

Special issue: Neuroendocrine Tumours

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Editorial: The management of patients with neuroendocrine tumours

Neuroendocrine tumours (NETs) are relatively rare, with little in the way of evidence based practice. In an era of great technological and therapeutic advances, many of which have been applied to NETs, there has to be a concerted effort to create a robust evidence base for both scientific and therapeutic progress. The only way forward for rare conditions is collaboration and hence the development of international organisations such as the European Neuroendocrine Tumour Group (ENET) and national bodies such as the UK Neuroendocrine Tumour Group (UK NETwork). This supplement is a result of a recent combined meeting of ENET and UK NETwork.

Neuroendocrine tumours are derived from the diffuse endocrine system and can be found anywhere in the body. The previous unitarian approach to classification, for example, Pearce's description of APUDomas (Amine precursor uptake and decarboxylation) (Pearce 1969) in retrospect was unhelpful, as a heterogeneous group of tumours were all classified under the same biological phenotype which misrepresented the biological and behavioural diversity of NETs. The latest WHO classification has therefore been a significant advance and provides a more informed description and diagnosis (Solcia *et al.* 2000).

For the optimal management of NETs, the following strategy has been suggested (Jensen 2002):

(i) suspect the diagnosis; (ii) perform appropriate biochemistry profiles including urine 24 hour 5 hydroxyindole acetic acid (5HIAA) and serum hormone, including gut peptides and chomogranin A measurements; (iii) assessment of histopathology to confirm diagnosis; (iv) determine the presence of inherited disorder such as Multiple Endocrine Neoplasia type 1 (MEN-1) or the Von Hippel–Lindau syndrome; (v) treat the symptoms or excessive hormonal state; (vi) determine the site and extent of disease using, for example, 'standard' contrast computed tomography (CT) or magnetic resonance imaging (MRI) as well as the most sensitive modality for detecting metastatic disease, the Indium-111 Octreotide scan; (vii) treat the disease – if possible with curative surgery, otherwise consider surgical debulking and the range of non-surgical treatments of metastatic disease; (viii) all patients will require long term follow-up preferably within treatment protocols.

NETs present in approximately half of all cases as functional/'hormone-active' non-metastatic tumours, e.g. insulinomas or as metastatic, e.g. ileal, NETs with carcinoid-syndrome. Diagnosis based on specific hypersecretion related symptoms and syndromes, e.g. Zollinger–Ellison syndrome, can be difficult since these tumours are already functional despite a relatively small, sometimes hardly detectable, tumour volume. By contrast, non-functional, hormone-inactive NETs remain symptomatically 'quiet' until a large tumour volume leads to non-specific symptoms such as jaundice, intestinal obstruction, etc. Patients may have non-specific symptoms and even today the median time to diagnosis can be three to seven years. Prognosis appears to be related to size; tumour differentiation with the more dedifferentiated tumours being more aggressive; angioinvasion; proliferative index using markers such as Ki67, in simplistic terms the higher the proliferation index the more aggressive the tumour; and metastases to other organs such as bone and liver, this obviously being a bad prognostic indicator.

The common feature for most NETs is the presence of somatostatin receptor with the type two form predominating. The expression of the somatostatin receptor has been utilised for (i) imaging using the Indium-111 OctreoScan, (ii) symptomatic therapy using somatostatin analogue Octreotide and Lanreotide preparations and (iii) tumour therapy with Yttrium-90 DOTA Octreotide and associated analogue peptide therapies.

There is good evidence to commend the use of somatostatin analogues in the treatment of serotonin-producing tumours associated with the carcinoid syndrome (O'Toole *et al.* 2000, Rubin *et al.* 1999). Many NET patients present with metastatic disease but there is little evidence for determining correct management in such patients. There appears to be a role for chemotherapy in pancreatic NETs but perhaps less so for what were previously classified as 'mid-gut carcinoid' tumours. There has been little advance in chemotherapy regimens since Moertel proposed regimens in the 1980s (Moertel *et al.* 1992). The role of interferon remains controversial and response may be associated with the type of NET (Obergh 2001). Ablation therapies such as embolization therapies have been shown to be of symptomatic and

survival benefit in monocentric studies (Brown *et al.* 1999, Chamberlain *et al.* 2000) however we don't know if chemo-embolization has any benefit over particle embolization alone. Thermal ablation such as radiofrequency ablation has been shown to be of benefit in patients with few and small liver metastases however its fit into the therapeutic strategy needs to be determined (Hellman *et al.* 2002). The preponderance of receptor types on NETs has enabled these tumours to be utilised for radionuclide therapies, originally I-131 meta-iodo benzyl guanidine (mIBG) therapy and most recently Yttrium-90 somatostatin analogue therapies as reviewed in this supplement. New therapeutic options are being developed and perhaps the closest in coming to clinical fruition are the anti-angiogenesis agents.

Controlled trials only will give us the answer to these therapeutic questions. Many NETs are slow-growing and therefore we have to be careful in selecting appropriate patients for therapy. One would recommend that anti-tumour treatment should be selected for patients with evidence of progressive disease. Crucially, we have to determine not only the effect of treatment on patient survival but also quality of life. The latter is perhaps of most importance, especially as patients can live some number of years and this is reviewed in this issue.

Finally, patients with NETs will present to a variety of medical and surgical specialities and hence it is imperative that patients are managed within the context of a multidisciplinary team. The potential role of the specialist nurse is highlighted in this supplement. In order to optimise the care of patients and recruitment to appropriate trials, NET patients should only be seen in centres with a specialist interest.

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Guest Editors

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