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Neuroendocrine tumors: recent progress in diagnosis and treatment

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Neuroendocrine tumors (NETs) present a diverse group of malignancies considered to be rare, but recent data are indicating a significant increase in both incidence and prevalence during the last few decades. Current figures indicate an incidence of 5.1/100 000 per year and a prevalence of 35/100 000 (Yao *et al*. 2008*a*; Fig. 1). The exact reason for this increase is not known, but it might be related to increased awareness among physicians as well as better diagnosis and treatment. A new WHO classification system has emerged that distinguished between well-differentiated and poorly differentiated neoplasms in order to prognostically stratify the NETs that are further classified according to a TNM grading system that was recently proposed by European Neuroendocrine Tumor Society (ENETS) and the AJCC/UICC (Capella *et al*. 2000, Rindi *et al*. 2007, Kloppel *et al*. 2010). The grading system is based on the proliferative activity (Ki-67 index, mitoses) of the tumor. The classification and the pathology of gastro-entero-pancreatic neuroendocrine neoplasms is discussed by Prof. Günter Klöppel (Klöppel 2011). A number of biomarkers has been developed during the last decades based on development of the immunoassays for various gut hormones and amines. The most applied general tumor marker is chromogranin A (CgA) with high sensitivity and specificity but must be evaluated in relation to other diseases and therapeutic agents that can increase circulating levels without any tumor (Nobels *et al*. 1997, Tomassetti *et al*. 2001). Plasma CgA also gives prognostic information, where high levels indicate a worse prognosis (Janson *et al*. 1997). Other general markers include pancreatic polypeptide, neuron-specific enolase, and HCG-subunits. Depending on the type of clinical syndrome, specific markers such as gastrin, glucagon, insulin, and so forth may be used. For patients with carcinoid syndrome, urinary-5HIAA is still an important biomarker. The majority of patients with NETs (>60%) present with metastatic disease, and therefore, there is a need for more sensitive and specific biomarkers in the future. It might also be of interest to see whether analysis of circulating tumor cells can be of value for the selection of specific treatments. Biomarkers are discussed by myself (Oberg 2011).

Nuclear medicine plays a pivotal role in the imaging and treatment of NETs. Somatostatin receptor scintigraphy (SRS) with Indium-111-DPA-octreotide has proven its role in the diagnosis and staging of NETs (Krenning *et al*. 1993). Positron emission tomography (PET) using short-lived isotopes that are specifically accumulated in NETs has increased in importance during the last years. The latter imaging modality especially in combination with computed tomography (CT) is of interest because of encouraging results in terms of improved imaging quality and detection capabilities but also prognostic information (Orlefors *et al*. 2005, Binderup *et al*. 2010). One such tracer might be Gallium-68-DOTA-octreotate that might, in the future, replace SRS as the gold standard. This PET/CT show higher sensitive and specificity and is also easily applied in the clinic because it is a one-stop procedure and the patient does not have to come back for repeated scanning (Gabriel *et al*. 2005). The tracer is also generated by a generator that makes it cheaper than traditional PET tracers developed by a cyclotron. Peptide receptors radionuclide therapy (PRRT) is a promising new tool in the management of patients with inoperable or metastasized NETs as it can induce symptomatic improvement and prolong survival. In the largest series of patients receiving PRRT with

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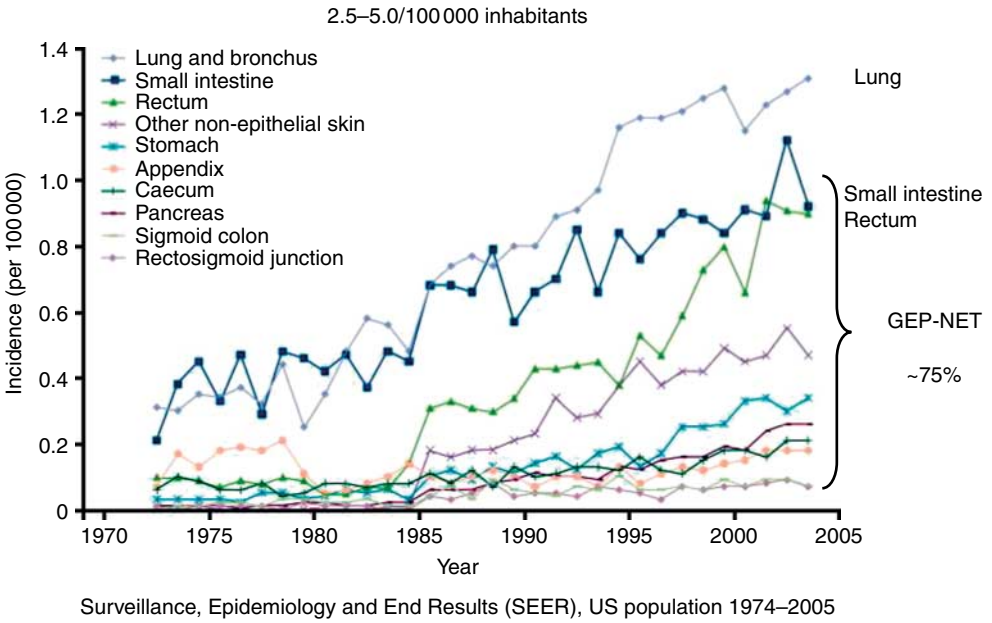

Figure 1 Incidence of neuroendocrine tumors in the western world. Reprinted from *The Lancet Oncology* **9**, Irvin M Modlin *et al.*, Gastroenteropancreatic neuroendocrine tumours, pages 61–72, Copyright (2008), with permission from Elsevier.

Lutetium-177-DOTA-octreotate, a survival benefit of several years compared to historical controls has been reported (Kwekkeboom *et al.* 2008). In this supplement, Doctors Teunissen, Kwekkeboom, Valkema, and Krenning discuss imaging and the PRRT treatment of NETs (Teunissen *et al.* 2011).

The treatment landscape has significantly changed over the last years with the introduction of not only PRRT but also new biological therapies such as targeted treatments with tyrosine kinase and mTOR inhibitors but also the introduction of a new cytotoxic treatment with temozolomide alone or in combination with capecitabine or bevacizumab (Kulke 2006, Kulke *et al.* 2008, Yao *et al.* 2008*b*, 2010).

In the last paper of this supplement, the overall management of patients with NETs is discussed. It is obvious that these patients with very complicated clinical symptomatology need to be treated in specialized centers as part of a multi-disciplinary team comprising gastroenterologist, oncologist, endocrinologist, gastrointestinal hepatopancreaticobiliary surgeons, pathologist, nuclear medicine physicians, technicians, and radiologist. Although the number of medical treatments and clinical trials has increased in the last decade, there is still a lack of prospective randomized trials. Thus, management is mainly based on limited and often single-center studies, although there are now formal guidelines based on consensus expert opinions (ENETS, NANETS guidelines; Ramage *et al.* 2005, 2008, Steinmuller *et al.* 2008). In the last paper, Dr Khan and Caplin discuss the current optimal management of patients with NETs (Khan & Caplin 2011).

There is still an unmet need for randomized trials in patients with various subtypes of NETs. Moreover, the new classification systems should be introduced in the daily management of these patients but also in the clinical trials. We need more sensitive and specific markers to diagnose and follow up these patients. Many of the new treatments are expensive, and therefore, it is necessary to develop specific markers and imaging modalities that can detect and present early clinical responses to the introduced treatment. It is also important to emphasize the need for further education of doctors in the field of NETs and also establish center of expertise or excellence worldwide to give these patients the best possible treatment. In the future, we will aim at personalized treatment based on tumor biology, genetics, localization, and performance status to give the patients a good quality of life even in those patients that cannot be cured by surgery, PRRT, or medical treatment. In general, many of these patients are living with the disease for 10–15 years, and therefore, future management of these patients must include quality of life aspects.

Declaration of interest

K Oberg is on advisory boards for Novartis, Ipsen and Pfizer, and has received lecture honoraria from Novartis, Ipsen and Pfizer.

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