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Treatment challenges in and outside a specialist network setting: Pancreatic neuroendocrine tumours

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ABSTRACT

Pancreatic Neuroendocrine Neoplasms comprise a group of rare tumours with special biology, an often indolent behaviour and particular diagnostic and therapeutic requirements. The specialized biochemical tests and radiological investigations, the complexity of surgical options and the variety of medical treatments that require individual tailoring, mandate a multidisciplinary approach that can be optimally achieved through an organized network. The present study describes currents concepts in the management of these tumours as well as an insight into the challenges of delivering the pathway in and outside a Network.

Introduction

With a European annual incidence of slightly less than 1:100 000 and comprising 8% of pancreatic tumours [1], pancreatic neuroendocrine neoplasms (PanNENs) are considered a very rare entity. Despite their rarity though, they have allured remarkable scientific attention and research resources. This is of course because rare medical conditions require exquisite efforts from various biomedical specialties, often beyond geographical limitations, with increasing requirements in terms of time, funding and dedication. But PanNENs also owe part of the focus they have earned to the significantly long survival that can be achieved, particularly compared to other tumours of the foregut, especially of the pancreas. In a clinical setting, patients with non-metastatic disease and completely resected primary tumours can have a survival of almost up to 100% and even in cases of liver metastases, a long-term survival has been reported [2]. The rarity of these tumours and their different biological behaviour, which ranges from indolent to very aggressive, pose inevitable challenges in the diagnosis and in the treatment of PanNENs. In this article an overview of these pathways is presented, highlighting the difficulties encountered within and outside a Network. A description is also provided of the outcome of European patients with a new diagnosis of PanNENs, during the period 2000–2007, with data deriving from population-based cancer registries contributed to the RARECARENet project [3].

The RARECARENet survival data

The European burden of rare cancers was estimated by the RARECARENet projects [3]. Among the 198 rare tumours defined by the project, four GEP NET entities were included as clinically distinct entities. PanNENs were 15% of all GEPNET [3]. Table 1 shows survival in PanNENs by year since diagnosis, and 5-year relative survival by sex, age and morphology subgroup. An analysis was performed of 4108 cases diagnosed during 2000–07 in 94 European countries that contributed data to the RARECARENet project [3]. Survival was 66, 49 and 41% at 1, 3 and 5 years after diagnosis respectively. Outcome was significantly better in women than men (50% versus 37%) and reduced markedly with the increasing age. Five-year survival rate was 66% in <25 aged patients and reduced to 31% in patients older than 65 years. Well differentiated, functioning endocrine carcinoma of pancreas showed the best outcome, 60%. The non-functioning tumours and the poorly differentiated ones showed intermediate outcome: 48% and 40%,

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Table 1
Survival in European patients with PanNEN tumours by sex, age and type of neuroendocrine tumour, diagnosed 2000–07 [3].

		Number of cases	Relative survival[a]	95% CI
Overall	1-year	4108	67.4%	65.9%–68.8%
	3-year	4108	51.0%	49.3%–52.7%
	5-year	4108	42.9%	41.0%–44.8%
Sex	Male	2156	36.7%	34.2%–39.2%
	Female	1952	49.6%	46.9%–52.3%
Age	<24	39	66.3%	48.0%–79.4%
	25–64	2449	49.0%	46.7%–51.3%
	65+	1620	31.0%	27.9%–34.0%
PanNEN type	Well differentiated/non-functional	858	48.2%	44.0%–52.3%
	Well differentiated/functional	331	60.1%	53.5%–66.2%
	Poorly differentiated	2780	39.9%	37.7%–42.2%
	Mixed	139	27.1%	18.3%–36.7%

[a] For sex, age and type of neuroendocrine tumour subtypes, 5-year relative survival is presented.

respectively. The mixed endocrine-exocrine carcinoma had poor 5-year survival (27%) (see Table 2).

Diagnostic and therapeutic challenges of NEN

Classifications of PanNENs is complex. The WHO classification divides these tumours into functional (28% of all PanNENs – Table 1) and non-functional, which comprise about 72% of all PanNENs. PanNENs can also be classified according to the European Neuroendocrine Tumour Society (ENETS) (Table 3). Well differentiated tumours (also called Low Grade or G1) are characterized by cellular monomorphism, good differentiation, a low mitotic rate, a Ki67 < 3% and absence of necrosis. Tumours of intermediate features are called G2 or Intermediate Grade with a Ki-67 between 3% and 20%, while high Grade/G3 tumours are characterized by cells that vary significantly in size, shape and nuclear density, with a high mitotic rate, poor differentiation and a Ki67 > 20% [4]. The latter comprise now a category different from neuroendocrine carcinomas, which are by definition poorly differentiated, but fulfil other criteria of malignant tumours as well, as recently proposed by the ENETS [5].

Patients with PanNENs will initially present either with symptoms related to a functional tumour or with the space-occupying effects caused by non-functioning tumours. Many are found incidentally whilst imaging is performed for non-related symptoms; a proportion of these patients might present with symptoms related to secondary deposits in other organs. PanNENs can also develop in up to 80% of patients diagnosed with Multiple Endocrine Neoplasia (MEN) and specifically MEN1 syndrome [6]. Other familial syndromes that are associated with the development of PanNENs are von HippeI-Lindau, Tuberosclerosis and neurofibromatosis, with the latter being associated with worse prognosis [7]. Serum Chromogranin A (CgA) is the most commonly used biomarker and has been found to correlate with prognosis [8], but its diagnostic value was questioned during the latest revision of relevant guidelines issued by the National Comprehensive Cancer Network (NCCN) [9]. The biochemical tests which are needed to rule out a functional tumour include the hormone that the tumour is expected to produce, such as insulin, pro-insulin, C-peptide and anti-insulin antibodies for insulinomas, or glucagon, somatostatin, VIP and gastrin for the corresponding tumours. Recent advances include NETest, which assesses the circulating tumour transcripts and is shown to be associated with response to treatment with Somatostatin

Table 2
Most common functional PanNENs, with main symptoms, anatomical location, malignancy likelihood and incidence. (Adapted with permission from Jensen et al., 2012[38]).

Tumour	Manifestation	Location	Malignancy	Incidence per million
Gastrinoma (Zollinger-Ellison syndrome)	Diarrhoea, peptic ulcers	60% pancreas, 30% duodenum	60–90%	0.5–3
Insulinoma	Hypoglycaemia, seizures, unconsciousness	99–100% pancreas	5–15%	1–3
Glucagonoma	Migratory necrolytic rash, anaemia, thromboembolic events	99–100% pancreas	60–80%	0.01–0.1
VIPoma	Severe diarrhoea, electrolyte disorders	90% pancreas	80%	0.05–0.2
Somatostatinoma	Diabetes, steatorrhoea	56% pancreas, 44% duodenum/jejunum	50–60%	<0.01
GRFoma	Acromegaly	30% pancreas, 54% lung, 7% jejunum	30%	<0.01
ACTHoma	ACTH	4–16% pancreas	>90%	<0.01

Table 3
ENET Classification of PanNENs according to histopathological characteristics. NET=Neuroendocrine tumour, NEC = neuroendocrine carcinoma. (Reproduced with permission from Falconi et al., 2012 [3]).

Biological behaviour	WHO Classification (2000)	WHO Classification (2010)	Metastases	Invasion	Tumour size, cm	Angio-invasion	Ki67, %
Benign	Well-differentiated endocrine tumour	NET G1 or NET G2	–	–	≤2	–	Usually around 2
Benign or low-grade malignant	Well-differentiated endocrine tumour	NET G1 or NET G2	–	–	>2	±	Usually around 2
Low-grade malignant	Well-differentiated endocrine carcinoma	NET G1 or G2	+	+	Any	+	Usually >2
High-grade malignant	Poorly-differentiated endocrine carcinoma	NEC or G3	+	+	any	+	>20

analogues [10], and measurement of circulating DNA and/or tumour cells [11] but these still need to be validated.

Several imaging modalities play a significant role in the diagnosis and staging process. Contrast enhanced Computed Tomography (CT) scans with arterial and venous phases comprise the cornerstone of investigation of pancreatic tumours, being the basis of current staging. However, since PanNENs can be very small and isodense, the sensitivity of this modality can be as low as 30% for primary tumours [12,13]. Magnetic Resonance Imaging (MRI), with specific sequences that enhance the accuracy for small lesions in the pancreas, have led to an increasing enthusiasm in favour of this modality. A recent study demonstrated that MRI can discriminate between Low/Intermediate tumours and High Grade tumours, with a sensitivity of 72.3% and a specificity of 91.6% [14]. Endoscopic Ultrasonography (EUS) is regarded as a particularly accurate modality for the assessment of the primary tumour as well to assess local lymph node involvement, allowing to locate tumours and obtain specimen for cytological or histological examination, with an adequacy rate of over 80% [15]. The diagnostic value of the method can be increased when ultrasonographic contrast is administered, as it demonstrated the different vascularization pattern between the tumour and the normal pancreatic parenchyma, while it has been suggested that it can also differentiate between PanNENs and pancreatic adenocarcinoma [16].

A definite challenge is the availability of the best and most accurate functional images from Nuclear Medicine departments. Somatostatin Receptor Scintigraphy offers a powerful differential tool for the discrimination of PanNENs and other pancreatic neoplasms.

Table 4
Sensitivities of Imaging modalities for PanNENs.

Modality	Sensitivity
Ultrasonography	20–80%
Computed tomography	64–94%
Magnetic resonance imaging	74–100%
Endoscopic ultrasonography	80–94%
PETs	50–80%

Diagnostic accuracy has been improving over the last years along with the advances in the used isotopes, with the most recent 68GaDOTA-TATE, 68Ga-DOTA°-1Na13, and 68Ga-DOTA-NOC demonstrating significantly higher spatial resolution and enhanced tumour-to-background contrast [17]. It is evident from the above, that each modality has limitations in terms of sensitivity and specificity (Table 4), thus optimal diagnostic approach consists of combinations of the aforementioned modalities (Fig. 1), with a view to identify the primary tumour, target it for biopsy, and complete tumour staging (Table 5).

Surgery remains the cornerstone of treatment of PanNENs, whether it aims to control symptoms, resect the radiologically detectable disease, or debulk it (usually aiming to remove >90% of visible disease) with a view to improve response to further treatment. The aim of the pancreatic endocrine surgeon is to completely resect the primary tumour with preservation of the maximum amount of parenchyma, and thus to minimize the risk for postoperative exocrine or endocrine insufficiency.

A technical challenge is the development of pancreatic fistulas which was reported in almost 23% of patients undergoing pancreatic resection for PanNENs as opposed to 17% in patients who had similar operations for other pancreatic malignancies [18]. This higher rate can be attributed to the relative soft and friable pancreas of patients with PanNENs, but also to the fact that enucleations are significantly more frequently performed in these patients than in patients with other pancreatic pathologies. A recent review has summarized the favourable prognostic criteria that include age of less than 55 years, liver involvement of less than 50%, resection of the primary tumour prior to transplantation, stable disease for at least 6 months and good differentiation (Ki67% < 10%), with the latter being associated with a 5-year survival of 90% [19]. Many of these surgical options would not be appropriate for other malignancies and can be controversial even for the most indolent PanNENs, suggesting that it is often the knowledge of the biological behaviour and natural history of these tumours which dictate the best therapeutic approach. This require a dedicated panel of specialists with a specific interest in PanNENs rarely available outside dedicated centres, which is equally crucial in the medical and radiological management of PanNENs.

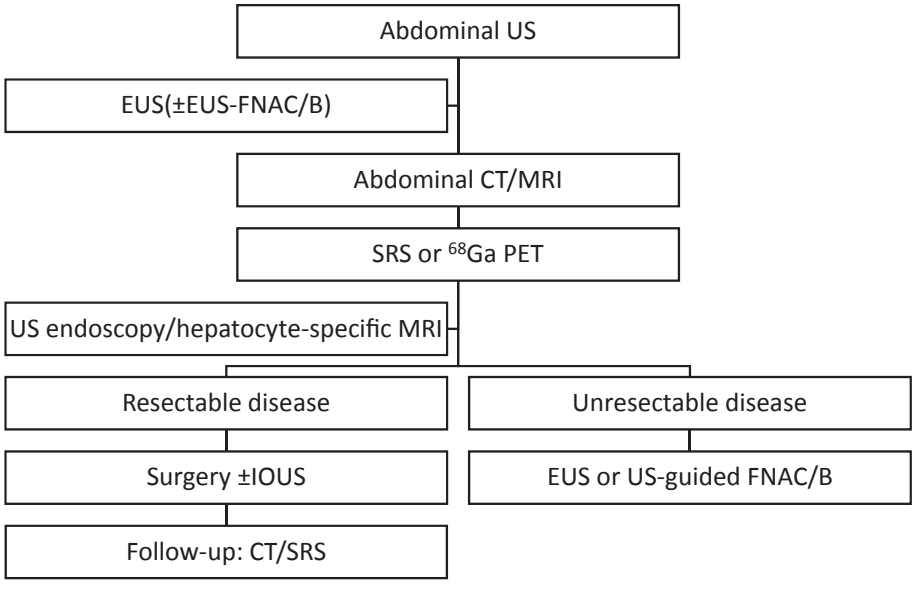

Fig. 1. Diagnostic algorithm for the radiological investigation of PanNENs. US=Ultrasonography, EUS = Endoscopic Ultrasonography, FNAC/B=Fine needle aspiration cytology/biopsy, CT=Computed tomography, MRI = Magnetic Resonance Imaging, SRS=Somatostatin Receptors Scintigraphy, IOUS=Intra-operative ultrasonography. (Reproduced with permission from Falconi et al., 2012[3]).

Table 5
The AJCC/UICC and ENETS staging of Pancreatic Neuroendocrine Neoplasms.

Stage 0	Tis Carcinoma in situ			
Stage IA	T1 Tumour limited to the pancreas, ≤2 cm			
Stage IB	T2			
	AJCC: Tumour limited to the pancreas, >2 cm	ENETS: Tumour limited to the pancreas, 2–4 cm	N0 No involved regional lymph nodes	
Stage IIA	T3			M0 No distant metastasis
	AJCC: Tumour extends beyond the pancreas, without vascular involvement	ENETS: Tumour confined to pancreas, >4 cm, invasion of duodenum or bile duct		
Stage IIB	Any T		N1 Regional lymph node metastasis	
Stage III	T4		Any N	
	AJCC: Vascular involvement	ENETS: Invasion of adjacent organs or vessels		
Stage IV	Any T			M1 distant metastasis

Medical treatment aims to manage symptoms, to downsize/downstage the disease with a view to surgical resection, to manage disease progression or to palliate. Syndrome-related symptoms are managed in the acute setting with blood glucose control in case of insulinomas and glucagonomas, volume and electrolyte loses in VIPomas, gastric pH control in gastrinomas and in all cases with somatostatin analogues that block the somatostatin receptors and reduce secretion of active peptides. Somatostatin analogues also exert an antiproliferative role in PanNETs, improving overall survival by delaying tumour growth [20]. Streptozocin and fluorouracil have been the backbone of chemotherapy regiments for many years, with a response rate of over 60% and increase of survival by more than 1 year [21,22]. Chemotherapeutic regimens vary, according to tumour features, with cisplatin and etoposide being used for higher grade lesions [23] and temozolomide with capecitabine for well differentiated tumours [24]. Liposomal and conventional doxorubicin have also been used whereas addition of the anti-angiogenesis monoclonal antibody Bevacizumab has been associated with a better progression free survival [25]. Recent improvements include the use of Everolimus, an mTOR inhibitor that demonstrated increase of survival 6.3 months, though not statistically significant [26], while the addition of pasireotide does not demonstrate any additional benefit [27]. Another agent that has recently demonstrated significant results is the tyrosine kinase inhibitor Sunitinib malate, which doubled the progression free survival, and was also associated with statistically significantly improved overall survival [28].

Several other modalities have been used to manage neuroendocrine tumours. Radionuclide therapy is being delivered to somatostatin receptors in an attempt for a focused irradiation of PanNENs, either in the form of Peptide Receptor Radionuclide Therapy (PRRT) or Selective Internal Radiation Therapy (SIRT), mainly aiming to stabilize the disease, with a major response rate of about 60% and inhibition of progression in 85% [29]. Liver metastases not amenable to surgical treatment have been managed with hepatic artery embolization aiming for mechanical obstruction of perfusion or also local delivery of high concentration of cytotoxic agents such as streptozocin and fluorouracil but also mitomycin C and cisplatin. This modality yields a highly successful control of symptoms of up to 100% and a partial response that can be up to 80% [2]. Finally, radiofrequency and microwave ablation have also been employed with symptom control rate of >90% and mean overall survival of 73 months [30], either in combination with surgical resection, or as an alternative in patients that were not deemed fit for surgery and tumours not amenable to surgical resection.

Medical treatment is frequently available in secondary and tertiary institutes but complex interventional radiology is frequently carried out in dedicated centres, especially for procedures requiring the input of nuclear medicine specialists such as for SIRT or PRRT.

Management within a network

Outcomes following management of any medical condition depend heavily on the expertise of healthcare delivery team. This can be quite challenging when it comes to diseases with relatively low occurrence, such as PanNENs. In 2013, about 1500 new diagnoses of PanNENs were estimated in Europe (EU28) [3]. The solution to this problem is usually centralization of patient's care and resources, so that NET Units can maintain a workload that guarantees adequate experience and enhanced outcomes. A systematic review on upper gastrointestinal surgery, demonstrated a clear benefit in terms of outcomes for high volume centres and surgeons [31], whilst another study focusing particularly on pancreaticoduodenectomy demonstrated improved overall resection rates and higher R0 resection rates when centralization was implemented [32]. Centralization has not been studied so far specifically in PanNENs, however, the expertise required is similar to the one required to manage other hepato-pancreato-biliary malignancies. Although it is extremely difficult to define a minimum number of patients per centre, it seems reasonable to support that most countries would need 2–10 Units to maintain expertise [33].

Patients with PanNENs can present with a remarkable variety of symptoms, thus the first clinician that they see might be a general practitioner, a family doctor, an Accident & Emergency doctor, a gastroenterologist, a general surgeon, an endocrinologist or even a radiologist, if in lines with the local healthcare service they can individually arrange a radiological investigation [34]. Quite frequently, the first working diagnosis is not this of an endocrine tumour, thus the next steps might be advised by any of the above specialties, as well as oncologists and hepato-pancreato-biliary surgeons. It is of course impossible for a PanNET Unit to exist wherever these specialists practice, but these Units need to maintain excellent communication and bidirectional feedback with local primary and secondary healthcare structures, so that an adequate level of awareness is maintained and all physicians are familiar with the first steps of relevant pathways.

Specific imaging investigation of PanNENs includes sophisticated modalities that require a certain level of radiological expertise. The histopathological features of these tumours are very specific and it is essential that involved pathologists are explicitly familiar with this entity. Surgical treatment of PanNENs usually involves major liver and pancreatic surgery and in some cases liver transplantation, which mandates management in a Hepato-Pancreato-Biliary Unit. Endocrine management of relevant symptoms can be very challenging and should thus be conducted by

Endocrinologists with thorough knowledge of the physiology of PanNENs. Systemic treatment is evolving rapidly, differs significantly from the systemic treatment of other neoplasms and thus requires an Oncology team with particular interest in the management of these tumours. It becomes clear from the above that a GI NENs unit needs to comprise of key medical specialties with a special interest in these lesions. However, since pancreatic surgery is very demanding with a significant higher mortality and morbidity rate in low-volume centres in comparison to high-volume centres, specific expertise is required.

Following treatment, patients with PanNENs will return to their local community, and in many cases it might be practically impossible for the follow-up to be carried in the PanNEN unit that delivers treatment. It is then necessary for PanNEN units to have an outreach team, consisted of Clinical Nurse Specialists or local Primary Care practitioners, than can follow patients up closely, according to relevant guidelines, and provide feedback to relevant Units. It becomes thus evident that the optimal treatment of patients with PanNENs requires a robust network of medical practitioners, connecting local primary and secondary services, with few large PanNEN Units that consult on patients' diagnostic evaluation and treatment, and audit current practice and outcomes. The above two-way communication can be facilitated through regional and superregional video-linked multidisciplinary meetings on a frequent basis. Moreover, PanNENs Units need to communicate with each other, to increase the collective experience, to organize trials in order to delineate all grey areas, and eventually to revise relevant guidelines.

This admirable effort does not come without costs of course. Potentially the greatest challenge is funding. Centralization of patients in few Units requires that these Units are able to bear the costs of very sophisticated and as such very expensive diagnostic and therapeutic techniques. From an administrative point of view, this arrangement requires a large number of staff providing office support to both physicians and patients, facilitating communication, data collection and maintenance, organization of meetings and educational events. In a network that involves many practitioners in different levels of healthcare and often working remotely from each other, accurate communication and documentation can be very challenging in order to avoid confusion and teleconference infrastructures can be imperative.

Within the UK, PanNENs units are closely attached to hepato-pancreato-biliary units, but cover is provided beyond the existing regional referral system, in order to tackle all the aforementioned difficulties. At European level, the European Neuroendocrine Tumour Society (ENETS), recognized the need for an international network of Neuroendocrine centres in 2007, and one year later an accreditation process began which by now has accredited 37 Centres of Excellence across Europe.

According to the Society, this effort has yielded improved cooperation between centres and improved quality of clinical trials. The involved centres have reported improved patient documentation, multidisciplinary team discussions, follow-up and quality control, while the collaboration of Centres of Excellence has also yielded valuable educational activities. It is without doubt difficult to quantify, measure and assess the improvement in patient-related outcomes, and the Society identifies this question as a key point at the moment, however the current experience of Centres of Excellence is very encouraging. The ENETS should consider the outcome inequalities in Europe [35], in term of outcome and consequently organization, the latter depends of the size of the population therefore of the expertise of clinicians and from the cancer or rare disease national programs [35]. Survival for patients with NET from population studies largely varied across country. For the group of GEP (including digestive system and pancreas) well differentiated not functioning endocrine carcinoma, 5-year survival ranged from more that 70% in the majority of the Nordic countries and Centre of Europe (between 70 and 83%) to 60% or less in Lithuania, Latvia and Bulgaria [3]. The reason for Bulgaria was even the lack of pathological facilities for accurately diagnosing rare neuroendocrine tumours [3]. One major issue remains the quality of diagnosis, mainly due to inadequate facilities and abilities to diagnose many complex rare cancers. The definition of national and international pathways for second opinions from expert pathologists was also deemed important. Having this in mind, the European Reference Networks should offer a good opportunity to improve pathologists' training through dedicated training schemes and fellowships across Europe. Cancer registration remains vital for monitoring progress in rare cancer diagnosis and treatment for these patients.

Conclusion

Pancreatic neuroendocrine neoplasms are an entity with particular epidemiologic and histological features, that require complex diagnostic and treatment strategies, optimally delivered by multidisciplinary teams with special interest and expertise. The challenges that emerge from this statement are best managed within a network of specialized Units, such as the Centres of Excellence currently accredited and supervised by the European Neuroendocrine Tumour Society, with an ultimate scope to continuously improve delivered care to patients with PanNENs.

Conflict of interest

The authors of the present study have no conflict of interest to declare.

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