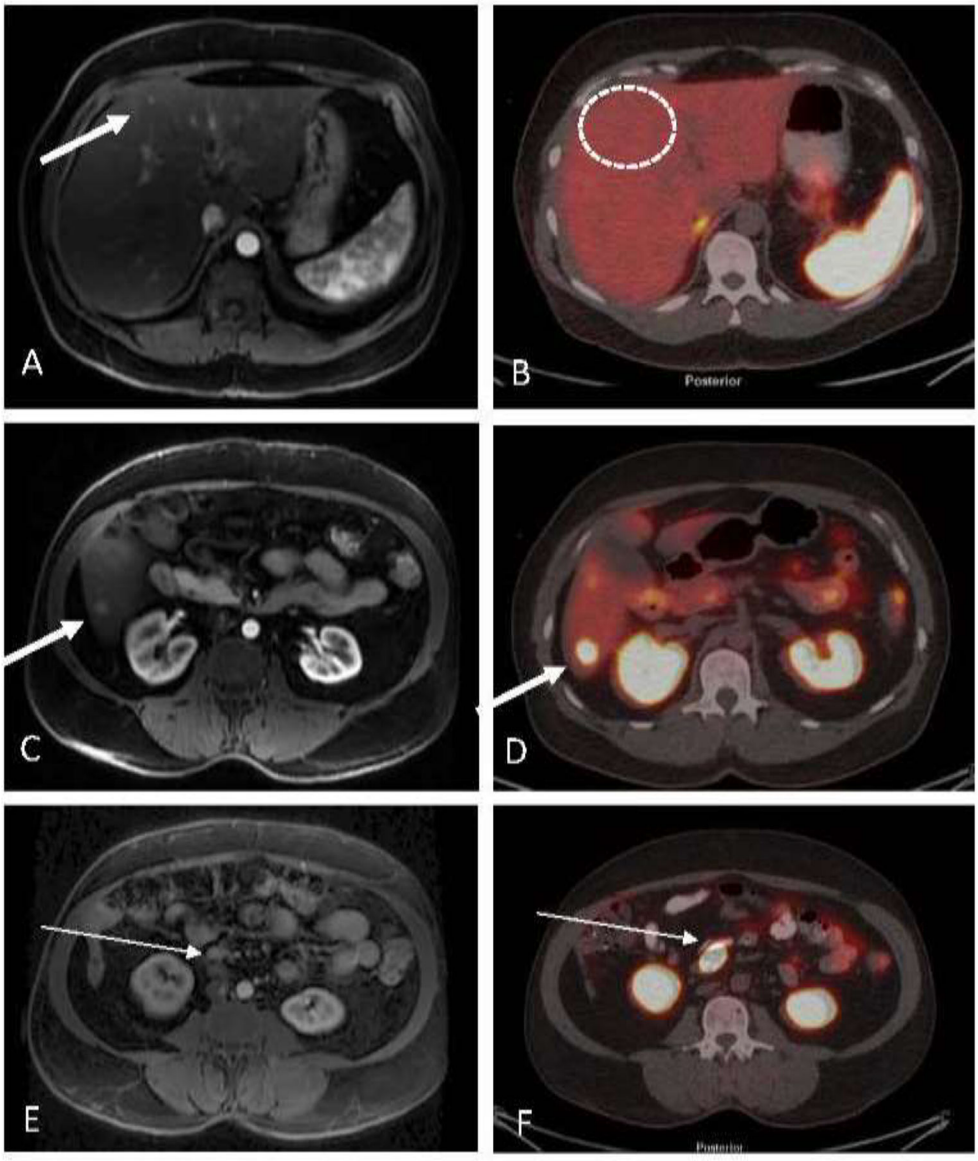

Figure 3. Benefits of integrating morphological and functional imaging.

Example of the synergistic information deriving from the integration of morphologic (*MR, Axial WATER LAVA, 1 min post gadobutrol*) and molecular (*^{68}Ga-DOTATATE PET/CT, axial fused images*) imaging in a patient with G2 neuroendocrine tumor of the ileocecal valve, status post-surgery and referred for restaging of known liver metastases. The MR (*A, solid arrow*) shows a 0.5 cm lesion in hepatic segment IVA which is not apparent on ^{68}Ga-DOTATATE (*B, dotted circle*). Other, bigger liver metastases, for example the 1.3 cm lesion identified in segment VI, are concordant on MR (C, solid arrow) and PET (*D, solid arrow*). In addition, ^{68}Ga-DOTATATE (*F, solid arrow*) showed intense uptake in a small short-axis node on MRI (*E, solid arrow*) which did not fulfill the criteria for lymphadenopathy

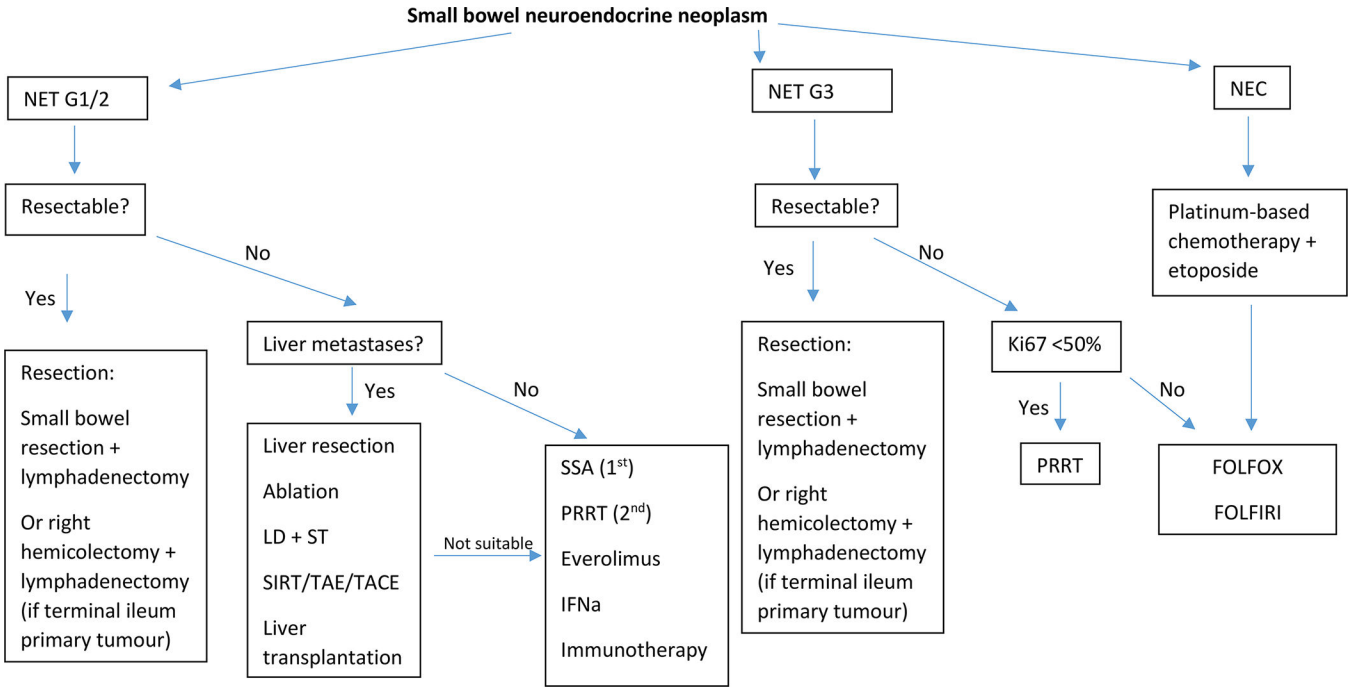

Figure 4. Therapeutic options for small bowel neuroendocrine neoplasms

Treatment algorithm for small bowel neuroendocrine neoplasms, displaying the options available for each sub-type. The ordering of treatments within the same box does not reflect any particular sequencing, rather the options available. NET = neuroendocrine tumour, G = grade, NEC = neuroendocrine carcinoma, SSA = somatostatin analogues, PRRT = peptide receptor radionuclide therapy, IFNa = interferon-alpha, LD + ST = combination of liver-directed and systemic therapies, SIRT = selective internal radiotherapy, TAE = transarterial embolization, TACE = transarterial chemoembolisation. SSAs are not suitable in higher grade NEN due to their de-differentiation and resultant lower expression of somatostatin receptors. Surgery and PRRT have also been utilised in higher grade NEN (G3/NEC) but data are limited to small-size case series.

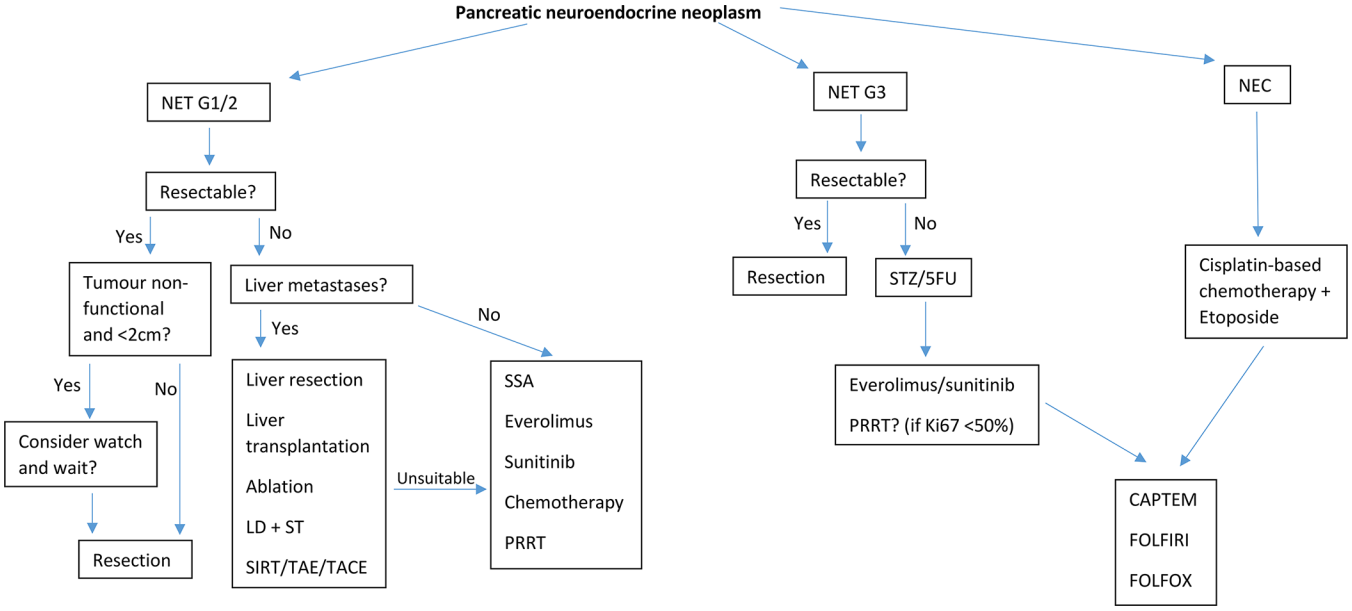

Figure 5. Therapeutic options for pancreatic neuroendocrine neoplasms

Treatment algorithm for pancreatic neuroendocrine neoplasms. The ordering of treatments within the same box does not reflect any particular sequencing, rather the options available. SSAs are not suitable in higher grade NEN due to their de-differentiation and resultant lower expression of somatostatin receptors. Surgery and PRRT have also been utilised in higher grade NEN (G3/NEC), but available data are limited [258]. NET = neuroendocrine tumour, G = grade, NEC = neuroendocrine carcinoma, SSA = somatostatin analogues, PRRT = peptide receptor radionuclide therapy, LD + ST = combination of liver-directed and systemic therapies, SIRT = selective internal radiotherapy, TAE = transarterial embolisation, FOLFIRI = folinic acid & fluorouracil & irinotecan, TACE = transarterial chemoembolisation, STZ/5FU = streptozocin & 5-fluorouracil, CAPTEM = capecitabine & temozolomide, FOLFOX = folinic acid & leucovorin & 5-fluorouracil, CTX = chemotherapy, either streptozotocin/5-fluorouracil (STZ/5-FU) or capecitabine/temozolomide (CAP/TEM) depending on availability and/or approval MTT, molecular targeted therapy, everolimus or sunitinib

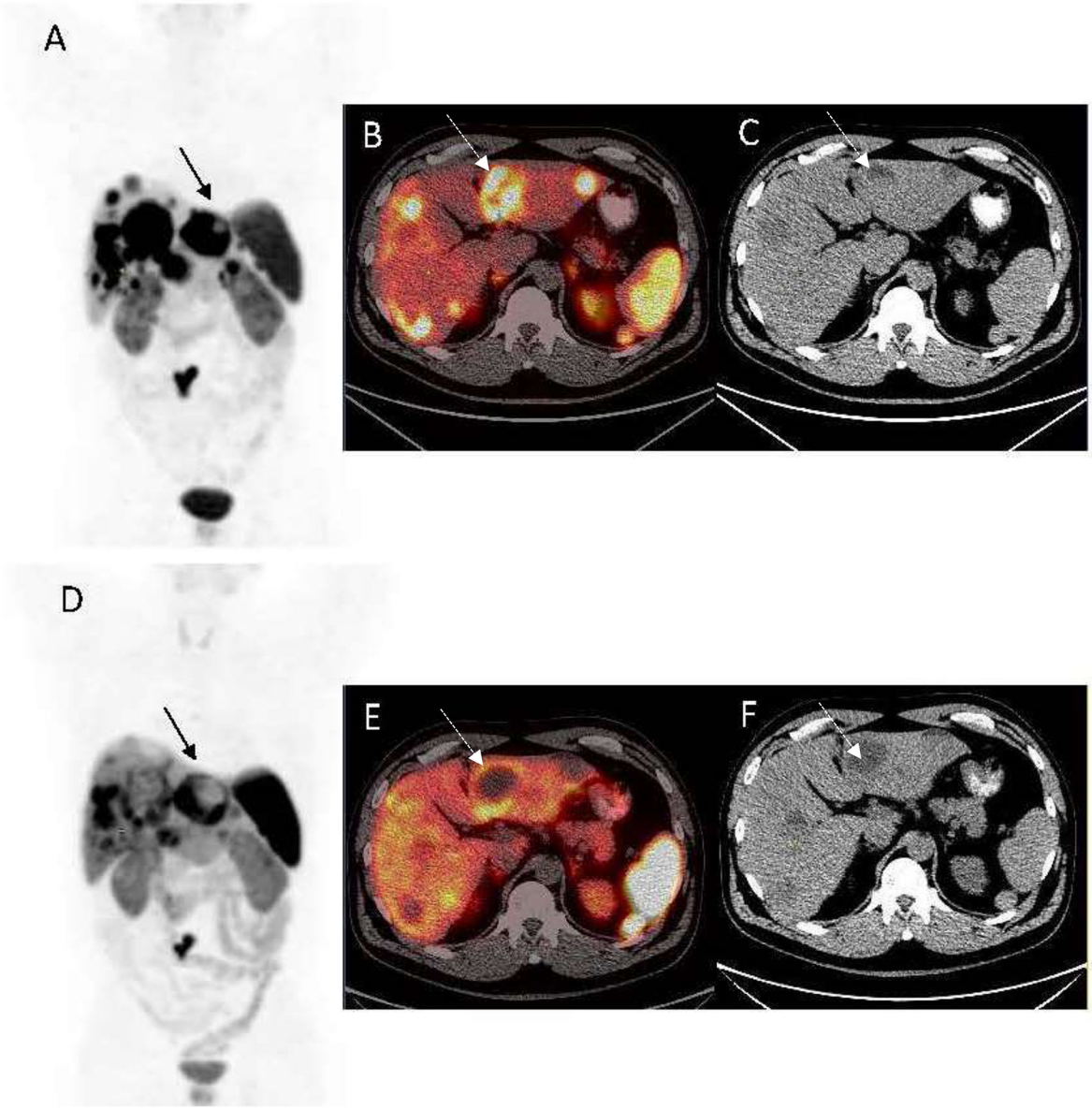

Figure 6. Response to peptide receptor radionuclide radiotherapy.

Response to PRRT with ^{177}Lu-DOTATATE in a patient affected by a functioning small bowel neuroendocrine tumor with hepatic and nodal metastases, before (*upper row, 68Ga-DOTATATE PET/CT: A, MIP image; B, fused axial image; C, axial non-contrast CT*) and after (*lower row, 68Ga-DOTATATE: B, MIP image; E, fused axial image; F, axial non-contrast CT*) treatment. The liver metastases have markedly decreased in extent and tracer avidity at the post-treatment PET/CT, some with increased central photopenia, consistent with central necrosis on CT (*A pre-, D, post-treatment, black solid arrow; B, C, pre-, E, F, post-treatment, dotted arrow*). The patient also manifested substantial symptomatic improvement (flushing and diarrhoea).

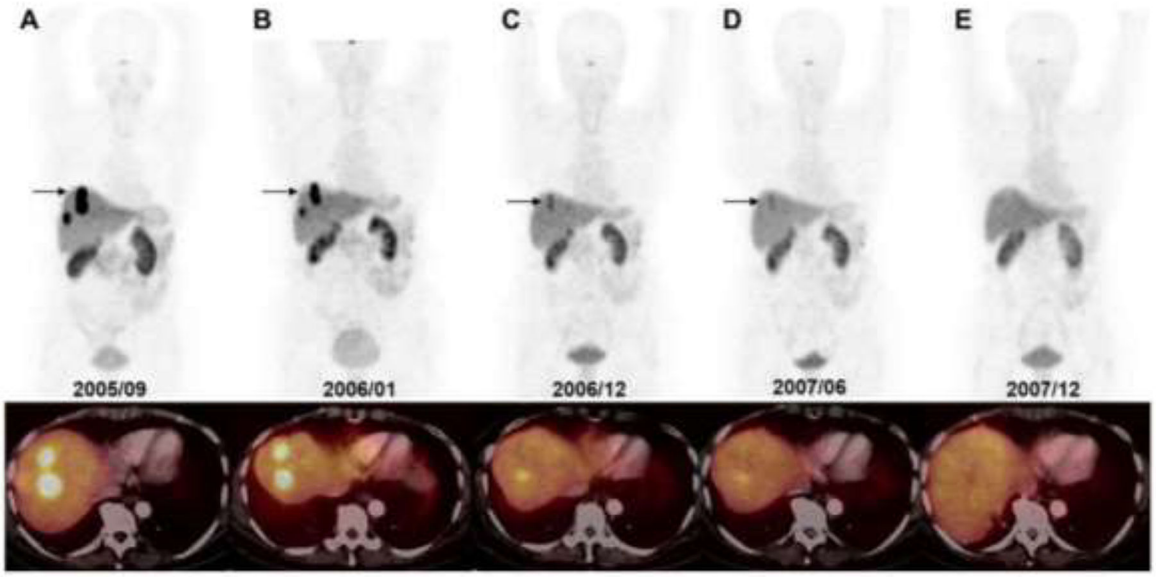

Figure 7. Response to multimodal treatment.

Serial ^{68}Ga-SSTR PET/CT MIP images of a 64-year-old woman with well-differentiated, functional pancreatic neuroendocrine neoplasm with liver metastases. The Ki-67 proliferation index was 5% for the primary tumor and 10% for the liver metastasis. Previous treatments were pancreatic tail resection, splenectomy, atypical liver segment resection and open radiofrequency ablation of three liver lesions. ^{68}Ga-DOTATATE PET/CT demonstrates significant somatostatin receptor expression in the hepatic metastases before start of PRRT (A, baseline). The patient was treated with four cycles of ^{177}Lu-DOTATATE (cumulative administered activity 26.4 GBq). Restaging ^{68}Ga-DOTATATE PET/CT at 4 months showed response (B) of the liver metastases, partial remission at 15 and 21 months, respectively (C, D) and complete remission of the disease at 27 months after PRRT (F).

Table 1.

Histological types of neuroendocrine neoplasms (NEN), their secreted hormones and associated clinical syndromes.

Tumour	Secreted hormone	Clinical syndrome and symptomatology
Small bowel NEN (mainly in stage IV) Some PanNET	Serotonin	*Carcinoid syndrome:* Flushing Secretory diarrhoea Bronchospasm Carcinoid heart disease
Gastrinomas (Duodenal or PanNEN)	Gastrin	*Zollinger-Ellison syndrome:* Resistant-to-treatment peptic ulcers (not related to NSAIDs or *Helicobacter pylori*) Severe reflux oesophagitis Chronic diarrhoea
Insulinomas (PanNEN)	Insulin	Fasting hypoglycaemia and associated neuroglycopaenic/autonomic symptoms
Glucagonomas (PanNEN)	Glucagon	New-onset diabetes Weight loss Characteristic rash: migratory necrolytic erythema
VIPomas (typically PanNEN)	Vasoactive intestinal peptide	*Werner-Morrison syndrome:* Severe diarrhoea with resultant dehydration, hypokalaemia and achlorhydria
Somatostatinoma (duodenal NEN or PanNEN)	Somatostatin	Diabetes mellitus Gallstone disease Diarrhoea Weight loss Steatorrhoea

Clinical syndromes are predicated by the supra-physiological secretion of the below hormones (i.e. hyper-secretion). VIP = vasoactive peptide, NSAIDs = non-steroidal anti-inflammatory drugs. There are several other peptides that may be secreted by NEN which may cause symptoms, but they are not assessed in routine clinical practice.

Table 2.

American Joint Cancer Committee (AJCC) staging classification for small bowel (jejunum and ileum) neuroendocrine tumours [17].

T – primary tumour	
T0	No evidence of primary tumour
T1	Tumour invades lamina propria/submucosa, and size ≤1cm
T2	Tumour invades muscularis propria or size ≥1cm
T3	Tumour invades sub-serosa (without penetrating serosa)
T4	Tumour invades peritoneum/other organs/adjacent structures
N – regional lymph nodes	
N0	No regional lymph node metastasis
N1	Regional lymph node metastases in <12 nodes
N2	Large mesenteric masses (>2cm) or ≥12 nodes
M – distant metastases	
M0	No distant metastasis
M1	Distant metastasis
M1a	Confined to liver
M1b	In at least one extra-hepatic site
M1c	Both hepatic and extra-hepatic
TNM stage	
Stage I	T1 N0 M0
Stage IIA	T2 N0 M0
Stage IIB	T3 N0 M0
Stage IIIA	T4 N0 M0
Stage IIIB	Any T N1 M0
Stage IV	Any T Any N M1

Table 3.

American Joint Committee on Cancer (AJCC) [17] and European Neuroendocrine Tumour Society [259] 'TNM' grading systems for pancreatic neuroendocrine tumours. 'Limited to pancreas' refers to lack of extension into adjacent organs or structure – this does not include invasion of peripancreatic adipose tissue. Pancreatic neuroendocrine carcinomas are staged as per the pancreas exocrine system.

	AJCC	ENETS
T – primary tumour		
T1	Limited to pancreas, <2cm	Limited to pancreas, <2cm
T2	Limited to pancreas, 2–4cm	Limited to pancreas, 2–4cm
T3	Tumour limited to pancreas, >4cm, or tumour invading duodenum or common bile duct	Limited to pancreas, >4cm, or invading duodenum or common bile duct
T4	Tumour invading adjacent organs	Invades local structures
N – regional lymph nodes		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastases	Regional lymph node metastases
M – distant metastases		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
	M1a – confined to liver	
	M1b – in ≥1 extrahepatic site	
	M1c – hepatic and extrahepatic	
TNM stage		
Stage I	T0 N0 M0	T1 N0 M0
Stage II	T2–3 N0 M0	IIa – T2 N0 M0
		IIb – T3 N0 M0
Stage III	T4 N0 M0 or Any T N1 M0	IIIa – T4 N0 M0
		IIIb – Any T N1 M0
	Any T Any N M1	
Stage IV		Any T Any N M1

Table 4.

Biomarkers of small bowel and pancreatic neuroendocrine neoplasms.

Marker	Normal Function	Outcome	Refs
Chromogranin A (CgA)	Considered to have broad spectrum of regulatory activities including endocrine, cardiovascular, and immune.	Diagnostic accuracy 40–70% * Prognostic significance: 20–45% *	[87,89]
Pancreastatin	Break-down product of CgA	Diagnostic accuracy 40–60% * Prognostic significance: 20–50% *	[87, 89]
Urinary 5-HIAA	Nil, breakdown product	SBNEN: 35–70% PanNEN: 2–5%	[87,89]
Neurokinin A	Excitatory effects on CNS, pain and inflammation	SBNEN: 20–40% PanNEN: not used	[87,89]
Insulin	Pancreatic endocrine function, glucose metabolism	SBNEN: not used PanNEN: 2% **	[87,89]
Gastrin	Endocrine regulation, mucosal growth	SBNEN: not used PanNEN: 2% **	[87,89]
Somatostatin	Inhibition of pancreatic hormone secretion including insulin and glucagon	SBNEN: not used PanNEN: 1–2% **	[87,89]
Vasoactive intestinal peptide	Vasodilator, regulates smooth muscle activity, epithelial cell secretion, and blood flow in the gastrointestinal tract	SBNEN: not used PanNEN: 1–2% **	[87,89]
Neuron-specific enolase	Located in cytosol of neurons and neuroendocrine cells	GEP NEN: elevated in 30–50%, sensitivity 38%, specificity 73%	[86,88]
Pancreatic polypeptide	Regulation of pancreatic secretory function	PanNEN: diagnostic accuracy 64% in MEN1	[87,89]
NETest	Neuroendocrine proliferation, metabolism, signaling pathways inc. RAF-RAS, epigenetic regulation and somatostatin receptor expression	Diagnostic accuracy: 90–100% * Prognostic significance: >90% *	[97]
PPQ/PRRedicTor	Neuroendocrine proliferation, metabolism and RAF-RAS signaling	Predictive accuracy for PRRT: 93–97% *	[114]
Circulating tumour cells	None	Diagnostic accuracy: 40–50% * Prognostic significance: 70% *	[89,92,93]
MicroRNAs	Various	SB NEN: diagnostic accuracy 95%	[91]

5-HIAA = urinary 5-hydroxyindole acetic acid, PRRT = peptide receptor radionuclide therapy, CS = central nervous system

* For both SBNEN and PanNEN

** Highly accurate as a diagnostic and predictive of tumor recurrence in specific PanNEN e.g., gastrin and gastrinoma, VIP and VIPoma etc.

Table 5.

Comparison of imaging modalities and endoscopic techniques utilised in neuroendocrine neoplasms

Imaging modality	Advantages	Disadvantages
CT	Widely available	Morphological information only May 'miss' small bowel NEN primaries
MRI	Widely available Multiple sequences, including diffusion-weighted, high sensitivity for liver metastases	Less sensitive than ^{68}Ga-DOTA PET for primary PanNEN
Somatostatin receptor scintigraphy (OctreoScan)	Widely available and used Can be 2-dimensional or 3-dimensional (planar or SPECT)	Poorer resolution of subcentimetric lesions Lengthy process for injection and scanning Poorer sensitivity for liver metastases Poor identification of multifocal primaries
^{68}Ga-DOTA PET	Higher resolution (4–6mm) Can be hybridised with CT or MRI High sensitivity for liver and extra-hepatic metastases with ramifications on treatment planning High sensitivity for most NEN types (G1/G2) Assesses for suitability of PRRT in theranostics approach	Not widely available outside of Europe/some US centres Lower sensitivity for insulinoma Poor identification of multifocal primaries
^{18}F-FDG PET	Possible role in disease prognostication (to be validated) Can be hybridised with CT or MRI High resolution (4–6mm)	Limited tracer uptake and therefore poorer sensitivity in low-grade lesions
Endoscopy	Can detect primary small intestinal NEN not visualised on CT Several modalities, such as video capsule	Skilled centres required Invasive Useful for evaluation of PanNEN Limited to luminal tumours (VCE) Risk of obstruction in SBNEN (VCE)
Ultrasound	Widely available Especial utility in screening for carcinoid disease in metastatic SBNEN	Morphological modality CT/MRI/PET more useful in disease staging – ultrasound not a standalone modality
^{18}F-DOPA PET; ^{11}C-5-HTP	Helpful in SSTR-negative imaging DOPA higher accuracy in SBNEN, HTP higher accuracy in PanNEN Can be hybridised with CT or MRI	Limited availability No clear evidence regarding superiority to other functional tracers

CT = computed tomography, MRI = magnetic resonance imaging, SSTR = somatostatin receptor targeted, SPECT = single positron emission CT, PET = positron emission tomography, NEN = neuroendocrine neoplasm, PRRT = peptide receptor radionuclide therapy, VCE = video capsule endoscopy.