Neuroendocrine Neoplasms of the Small Bowel and Pancreas

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Keywords

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Abstract

The traditionally promulgated perspectives of neuroendocrine neoplasms (NEN) as rare, indolent tumours are blunt and have been outdated for the last 2 decades.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 (SB) or pancreas typically occur sporadically; the latter may occur within the context of hereditary tumour predisposition syndromes. NENs 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 SB and pancreatic neuroendocrine tumours (NET) may be challenging, and often comprises a multidisciplinary approach wherein surgical, medical, interventional radiological and radiotherapeu-

tic modalities are implemented. This review provides a comprehensive overview of the epidemiology, pathophysiology, diagnosis and treatment of SB and pancreatic NETs. Moreover, we provide an outlook of the future in these tumour types which will include the development of precision oncology frameworks for individualised therapy, multi-analyte predictive biomarkers, artificial intelligence-derived clinical decision support tools and elucidation of the role of the microbiome in NEN development and clinical behaviour.

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Introduction

Neuroendocrine neoplasms (NEN) comprise a heterogeneous collection of tumours derived from widely distributed neuroendocrine cells, most commonly arising from the gastroenteropancreatic (GEP) 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 regard to their protean clinical manifestations ranging from incidental discovery to flor-

id 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 practices, 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 2 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 SBNEN and PanNEN. 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.

Fig. 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% CI. The SEER analysis of 1997 [253] 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. The continued increase in “incidence” suggests that maximal detection levels of NET disease have not been reached. This reflects the failure of histopathology, imaging and awareness 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 are derived from [5, 8, 19]. NEN, neuroendocrine neoplasms.

Epidemiology and Risk Factors

Epidemiology

In 1973, the annual incidence of NEN in the United States 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 United States is 6.98/100,000 (Fig. 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 version 18, 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 SB (median OS: 14 years), this ranges from 70 months (advanced disease with distant metastases) to 170 months (localised 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 (localised 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. SB 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.

OS (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 (SSA). 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 tech-

niques, 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 and 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 tumour progression in SBNEN and PanNEN [26]. These are hypothesised 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% lifetime risk for developing PanNEN [27]. Other factors include ever smoking, drinking and diabetes mellitus. Alcohol is a known pancreatic carcinogen, whereas 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 tumourigenesis. 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 that release hormones subsequent to stimulation from the nervous system and are distributed throughout the body in many

Table 1. Histological types of 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	<i>Carcinoid syndrome:</i> Flushing Secretory diarrhoea Bronchospasm Carcinoid heart disease
Gastrinomas (duodenal or PanNEN)	Gastrin	<i>Zollinger-Ellison syndrome:</i> Resistant-to-treatment peptic ulcers (not related to NSAIDs or <i>Helicobacter pylori</i>) Severe reflux oesophagitis Chronic diarrhoea
Insulinomas (PanNEN)	Insulin	Fasting hypoglycaemia and associated neuroglycopenic/autonomic symptoms
Glucagonomas (PanNEN)	Glucagon	New-onset diabetes Weight loss Characteristic rash: migratory necrolytic erythema
VIPomas (typically PanNEN)	Vasoactive intestinal peptide	<i>Werner-Morrison syndrome:</i> 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 detailed hormones (i.e. hyper-secretion). There are several other peptides that may be secreted by NEN which may cause symptoms, but they are not assessed in routine clinical practice. NEN, neuroendocrine neoplasms; VIP, vasoactive intestinal peptide; NSAIDs, non-steroidal anti-inflammatory drugs.

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, NENs are tumours that 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 GEP NEN are sporadic, but approximately 5% arise in the context of cancer 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 3 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 (VHL) syndrome is another rare, multi-organ genetic disorder associated with pancreatic lesions, commonly non-secreting PanNEN [34]; it also includes cerebral hemangio-

blastomas, clear cell renal carcinomas, pheochromocytomas 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 SBNET 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 SBNET 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 SBNET

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 SB 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 1,230 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 SBNET (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, that is, 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 2 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 3 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 vascular endothelial growth factor (VEGF), estimated glomerular filtration rate and mTOR pathways, suggesting clear vari-

ation in epigenetic pathogenic mechanisms and possibly molecularly-based treatment stratification, but crucially, significant differences in progression-free survival (PFS) were observed in a sub-set of 32 sample from patients followed-up after resection of the primary tumour: PFS in groups A, B and C was: not reached, 56 months and 21 months, 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 may be seen in 74% of SBNET, and promoter/gene body hypermethylation as well as increased *gastric inhibitory polypeptide receptor* 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, platelet-derived growth factor receptor beta 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 SBNET tissue is deranged compared to normal SB [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 SBNET [64]. Divergences in the “miRNomes” of localised, locally metastatic and distantly disseminated SBNET manifest as the downregulation of miR-1 and miR-143-3p in the latter 2 (most floridly in hepatic metastases), which may in turn bear impact on the expression of FOSB and NUA2 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 signal-

ling, 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 were 40 and 50% for patients with *DAXX/ATRX*-negative PanNET, versus 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) versus mean 2.62 (range 0.65–28.2) [73]. Five forms of mutational signatures were identified: deamination (spontaneous removal of amine groups from nucleotides, particularly cytosine that 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, 4 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 that 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 that 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 hypermethylation 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 miRNA 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 miRNAs, and notably miR-21 expression correlated with increased tumour grade (Ki67) and the existence of hepatic metastases. The miRNA 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 VEGF, platelet-derived growth factor, fibroblast growth factor and angiopoietin-2 (more so in PanNEN) [78], NETs 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 tumourigenesis, its role in metastasis in NEN is not yet fully clear.

Fibrosis is an appreciated phenomenon not only 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 SBNET, this landscape is heterogeneous, and the

Table 2. AJCC staging classification for small bowel (jejunum and ileum) neuroendocrine tumours [17]

<i>T – primary tumour</i>	
T0	No evidence of primary tumour
T1	Tumour invades lamina propria/submucosa, and size ≤1 cm
T2	Tumour invades muscularis propria or size ≥1 cm
T3	Tumour invades sub-serosa (without penetrating serosa)
T4	Tumour invades peritoneum/other organs/adjacent structures
<i>N – regional lymph nodes</i>	
N0	No regional lymph node metastasis
N1	Regional lymph node metastases in <12 nodes
N2	Large mesenteric masses (>2 cm) or ≥12 nodes
<i>M – distant metastases</i>	
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
<i>TNM stage</i>	
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

AJCC, American Joint Cancer Committee; TNM, Tumour, Nodes, Metastasis classification.

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 Pan-NEN 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 SBNET 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 NETs or NEC. Grade 1 (NET) have a Ki67 of <3% or <2 mitoses per 10 HPF. Grade 2 (NET) have a Ki67 index of between 3 and 20%, or between 2 and 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 that may be measurable analytes specific to an individual cell/tumour type. In addition, many NEN co-secrete chemicals associated with granule exocytosis or maturation, for example, chromogranin A (CgA) or neuron-specific enolase (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)

Table 3. AJCC [17] and ENTS [255] TNM grading systems for pancreatic NET

AJCC		ENETS
<i>T – primary tumour</i>		
T1	Limited to pancreas, <2 cm	Limited to pancreas, <2 cm
T2	Limited to pancreas, 2–4 cm	Limited to pancreas, 2–4 cm
T3	Tumour limited to pancreas, >4 cm, or tumour invading duodenum or common bile duct	Limited to pancreas, >4 cm, or invading duodenum or common bile duct
T4	Tumour invading adjacent organs	Invades local structures
<i>N – regional lymph nodes</i>		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastases	Regional lymph node metastases
<i>M – distant metastases</i>		
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	
<i>TNM stage</i>		
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
Stage IV	Any T Any N M1	Any T Any N M1
<p>“Limited to pancreas” refers to lack of extension into adjacent organs or structure – this does not include invasion of peripancreatic adipose tissue. Pancreatic NEC are staged as per the pancreas exocrine system. AJCC, American Joint Committee on Cancer; ENTS, European Neuroendocrine Tumor Society; NET, neuroendocrine tumours; NEC, neuroendocrine carcinomas; TNM, Tumour, Nodes, Metastasis classification.</p>		

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 Pan-NEN, for example, 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 [93] (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-hydroxy-indole acetic acid. Metabolic phenotyping of urine has been shown to

Table 4. Biomarkers of small bowel and pancreatic NEN

Marker	Normal function	Outcome	References
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]
VIP	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%*	[96]
PPQ/PRRedicTor	Neuroendocrine proliferation, metabolism and RAF-RAS signaling	Predictive accuracy for PRRT: 93–97%*	[112]
Circulating tumour cells	None	Diagnostic accuracy: 40–50%* Prognostic significance: 70%*	[89, 92, 93]
MicroRNAs	Various	SBNEN: diagnostic accuracy 95%	[91]

* For both SBNEN and PanNEN. ** Highly accurate as a diagnostic and predictive of tumor recurrence in specific PanNEN, for example, gastrin and gastrinoma, VIP and VIPoma etc. NEN, neuroendocrine neoplasms; CgA, chromogranin A; 5-HIAA, 5-hydroxy-indole acetic acid; VIP, vasoactive intestinal peptide; NET, neuroendocrine tumour; PPQ, positive predictor quotient; PRRT, peptide receptor radionuclide therapy; CNS, central nervous system.

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) [95]. 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 [96, 97]. Measurements appear robust and exhibit a consistent and reliable high degree of sensitivity and specificity (both >95%) [96]. The values are standardised, reproducible and are not influenced by age, gender, ethnicity, fasting or acid suppressive medication [98, 99]. The assay has been independently validated [100]. 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 [101–103] (Fig. 2). One prospective study compared the NETest to

Fig. 2. Clinical utility of the NETest. As a diagnostic test (a) for SB or pancreatic NET disease, the percentage positive score is 95–100% ($n = 212$). 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) 1 month after surgery identifies residual disease and predicts recurrence. Low scores (blue circles) at 6 months indicates complete resection. El-

evated 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 SSA (d) demonstrates that SSA therapy with disease stabilisation exhibits a low NETest. A high NETest on an SSA indicates disease progression. Thus, NETest has utility as a monitoring tool. NET, neuroendocrine tumour; CgA, chromogranin A; SSA, somatostatin analogue; GEP, gastroenteropancreatic.

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 AUC for the NETest was 0.93 compared to ~0.6 for the others [101]. The NETest was 93% positive, whereas single analytes were positive in ~40%. In 2 other independent studies, a daily clinical practice registry audit (NCT02270567) of NEN

[102] and a prospective, university-based study [100] 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

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 (4–6 mm) 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 (4–6 mm)	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 Especially 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.

intervention. In this respect, a NEN-relevant example is high-grade (G3) lesions, which have a significantly worse prognosis than G1/G2 neoplasia [104]. A highly elevated CgA (>6× upper limit of normal) has been associated with a poorer prognosis for SBNEN but not PanNEN [105], which reflects the low diagnostic accuracy of CgA for PanNEN [106]. High NETest levels (≥80), in contrast, have been demonstrated in 3 separate studies to be an effective (accurate in ≥95% of patients) prognostic marker [102, 107, 108]. Moreover, a positive NETest score after “complete resection” in lung and GEP-NEN is associated with disease recurrence [109, 110]. Overall, elevated NETest levels are >80% more accurate than CgA as a prognostic marker [109, 111].

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 (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) was demonstrated to be ~95% accurate as a predictive tool in a de-

Fig. 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.

developmental cohort [112]. Accuracies in subsequent independent prospective validation in 2 PRRT studies were 93–97%, versus 0% in 2 cohorts either receiving SSAs or no treatment. Thus, a specific multianalyte test can function as a predictive biomarker for a specific treatment modality [113].

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 (TMZ) for PanNET – lower expression of MGMT is correlated with favourable PFS, treatment response and OS in a retrospective study [114], 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 techniques). Scintigraphy with ^{111}In -pentetreotide (or $^{99\text{m}}\text{Tc}$ -EDDA-HYNIC-TOC) has almost universally been replaced by PET with ^{68}Ga -labeled SSAs (^{68}Ga -SSA) [115]. Other PET techniques include ^{18}F FDG, ^{18}F -DOPA, ^{11}C -5-HTP, GLP-1, ^{64}Cu -SSA and ^{68}Ga -labeled somatostatin receptor an-

tagonists [115–117]. No modality, however, is entirely effective, and the overall sensitivity and specificity are ~80 to 90% [118]. Typically, sensitivity and specificity can be optimised by integrating anatomic and molecular imaging (Fig. 3) [119, 120]. Despite substantial advances, a number of critical unmet need 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 [121, 122].

Morphologic Imaging

SB 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) [123]. 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) [124, 125]. CT enteroclysis is inferior to video capsule enteroscopy (sensitivity and specificity: 50 and 25% vs. 38 and 100%, respectively) [126]. Morphologic imaging in general understages disease significantly [127].

PanNEN are highly vascularised and enhance during the arterial and venous phases on CT. Heterogeneous enhancement may occur in larger necrotic lesions [128]. 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 [129]. An overview of 11 studies (343 PanNEN) 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 [116]. A combination of CT and EUS may reach 100% sensitivity for the localisation of a primary pancreatic lesion [130].

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 [131]. 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 images. After

gadolinium, they demonstrate arterial enhancement and washout [132]. Hepatic arterial phase and fast spin-echo T2-weighted sequences are the most sensitive [133]. The introduction of liver-specific contrast gadoxetate allows for greater detection sensitivity (anatomic detail, spatial/contrast resolution) [132]. Overall, MR has a higher sensitivity than CT [134]. 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 [135]. However, none of these studies referenced histopathology, which demonstrates that ~50% of lesions are not detected by imaging [127].

Molecular Imaging

Functional imaging using PET/CT is essential for detecting small lymph node metastases (<10 mm in size), tiny primary tumours in the SB (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 characterised 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 using the γ -emitters Indium-111 (^{111}In) or technetium-99 ($^{99\text{m}}\text{Tc}$) [136]. Numerous advantages including easy synthesis (with a $^{68}\text{Ge}/\text{Ga}$ generator), high spatial resolution (~4 to 5 mm), simple image quantification, favourable dosimetry and the possibility of modifying clinical management in 44% of patients has made ^{68}Ga -SSA PET/CT the technique of choice [137–139].

The sensitivity of ^{68}Ga -SSA PET/CT for NEN is >90%, with specificity ranging between 92 and 98% [140–143]. It is essential for the detection of the primary tumour and identification of mesenteric lymph nodes and/or local tumour 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 diffusion-weighted-MRI in the detection of PanNEN in a direct head-to-head comparative study [144]. ^{68}Ga -SSA PET/CT, if available, should be considered as the first-line diagnostic imaging method for staging in patients with PanNEN [145]. ^{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 Pan-

Fig. 4. Therapeutic options for SBNEN. Treatment algorithm for SBNENs, 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. SSAs are not suitable in high-grade NEN due to their de-differentiation and resultant lower expression of somatostatin receptors. Surgery and PRRT have also been utilised in high-grade NEN (G3/NEC), but

data are limited to small-size case series. 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 embolisation; TACE, transarterial chemoembolisation.

NEN. In a series of 52 patients with neuroendocrine liver metastases (NELM), results of ^{68}Ga -DOTATOC PET/CT altered the initial treatment decisions based on CT and/or MRI alone in nearly 60% of patients [146].

Establishing the extent and progression of NEN is necessary to decide which treatment option to choose. The uptake in the tumour lesions as shown by ^{68}Ga -SSA PET/CT, tumour dynamics (doubling time, new lesions after previous treatments), extra-hepatic tumour burden, functional activity of primary tumour and the metastasis, as well as tumour size, location with/without liver metastasis are important factors to select targeted therapies and to optimise individualised treatment planning. Following the determination of high expression of SSTRs of the tumours 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 personalised treatment, that is, 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 [147, 148] 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 [149]. Its optimal application, however, may be G2 NEN with Ki67 >15–20% for which ^{68}Ga -SSA PET/CT is less reliable [150]. Increased metabolic uptake can provide predictive information regarding survival [151]. 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 tumours [149]. It has recently been proposed that FDG may be an independent prognostic marker using a 3-tier metabolic grad-

Fig. 5. Therapeutic options for pancreatic NEN. Treatment algorithm for pancreatic NENs. The ordering of treatments within the same box does not reflect any particular sequencing, rather the options available. SSAs are not suitable in high-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 [254]. 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 and fluorouracil and irinotecan; TACE, transarterial chemoembolisation; STZ/5FU, streptozocin and 5-fluorouracil; CAPTEM, capecitabine and temozolomide; FOLFOX, folinic acid and leucovorin and 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.

ing system based on the tumour to background ratio of uptake [152].

^{64}Cu -SSA-PET/CT may improve the resolution of liver lesions [153]. Radiolabeled SSTR antagonists, characterised 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 -DOT-ATOC [117, 154]. Other receptor-targeted imaging, for example, the chemokine receptor CXCR4 appears promising in higher-grade tumours and glucagon-like peptide-1 receptor PET/CT in benign insulinomas, which are usually characterised by a low expression of SSTRs [155]. Finally, GLP1 receptor peptides for imaging of well-differentiated insulinomas (exendin analogs labeled with ^{68}Ga) have shown encouraging results [156] but have limited availability outside of select centres.

Therapeutic Strategies

Management strategies for SBNEN (Fig. 4) and Pan-NEN (Fig. 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 OS. 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 (PC) are independent prognostic factors for OS in SBNEN [157]. Bone metastases have a distinct prognostic impact to that of other distant metastases (inferior OS with the former) [158], and although occurring only in approximately 5% of metastatic GEP NEN, lung metastases have significant detriment to OS which is in addition to that presented by distant metastases at other sites [159]. Multivariate prognostic scores have been developed for both SBNEN and PanNEN in terms of OS or recurrence post-surgery [160–163].

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 mesentery should be considered for curative resection [164, 165]. As part of the surgical approach, meticulous intra-operative exploration of the abdomen and SB palpation is advised [166]; 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 [167]. This is particularly important as approximately 30–54% of SBNEN are multifocal [168] and often only a few millimetres in size, which is rarely appreciated on imaging [167]. 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 SB 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 [169], 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 [170]. 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 OS – patients with 12 or more resected and examined lymph nodes had the best survival outcomes [171].

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 [172]. Up to 30% of SBNEN are associated with PC [173], which is infiltration of the peritoneum with tumour deposits and an independent negative prognosticator [157]. As PC may cause intestinal obstruction and cause death in 40% of SBNEN if not treated [173], resection of peritoneal lesions should be part of locoregional surgery [174].

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 [175–177], which in a retrospective study was irrespective of tumour grade [178]. 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 [179].

Surgical Intervention for Primary Tumours: PanNEN

Patients with functional PanNEN irrespective of size, and those with non-functional and, therefore, asymptomatic PanNEN >2 cm should be evaluated for surgery [180]. However, the relatively arbitrary 2 cm cut-off may not be valid as a standalone arbiter of potential for malignant behaviour in non-secretory PanNEN, as 38% of these tumours ≤2 cm display malignant features (i.e., metastasis to nodes) and a 2 cm cut-off for surgery has an 84% sensitivity for malignancy [181]. 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) [182]. Post-operative complications with pancreatic surgery do not appear to associate with the risk of recurrence of PanNEN [183].

Surgical exploration is advised for MEN1-associated gastrinomas as they are frequently metastatic, necessitating aggressive surgery [184]. There is lack of consensus regarding appropriate aggressiveness in MEN1-associated insulinomas [185]. Conservative management of MEN1-associated non-functioning PanNEN ≤2 cm may be associated with low disease-specific mortality [186], whereas this is inappropriate in tumours 3 cm or larger [187].

Endoscopic ablative technologies may also be utilised in PanNEN patients that would be poor candidates for surgery, or where extensive resection is not desired [188].

In line with the specific considerations for MEN1-associated PanNEN, PanNEN arising in the context of VHL disease are also subject to focussed strategies. In a multinational registry of over 2,000 patients, it was identified via multivariate prediction modelling that VHL-PanNEN should be considered for operated if their size approaches 2.8 cm in diameter [189]. A genotype-guided approach integrating genetic sequencing and tumour diameter data have 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 [190].

Surgical Management of NELMs

Surgery is an integral component of multimodal strategies for NEN: 67–91% of SBNEN and 28.3–77% of PanNEN treated at specialist centres display metastasis to the liver [15], and surgery is associated with the most favourable outcomes [3, 191] but also constitutes an important palliative option [192]. 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 [193]. Radical resection of disease with curative intent, that is, partial hepatectomy, is associated with median 5- and 10-year OSs 70.5% (range 31–100%) and 42% (range 0–100%), respectively [194], 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 NEC improves OS (median OS 35.9 vs. 8.4 months without) [195]. Advanced surgical procedures such as 2-step resections may be considered [196]. Cyto-reductive 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 [192, 197]. Regardless of the resection margin attained, NELM almost invariably recur – median 5- and

10-year disease-free survival after surgery with curative intent is only 29 and 1%, respectively [194]. 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 [127, 198].

Patients with traditionally non-resectable liver metastases due to small-for-size liver remnant may be considered for 2-stage hepatectomy with portal vein ligation/separation or associated liver partitioning and portal vein ligation for staged hepatectomy.

Patients with unresectable disease may be considered for orthotopic liver transplantation, and a recent systematic review has detailed median 5-year OS of 63%, comparable to hepatocellular carcinoma [199]. 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 [200]. 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 NELMs [201], 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, that is, 10-year overall and disease-free survivals of 88.8 and 86.9%, respectively [201]. 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 [177]. 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 introduce bias and may optimise OS regardless of the true treatment effect.

Multivisceral transplantation has been used in a very small number of cases [202, 203]. Novel concepts include neoadjuvant PRRT [179, 204, 205], or adjuvant SSA therapy post-transplant to reduce the risk of recurrence.

Non-Surgical Therapeutic Strategies for Liver Metastases

Alternatives in the armamentarium for NELMs include locally ablative techniques (i.e., radiofrequency, microwave, laser or “cryo” ablation) and percutaneous interventional procedures (i.e., transarterial embolisation, transarterial chemoembolisation [TACE] and selective internal radiotherapy [SIRT] with yttrium-90 particles). Some studies have also detailed selective hepatic artery infusion of peptide receptor radionuclide therapeutics [206].

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 OS rates of 37–57%, with the best results obtained in liver metastases smaller than 5 cm in size and ablation margins >1 cm [207, 208].

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 OS from first procedure is 34.9 months [209]. The average objective response rate for SIRT is 51% (95% CI 47–54%), the average disease control rate is 88% (95% CI 85–90%) [210] and the response rates may correlate with survival [211]. One-, 2- and 3-year survival post-SIRT is 72.5, 57 and 45%, respectively [212]. 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, 213].

Treatment with transarterial embolisation, TACE and SIRT may be associated with the post-embolisation syn-

drome, 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 [209].

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 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 [214]. Long-acting SSA formulations have been developed, such as octreotide LAR [215]. 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 [216]. Data on symptomatic responses (diarrhoea and flushing) to octreotide LAR and long-acting Lanreotide have been reported to be 74.2 and 67%, respectively [217]. Side effects of SSAs 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 [216]. A review of trials conducted between 1987 and 2011 [218] and randomised controlled trials revealed that octreotide and Lanreotide can contribute to achieving stable disease and tumour reduction and increase median time to progression [10, 219]. Whilst the anti-proliferative effect has manifested as prolonged PFS, their effect on OS 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 and 83.7 months (HR 0.83, 95% CI 0.47–1.46, $p = 0.51$). Pasireotide LAR binds to 4 out of 5 SSTRs and demonstrated

Fig. 6. Response to peptide receptor radionuclide radiotherapy. Response to PRRT with ^{177}Lu -DOTATATE in a patient affected by a functioning SB neuroendocrine tumor with hepatic and nodal metastases, before (^{68}Ga -DOTATATE PET/CT: **a** MIP image; **b** fused axial image; **c** axial non-contrast CT) and after (^{68}Ga -DOTATATE: **d** 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).

symptom control (reduced diarrhoea and flushing) in patients with SBNETs in a phase II multicentre study [220]. Additionally, pasireotide LAR and octreotide had a similar effect on symptom control patients with advanced GEP-NETs whose disease-related symptoms were uncontrolled by first generation SSAs [221]. However, further development of pasireotide LAR in GEP NEN is currently on hold. Tryptophan hydroxylase, 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 tryptophan hydroxylase-inhibitor that can reduce bowel movement frequency in patients with the carcinoid syndrome [222].

Interferon Therapy

Interferon alpha is considered to be a second-line therapy in neuroendocrine tumours that are functionally ac-

tive with low proliferation capacity, such as G1/G2 SBNEN and well-differentiated PanNEN [223]. It may be suitable to use interferon alpha as an add-on therapy to SSAs 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 [224].

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, thrombocytopenia and leukocytopenia may occur in 25%, 10–20% and 40–60% of patients, respectively [225].

Fig. 7. Response to multimodal treatment. Serial ^{68}Ga -SSTR PET/CT MIP images of a 64-year-old woman with well-differentiated, functional pancreatic NEN 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 3 liver lesions. ^{68}Ga -DOTATATE PET/CT

demonstrates significant somatostatin receptor expression in the hepatic metastases before start of PRRT (**a**). The patient was treated with 4 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 (**e**).

Peptide Receptor Radionuclide Therapy

Patients with G1/G2 disease with non-resectable metastases may be suitable for PRRT; this utilises radio-labeled octreotide derivatives, such as ^{90}Y -octreotide (^{90}Y -DOTA-Tyr³-octreotide) and ^{177}Lu -DOTATATE or ^{177}Lu -DOTATOC (^{177}Lu -DOTA-Tyr³, Thr⁸-octreotide) for NEN treatment [226]. 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 (Fig. 6, 7) occur in 28–39% [227, 228], symptomatic improvements have been noted and a positive impact on survival parameters is documented [152, 228, 229]. 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 vs. 8.4 months), resulting in a 79% reduction of the risk of progression and a significant symptomatic improvement (e.g., fatigue, diarrhoea, pain) [9, 230]. ^{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%) [231]. Subacute effects include mild to moderate fatigue, mild alopecia and mild hematologic toxicity (WHO grades 1 or 2) transiently in 85–90% of patients [232]. 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 [231]. The spectrum of permanent myelotoxicity ranges from reduction of bone marrow reserve to secondary myeloproliferative diseases (myelodysplastic syndrome and leukaemia) but these are rare (approximately 2%). They do not occur more frequently than with other myelotoxic treatments [232–234].

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%) [235]. As an alternative, measurements of the expression of specific NEN transcripts in blood integrated with the tumour grade provide a PRRT-positive predictive quotient, which stratifies PRRT “responders” from “non-responders” and may become an additional important option. This quotient

exhibited a 95% accuracy in 3 independent cohorts demonstrating patients can be effectively identified prior to PRRT [113].

Chemotherapy and Targeted Agents

Prior to the realisation of biologic or molecular-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 utilised, whilst the overall impact on survival was rather low [236]. Thereafter, several typically retrospective series have demonstrated a role of systemic chemotherapy in G3 NEN (either poorly differentiated NECs or well-differentiated tumours), and in PanNEN, whilst its role in small intestinal NEN remains doubtful [237]. 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 [238]. Recently, oral 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 [239]. 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 [240]. 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 [15]. 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 randomised phase III trials, which included patients with advanced and progressive PanNEN (11 vs.

4.6 months of placebo) and non-functional gastrointestinal NEN (11 vs. 3.9 months of placebo) [12]. Similar results were noted with oral sunitinib, a TKI, in a randomised phase III trial with progressive PanNEN, where the median PFS was 11.4 vs. 5.5 months with placebo [241]. Although the objective response rates have not been impressive ($\leq 5\%$) with these agents, there is a trend towards prolonging OS (sunitinib) [242]. 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 as a second-line treatment in progressive, non-functioning, G1 NEN [15]. 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 [243].

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. [244]. 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 (HR and 95% CI, HR 0.35 [0.25–0.51]), interferon plus SSA (HR 0.31 [0.13–0.71]) and everolimus plus bevacizumab plus SSA (HR 0.44 [0.26–0.75]). In gastrointestinal NEN, effective combinations included: everolimus plus SSA (HR 0.31 [0.11–0.90]), PRRT plus SSA (HR 0.08 [0.03–0.26]) and bevacizumab plus SSA (HR 0.22 [0.11–0.90]). 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 well-being 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 [245], 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 [246] may be more sensitive to aspects of treatments such as toxicity, symptoms and tumour progression. The Norfolk QOL-NET questionnaire represents an alternative to the EORTC QLQ-C30 GINET21 with certain added advantages [247] 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 [245].

A systematic review showed that symptoms and quality of life issues in PanNEN differ in the various subtypes [248]; this emphasises the need to develop subtype-specific HRQoL measures for PanNEN.

Quality of life impacts with specific treatments that 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 [249]. The HRQoL of patients with progressive mid-gut NEN treated with Lutetium-177-DOTATATE PRRT or high-dose Octreotide LAR (control arm) has also been evaluated in the phase III NETTER-1 trial [230]. 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 vs. 6.1 months), physical functioning (25.2 vs. 11.5 months), as well as fatigue, pain, diarrhoea and disease-related worries and body image. Clearly, the significant impact of PRRT on PFS 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 NENs: 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 regard 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 PFS with medical therapies in advanced NEN; this is certainly a function of inadequate follow-up time to as yet rigorously evaluate effects on OS. Preliminary data suggested a favourable OS 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 2–3 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 2 histological/radiological parameters. Accordingly, results from any NEN randomised controlled trial 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 NET'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.

Define the Mechanistic Basis of Tumour Biology

The use of systems biology and algorithm-based analysis is 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.

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 prioritised 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.

Assessment of the Role of the Immune System in Tumour 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.

The Development of Imaging Modalities and Strategies That Better Define Tumour 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.

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 is effective strategies in predicting efficacy when expensive and potentially toxic isotopic therapy is delivered.

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.

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.

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 PFS 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.

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 2 cell systems. For example, gut microbiota is considered a virtual endocrine organ that has metabolic implications. It produces and regulates multiple compounds, such as butyrate or propionate, that directly regulate the host digestive system [250]. 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 [251]) and treatment responses, for example, to anti-PD-1 therapies (largely

through immune regulation) [252]. 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

NENs of the SB and pancreas not only 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, utilise 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 utilising specialised treatment and research networks that integrate objective strategies to predict or assess treatment efficacy. In this respect, 3 key areas need to be developed and applied: first, the development of increasingly informative functional imaging using artificial intelligence and metabolic tracers; second, the integration with imaging of real-time multi-analyte genomic analysis of individual tumours (liquid biopsy); and third, 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.

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