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Review

Treatment challenges in and outside a network setting: Gastrointestinal neuroendocrine tumours

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are relatively rare neoplasms arising from the enterochromaffin cells of the gastrointestinal tract. They comprise a heterogeneous group of tumours with a diverse natural history, variable biological behaviour and different clinical outcomes. Their management is often complex and may include a combination of surgery, systemic treatments and locoregional approaches. A multidisciplinary team approach is therefore essential for the optimal care of patients with GEP NETs. In this article, the authors review the role and structure of multidisciplinary care models, the importance of regional centres of expertise and institutional networks for the management of these rare neoplasms, as well as the multidisciplinary therapeutic challenges that NET clinicians are often faced with.

Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are rare neoplasms with an annual incidence in the US of 3.56 per 100,000 according to the latest analysis of the Surveillance, Epidemiology and End Results (SEER) database (2000-2012 diagnosed) [1]. In Europe, according to the RARECARE net project [2], incidence of malignant GEP NET for the period 2000-2007, was lower: 1.7 per 100,000/year with an estimated number of about 26,000 new diagnoses and a complete prevalence of 72,200 cases. GEP NETs incidence is rising in the US, while, in Europe, rates remained constant between 1995-2007. The increase in the US may be partly due to a different definition of malignancy over the years, advances in diagnostic technology, the increased use of endoscopic procedures, increased awareness and varying rules of registration [3]. The same reasons can explain the incidence differences between the US and European populations. The management of GEP NETs is complex and has evolved significantly over recent time [4]. Patient care pathways have also changed substantially in recent decades with a transition from traditional paternalistic models of care to more patient-centric, integrated, multidisciplinary approaches [5]. The development of centres of expertise and institutional networks for the management of NETs has led to centralisation of care and improved patient access to specialised diagnostic facilities and treatments [6].

In this article we review the role of a multidisciplinary team approach and the therapeutic challenges in the management of GEP NETs in and outside a network setting.

Multidisciplinary care and role of network settings in the management of NETs

A. Multidisciplinary care in the oncology setting

Tumour boards and multidisciplinary care teams offer coordinated delivery of care by a broad range of healthcare professionals from various specialties and aim to streamline care and optimise patient outcomes [7]. Multidisciplinary care is highly patient-centric, because it facilitates the implementation of complex individualised treatment plans (Fig. 1a), as opposed to traditional care models, in which patients are referred in sequence from primary care to a specialist and from specialist to specialist (Fig. 1b) [5]. This multidisciplinary approach minimises delays in diagnosis and treatment, which are commonly encountered in a referral-based system, and improves patient satisfaction and quality of life [8]. In addition, it decreases fragmentation, facilitates continuity of care and promotes good clinical practice through adherence to national/international guidelines and appropriate alterations in personalised treatment plans [7]. There is a growing body of

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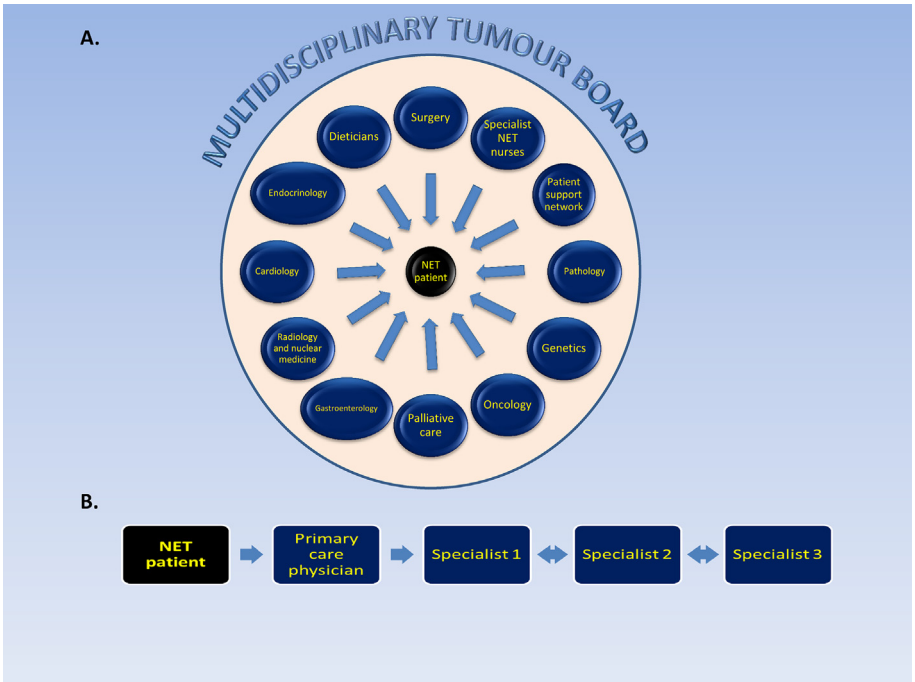

Fig. 1. Example illustrating the management of a patient with a neuroendocrine tumour (NET). A. Patient-centred flow of care, in which the patient is at the centre of the decision-making process. B. In contrast to figure 1A, the typical flow of care for a NET patient without integrated care involves multiple referrals, duplicate testing and delays.

evidence that the implementation of multidisciplinary clinics is associated with improved survival in many types of cancer [7,9]. A multidisciplinary model of care has also been shown to improve physician satisfaction and enhance graduate medical education, research and patient recruitment in clinical trials [10]. Therefore, multidisciplinary care teams or tumour boards are an accepted component of cancer care in many countries. In the United Kingdom, a National Cancer Plan was published in 2000 that emphasised the important role of multidisciplinary teams in the management of cancer patients and suggested that all patients with cancer should be formally reviewed by a specialist team [11]. Similarly, in the United States the Commission on Cancer and the American College of Surgeons both require multidisciplinary cancer conferences for the accreditation of health centres delivering multidisciplinary oncological care [10]. Although a multidisciplinary approach is the foundation for optimal cancer care delivery, it should be considered that the function and performance of multidisciplinary teams is often influenced by several external factors, such as institutional constraints, technical factors and linkage environments (Fig. 2) which may also have a substantial impact on care processes and patient outcomes [12].

Although the value of a multidisciplinary approach has been established in many types of malignancy, there is surprisingly a paucity of studies assessing the impact of multidisciplinary care on the management and outcomes of patients with NETs. There is also limited literature regarding the proposed structure, function and implementation of such care and the influence of network settings.

B. Rationale for the development of multidisciplinary reference centres (centres of expertise) for the management of gastrointestinal NETs

GEP NETs are rare neoplasms that present many clinical challenges due to their heterogeneity and wide range of morphological, functional and behavioural characteristics [13]. Because of their rarity and indolent natural history, many physicians may not have a high index of clinical suspicion which typically results in misdiagnosis and delayed diagnosis [14]. An effective diagnosis requires a multimodal approach that often entails assessment of clinical symptoms, biomarkers, histology, radiological and nuclear medicine imaging [6]. Following an accurate diagnosis and staging assessment, the choice of therapy should be highly individualised on the basis of current symptoms, tumour type and disease burden and other prognostic information. The general health and preferences of the patient as well as the potential impact of available treatments on quality of life should also be considered [14]. Given the paucity of adequately powered randomised controlled trials and the fact that many of these studies have enrolled heterogeneous patient populations with variable follow-up periods, making the right treatment choice or selecting the appropriate sequencing of different therapies represents a major clinical challenge and considerable clinical expertise is needed to make such decisions. A multidisciplinary setting can provide a platform for discussion and complex decision-making [15,16]. The need for specialised expertise together with the rarity of the disease, creates a compelling rationale for centralised multidisciplinary care in NETs. A retrospective analysis of gastrointestinal NETs diagnosed in a district general hospital in the United Kingdom serving a population of 160,000 demonstrated that only a total of 35 patients were diagnosed over a 10-year period [17]. Therefore, the establishment of regional centres of expertise, in which patients with NETs are seen and treated in higher volumes, is needed to acquire and maintain expertise in the management of this disease. In addition, these centres are important for the development of tumour tissue and clinical data banks, which are necessary to advance translational research in this field, and they can improve patient recruitment and participation in clinical trials. They can also allow in-depth training and provide experience for young investigators or clinicians interested in these disorders [14]. Therefore, the creation of regional multidisciplinary reference centres was considered an important priority for improving the management of GEP NETs in a National Cancer Institute summit meeting held in 2007 [14]. The idea of a

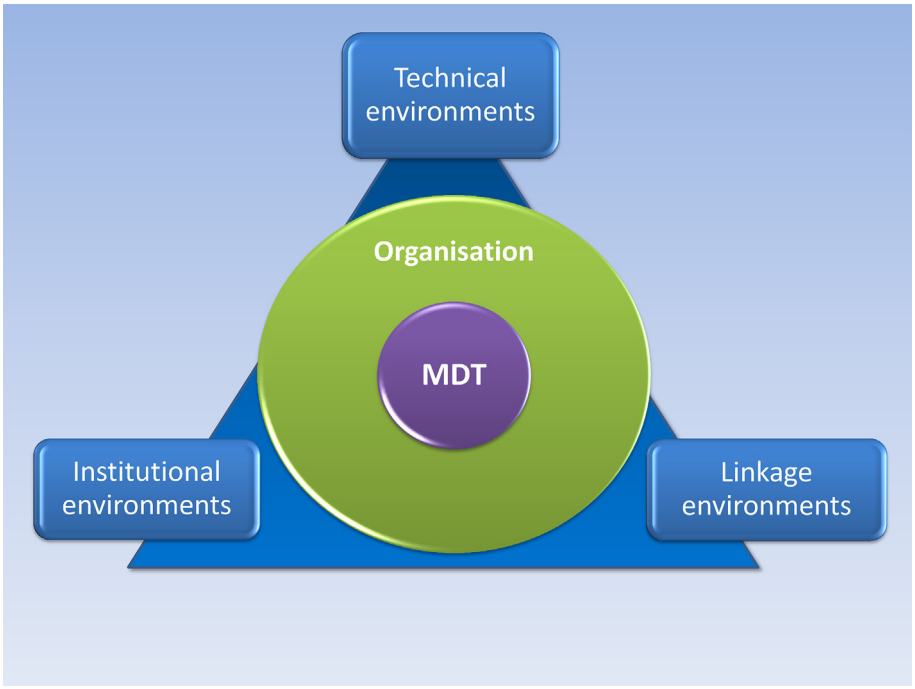

Fig. 2. The microsystem of provider and patient interfaces is influenced by the mesolevel of organisational structures and the macrolevel of network settings and other external factors. Thus, while a multidisciplinary team may operate in a hospital setting, its efficiency may be limited by organisational constraints or other factors, such as funding issues or limited access to state-of-the-art equipment (MDT: Multidisciplinary Team).

multidisciplinary team approach to NET patient care within an expert centre was formally introduced almost two decades ago [18]. Just prior to this in the mid-1990's the first specialist multidisciplinary NET interest group had formed including specialists across Europe and this was later to evolve officially into the European Neuroendocrine Tumour Society (ENETS) in 2004 producing the first guidelines and collaborative international research proposals. In Europe centralisation of GEPNET treatment, as studied in seven European countries (Belgium, Bulgaria, Finland, Ireland, Slovenia, the Netherlands, and Navarra for Spain), during the period 2000-2007, was low. For GEP NET, 75% of patients were centralised in 44 and 46 hospitals in the Netherlands and Belgium, respectively, between 13 and 21 hospitals in Finland, Bulgaria and Ireland, and 3 hospitals in Slovenia and Navarra [2]. This result will be useful for evaluating centralization in the European countries in the years following the ENETS initiatives.

To address the need for centralised care, ENETS undertook the initiative to establish criteria for NET Centre of Excellence (CoE) certification throughout Europe and thus far 37 CoE have been accredited since 2008 [19]. The benefits of this initiative have been reported by certified centres and are listed in Table 1 [19]. This network of ENETS CoE is important for international research collaborations and has led to the development of international guidelines and protocols that aim to streamline patient care. Another development in Europe is the establishment of European Reference Networks (ERNs) for the management of rare diseases. The directive 2011/24/EU of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare, provided new opportunities for cross-border collaboration and healthcare organisation with the development of networks of highly specialised teams across Europe. The focus of this cross-border co-operation is on information and knowledge exchange and only in rare circumstances would patients be required to receive treatment in a foreign healthcare system [20].

Therefore, in contrast to traditional referral-based models of care, the optimal management of NET patients in a modern multidisciplinary care model can be conceptualised as depicted in Fig. 3.

C. Impact of NET centres of expertise on survival outcomes and patient perspectives of a multidisciplinary team approach

According to a previous SEER database analysis by Yao et al. (2008), median overall survival in distant metastatic disease was 56 months in small intestinal NETs and 24 months in pancreatic NETs [21]. In specialised centres for the treatment of NETs, overall 5-year survival rates for patients with metastatic pancreatic and

Table 1
Benefits of Centre of Excellence certification[a].

Improved recognition
Increased number of referrals of NET patients
Improved MDT meetings with in-depth discussions, structured co-operation and consistent specialist participation
Improved patient documentation
Improved patient follow-up
Quality control/audits
Improved research and clinical trial co-ordination
Fruitful discussions with external peers during audit process
Development of international guidelines/protocols

[a] adapted from European Neuroendocrine Tumour Society, www.enets.org/about-enets-coe.html.

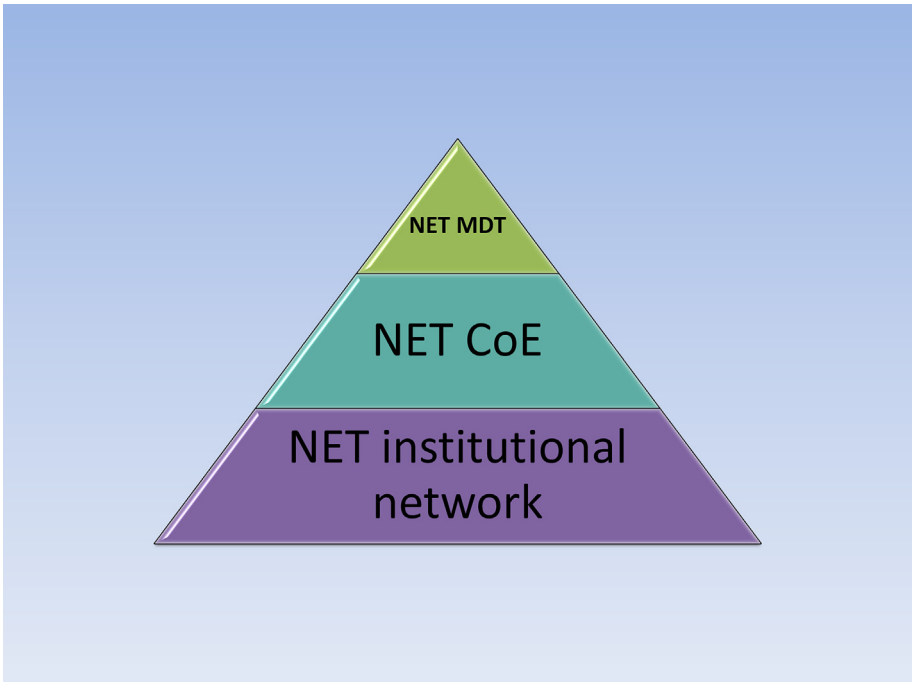

Fig. 3. A conceptual model of modern multidisciplinary care for NET patients (MDT: Multidisciplinary Team, CoE: Centre of Excellence).

small intestinal NETs were much higher than those reported in the SEER database according to institutional series published around the same time [22,23]. In such centres, 5-year survival rates of patients with metastatic GEP NETs were over 50% [24]. In large series of patients with metastatic midgut and pancreatic NETs managed in tertiary referral centres median overall survival periods as high as 100 and 70 months, respectively, have been reported [25–27]. The most recent analysis of the SEER database revealed that the overall survival of NETs has improved over time, especially for distant-stage gastrointestinal and pancreatic NETs [1]. This trend may reflect the impact of multimodal treatment as well as the management of these patients within the multidisciplinary environment of referral centres in more recent years. In Europe, according to the RARECARENet, a population-based project, 5-year relative survival was 72% and 61% for the well differentiated not functioning and the functioning GEP NET, respectively. Lower 5-year survival for poorly differentiated GEP NET (35%) and GEP - mixedendocrine-exocrine carcinoma (26%) patients, was assessed. The analysis was performed on slightly less than 27,000 European cases. As expected, prognosis was poorer, for these histological aggregations affecting pancreas: 5-year relative survival ranged between 60% (well differentiated functional) and 27% (mixed) [28].

A large audit assessing the impact of a systematic multidisciplinary approach on the management of patients with GEP NETs was conducted at St James's Hospital in Dublin, Ireland. Based on data collected over a 15-year period (1993–2008) the authors concluded that, following the establishment of a multidisciplinary meeting in their institution, the diagnostic (biochemical, imaging and pathological) assessment and therapeutic approach to GEP NET patients improved significantly and was more consistent with best international practice. In addition, a better referral pathway of patients from the community or peripheral hospitals to their tertiary referral centre was observed. Furthermore, peptide receptor radionuclide treatment (PRRT), which at the time of publication was not available in Ireland, became an option for patients attending this institution by referral to other nuclear medicine centres. These improvements in patient management as a result of centralised multidisciplinary care within a tertiary referral centre would conceivably translate to better patient outcomes [29].

Evidence of improved survival in patients with NETs treated at specialty centres was also provided by a retrospective study which described evolving trends in the management of patients with metastatic gastrointestinal NETs in the North West Adelaide Health Service, Australia over a 22-year period (1985–2007). Townsend et al. found that the median survival for patients managed by a specialty team was 112 months compared to 32 months for those receiving standard care. In addition, patients in the medical oncology unit benefited from more accurate diagnostic assessment (biochemical, radiological), better access to treatment options (somatostatin analogues, chemotherapy, targeted radionuclide therapy) and were more likely to enrol in clinical trials. An increase in the number of referrals to the medical oncology unit was observed over time, reflecting improvements in the referral pathway of NET patients [30].

A small number of studies have investigated patient perspectives of a multidisciplinary model of care [6,31]. Several issues related to the cancer journey experience of NET patients have been highlighted in these qualitative studies, such as difficulties obtaining a diagnosis, finding appropriate information about NETs, accessing NET-specific treatments or specialist care and finding specific support to manage physical and psychological aspects of their disease. As a result, patients often felt that there was lack of a clear pathway of care and appreciated the value of multidisciplinary NET specialist clinics and the important role of NET nurses in providing disease-specific support to patients and their families [31].

D. Structure and function of a NET multidisciplinary team

There is a general consensus in the literature that the NET multidisciplinary team should consist of a wide range of specialists given the complex nature of the disease that often requires multimodal therapeutic approaches (Fig. 1a). This usually includes specialists in gastroenterology/hepatology, hepatobiliary and GI

surgery, medical and surgical oncology, endocrinology, pathology, diagnostic and interventional radiology, nuclear medicine, cardiology and specialist nursing [16,18]. However, the literature is limited regarding the exact structure and proposed function of this team. Metz et al. suggested a team structure consisting of the co-ordinating physician (the senior physician ultimately responsible for a specific patient's care), a core and an extended team. The core team is more closely involved in the management of a given patient and its composition may change over time, as the disease progresses. The extended team mainly includes community health professionals, such as primary care physicians, mid-level providers (e.g. advanced nurse practitioners or local specialists) who are also involved in supporting NET patients in the community and play a role in implementing the individualised integrated management plan formulated by the core NET specialist team [5]. The multidisciplinary care team should hold regularly scheduled meetings for discussion of challenging cases, in which specialists in different disciplines can challenge each other's opinion and engage in fruitful and productive discussions to facilitate patient care and formulate a co-ordinated treatment plan [6]. At an institutional level the optimal and successful function of multidisciplinary teams requires effective administration, nursing support, adequate space and resources (e.g. videoconference facilities), co-ordination of the work of multiple colleagues and is often supplemented by interactions with community practitioners and patient support groups [5,6].

E. Patient support, specialist nurses and research

As for all rare cancer patients, NET patients need support and this can be less available than for common cancers. This highlights the importance of patients being able to access patient support and advocacy groups, such as the International Neuroendocrine Cancer Alliance (INCA), NET Patient Foundation and European Multiple Endocrine Neoplasia Alliance (AMENA).

The role of specialist nurses is also central to the management of NET patients [6]. Their role has evolved over the last ten years and such specialist NET nurses would only be viable in specialist centres with significant number of patients. They are not only important as an interface between doctor and patients, but also play a key role in the coordination of patient pathways and independent nurse clinics.

In addition, the role of the MDT is not only to ensure the best patient pathways for care but also to identify patients appropriate for relevant research and clinical trials [6].

Diagnostic and therapeutic challenges in the multidisciplinary management of gastrointestinal NETs in and outside a network setting

The multidisciplinary management of GEP NETs is complex due to a number of diagnostic and therapeutic difficulties. The pathologic classification of NETs, for example, often represents a significant challenge because of a range of nomenclature, grading and staging issues [32]. NETs comprise a large, heterogeneous family of tumours which are highly diverse in terms of origin, mechanism of development, functionality, histologic patterns and biologic behaviour. As a result, a variety of diagnostic terms and classification systems have arisen, which may often be a source of confusion [33–35]. The lack of a single, uniform system of nomenclature, grading and staging led a multidisciplinary team of experts to develop a minimum pathology data set through a Delphic consensus approach, in order to facilitate prognostication and reproducibility of data among different institutions [32]. Despite efforts to improve consistency, a number of inherent difficulties remain, such as issues related to accurate assessment of tumour grade which is an important prognostic factor. NETs often display significant intra-tumoral (within an individual tumour) and inter-tumoral (between different lesions) heterogeneity and therefore grading based on a single biopsy of a metastatic site (e.g. liver) may not adequately reflect tumour biology in metastatic GEP NETs [36]. In addition, over time NETs can undergo dedifferentiation or treatment-related redifferentiation (after chemotherapy or targeted drug therapy) and thus historic biopsies may not be a reliable source of prognostic information, particularly when there is clinical evidence of change in tumour behaviour [37]. Most grading systems (including the World Health Organisation [WHO]/ENETS classifications) rely extensively on the proliferative rate (Ki67 index) to separate low, intermediate and high-grade tumours [31,36]. However, evaluation of the Ki67 index is subject to reproducibility issues, interobserver and likely intra-observer variability, especially in cases harbouring a low proliferation fraction (i.e. 1–3%) [32,35]. In these cases separation of low and intermediate grade tumours can be difficult, particularly if the amount of available tumour tissue is limited (biopsy material). From a biological point of view, however, the actual strict separation into these two prognostic groups can be questioned and in fact it seems more likely that there might be a more gradual increase in the malignant potential of a tumour as the Ki67 index increases incrementally [34,38].

Another challenging area in the management and therapeutic monitoring of GEP NETs is imaging assessment and interpretation. This area requires considerable expertise and discrepancies in assessment of progression events are often observed between peripheral and central radiological review [39]. Anatomic (morphological) imaging has known limitations in the assessment of NETs, such as strict dependency on the exact contrast phase and dosage, which may complicate the evaluation of (especially hypervascular) lesions. This may be an issue particularly for accurate comparative assessment of scans that have been performed in different institutions. Other limitations include resolution inadequacies and difficulties in measuring small volume disease (e.g. peritoneal disease or small lymph nodes) [40]. In addition, conventional tumour size criteria (e.g. WHO, Southwest Oncology Group [SWOG], Response Evaluation Criteria in Solid Tumours [RECIST]) that are used in general oncology are less suitable for the assessment of NETs, because of the indolent nature of the disease and the fact that most therapies lead to disease stabilisation rather than tumour shrinkage. Furthermore, there are difficulties in the evaluation of poorly demarcated large volume liver disease due to coalescence phenomena [41]. Another limitation of these criteria especially in the setting of molecular targeted treatments is that they are not appropriate for assessment of atypical responses, such as intra-tumoral haemorrhage, fibrosis, pseudo-progression and mixed response patterns. Recognition and accurate interpretation of these patterns requires a multidisciplinary approach and appropriate expertise [42]. Integration of attenuation changes on computed tomography (CT) (Choi criteria) or functional magnetic resonance imaging (MRI) parameters with anatomical imaging may also be useful in the assessment of tissue modifications, such as necrosis, fibrosis and tumour liquefaction, but these additional parameters require further validation as response criteria [40,43,44]. On the other hand, functional (molecular) imaging provides information on tumour physiology and may have greater potential to measure treatment response in slow-growing tumours [41]. Changes in the physiologic or metabolic characteristics of the tissue can be detected much earlier than changes in size and may be more predictive of outcome compared to conventional size criteria [41]. This is an area of ongoing research and the role of monitoring somatostatin receptor density (^{68}Ga-DOTA-SSA-PET) or tumour metabolic activity (^{18}F-DOPA, ^{11}C-5-HTP PET) as a measure of early response prediction during treatment follow-up remains to be

established [43,45–48]. At present, there is no defined role for nuclear medicine techniques in response evaluation besides diagnosing progressive disease by visualising new lesions at an earlier stage, when these techniques are combined with morphological imaging [49,50]. Functional (molecular) imaging may also have a useful role during follow-up of patients with GEP NETs, in cases of tumour dedifferentiation which can occur over time. This typically results in decreased tracer uptake on somatostatin receptor imaging and increased uptake on ^{18}F-FDG PET, because a higher proliferative activity is associated with increased glucose metabolism. Overall, a high uptake on ^{18}F-FDG PET predicts a poor prognosis, although additional clinical studies are needed to gain more insight into the use of molecular imaging in patient prognostication [40,50,51]. It is therefore clear that anatomic (morphological) and functional (molecular) imaging currently have several limitations, but are complimentary tools and in combination may provide useful clinical and prognostic information for the management of GEP NETs. However, considerable expertise and a multidisciplinary team approach are often needed for the appropriate selection of radiological investigations and the accurate interpretation of imaging studies.

As described earlier (Fig. 2), healthcare teams operate within the context of organisational constraints or under the influence of other external factors, which may create additional challenges in the management of patients with GEP NETs. In a recent global survey of 1928 patients with NETs, a large proportion of participants reported access issues to NET-specific treatment options. More specifically, PRRT was reportedly available to 28%, interventional radiology to 30%, chemotherapy to 38%, drug therapy (other than chemotherapy) to 56% and surgery to 76% of patients [52]. This may reflect poor access to NET experts or NET specialist centres or relate to other issues, such as healthcare economics. For example, PRRT availability in England is limited, as this drug therapy was removed from the NHS Cancer Drugs Fund in November 2015 (it is currently under review by the National Institute for Health and Care Excellence) mainly on the basis of cost-effectiveness considerations, although it remains available in other parts of the United Kingdom (Wales, Northern Ireland and Scotland) [53,54]. Similarly, many healthcare organisations may not have access to state-of-art equipment and may not be able to offer certain imaging modalities (such as ^{68}Ga-DOTA-SSA-PET for the detection, staging and re-staging of NETs or GLP-1 [Glucagon-Like Peptide-1] receptor imaging for the localisation of occult benign insulinomas) [43,50]. However, as mentioned earlier, centralisation of patient care through the development of centres of expertise within network settings has the potential to improve patient access to specialised facilities, therapies and research trials.

The management of GEP NETs is undoubtedly complex and has evolved significantly over time. The aim of treatment is to control tumour growth, prolong survival and improve symptoms and quality of life [55]. While surgical resection followed by active surveillance remains the mainstay for the treatment of localised NETs, the majority of patients present with metastatic disease and their management often requires a combination of systemic and locoregional approaches. A range of systemic therapies are available. Somatostatin analogues are commonly used as first-line therapy due to their favourable side effect profile as well as their antisecretory and antiproliferative properties [56,57]. Other systemic therapies include interferon-alfa, a biological therapy which is also effective in exerting an antisecretory effect and controlling tumour growth, but is often poorly tolerated, and chemotherapy, which is usually reserved for poorly differentiated neuroendocrine carcinomas, as well as for patients with low-to-intermediate grade pancreatic NETs who have bulky, rapidly progressive and/or symptomatic disease [4,23,58]. Another form of systemic therapy is PRRT which allows targeted delivery of radionuclides to tumour cells expressing high levels of somatostatin receptors. The two radionuclides most commonly used, ^{90}Yttrium-DOTATOC and ^{177}Lutetium-DOTATATE, have been successfully employed for more than a decade in the management of advanced NETs and more recently the phase III, randomised NETTER-1 trial demonstrated exceptional tolerability and efficacy in patients with progressive, metastatic midgut NETs [59–61]. Furthermore, randomised phase III trials have demonstrated the efficacy of newer molecular targeted therapies (mTOR inhibitor everolimus, tyrosine kinase inhibitor sunitinib) and these drugs have been a useful option in the medical armamentarium for the management of GEP NETs with progressive disease [39,62–65]. Liver-directed therapies (surgical resection, radio-frequency ablation [RFA], trans-arterial bland embolization [TAE], trans-arterial chemoembolization [TACE], selective internal radiotherapy with ^{90}Y radio-coated beads [SIRT]) may also be effective in both symptom control and as an antiproliferative treatment in patients with liver-predominant disease, but have never been compared to systemic agents [66,67]. More recently, telotristat ethyl, a novel serotonin synthesis inhibitor, has demonstrated efficacy in palliating diarrhoea in patients with poorly controlled carcinoid syndrome [68]. It is therefore apparent that the therapeutic landscape of GEP NETs has evolved substantially in recent years and with the increasing number of available treatment options, several questions have arisen regarding the optimal timing, sequencing, selection and the potential role of combination of therapies. Navigating through a complex therapeutic algorithm can be challenging and requires considerable expertise and clinical judgment. Selection of treatments should be individualised and based on tumour-, patient- and treatment-related characteristics. However, many of these factors may change over time in the same patient and may affect therapeutic choices [4]. Another challenging area in the management of GEP NETs is the careful consideration of quality of life issues and patient preference, which are often overlooked in clinical trials that focus more on measures of efficacy and safety. Treatment tolerability and quality of life is an important aspect of management of these patients, who often have indolent tumours with relatively good prognosis and may receive a number of different treatments during the course of their disease [4]]. Furthermore, the lack of reliable predictive biomarkers to guide management, monitor the efficacy of therapy and provide a prognostic assessment of disease progress is an additional clinical challenge [69,70]. As a result, therapeutic decisions are often based on clinical and pathological data, which as described earlier have several limitations.

Conclusions

GEP NETs represent a heterogeneous and diverse group of neoplasms that are commonly diagnosed at an advanced stage. A wide range of treatment options are available but navigating the therapeutic algorithm may be challenging. A multidisciplinary approach within a centre of expertise, often linked with other institutions as part of a national/international network setting, should be considered standard of care, as it offers the potential to streamline patient care and facilitate the implementation of complex personalised treatment plans. Improvements in clinical outcomes and overall survival observed in recent years are likely to reflect not only advances in diagnostic technology and therapies, but importantly also improvements in care pathways and the transition from traditional models to integrated, patient-centric, multidisciplinary

approaches for the management of patients with neuroendocrine tumours. Advocacy and specialist nursing support for patients has improved and one also needs to ensure access to information enabling recruitment for basic research and clinical trials. In Europe the population-based registries, within the RARECARE net project, showed up to 2007 a low level of centralisation and no significant improvement for GEP NET patients. These data should be used to evaluate future improvement in GEPNET prognosis and management, in the real world, after the ENETS initiatives.

Conflicts of interest statement

None declared.

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