Management of gastro-entero-pancreatic neuroendocrine tumours (GEP NET) : an introduction

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Since the discovery of secretin by Bayliss and Starling in 1902 many hormones have been identified in the gut, so that the gastro-intestinal-pancreatic tract can be considered the largest endocrine organ in the human body. Gut endocrine cells constitute a complex regulatory network for local control of secretion, absorption, motility, mucosal cell proliferation and differentiation.

Endocrine committed cells in the gut may undergo proliferative changes leading to hyperplastic and dysplastic lesions and sometimes giving origin eventually to gut or pancreas endocrine tumours, also called neuroendocrine tumours (NET) (1). They are characterized histologically by the intracellular presence of markers of endocrine tissue, such as chromogranin A and neuron-specific enolase, which can be used in the diagnosis of these tumours.

NETs are rare and account for less then 2% of all gastro-intestinal malignancies with an incidence of approximately 2-4 per 100 000/year (2). A valuable effort to define the incidence and characteristics of NETs in Belgium is ongoing through the NET-Registry, initiated by the Belgian Group for Digestive Oncology (www.bgdo.be).

In accordance with the anatomical and functional heterogeneity of the cells of origin, NETs represent a heterogeneous group of neoplasms with remarkable clinicopathologic differences. Recently new WHO-classifications allow to better define and diagnose NETs. They can be classified on an anatomical basis (foregut with pancreas, midgut including the appendix and hindgut) or according to cell type and status of differentiation (well-differentiated tumours, well-differentiated carcinomas and poorly-differentiated carcinomas). Especially the Ki67 proliferation index seems to be a helpful marker to assess the biological aggressiveness of the tumour, although the cut-off value remains a matter of debate.

Despite their relatively low incidence, NETs represent a significant clinical challenge. Due to their peculiar heterogeneity in terms of biological and clinical features, which also reflects different prognosis, a multidisciplinary approach is mandatory to obtain an optimal management of this disease. In this management a number of specific features have to be recognized :

– All NETs probably have a malignant potential, but their biological behaviour differs from one tumour type to another.
– They grow, in general, slowly compared with the more aggressively proliferating adenocarcinomas of the gastrointestinal tract.
– NETs are mostly functionally inactive. However some are functionally active and lead to well-known, sometimes dramatic, clinical syndromes as a consequence of excess release of endogenous hormones or vasoactive substances by the tumour cells.
– The quality of life of patients with non-functioning tumours is mostly minimally compromised, even in those with diffuse metastatic spread.
– Some NETs never develop metastases and only the primary tumour grows.
– Others develop lymph node metastases or metastases into the liver or elsewhere.
– Some patients reveal few (low tumour load), others many metastases (high tumour load).
– Although the histology is very similar in most tumours despite a different origin, the biological behaviour of the tumours may vary considerably.
– Histological differentiation of the tumours can change with time. After years of very slow progression of a highly differentiated tumour, growth can explode as a result of tumour dedifferentiation. This will obviously modify the therapeutic strategy over time.
– NETs can arise solitarily or as part of genetic and heritable tumour syndromes such as MEN1 syndrome and others.

Consequently, it is easy to understand that management strategies have to be individualized according to these differences in origin, biology, growth pattern and, most importantly, according to the quality of life of an individual patient.

Several questions have to be addressed properly in taking care of a patient with a NET :

– diagnosis and staging, including modalities of follow-

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up. Initial imaging studies to locate the tumour may be inconclusive.
- operability and surgery for the primary tumour
- control of hormonal excess and possibilities of medical treatment
- If surgery is not possible or in case of metastatic disease, treatment can be complicated. Multiple cytoreductive therapeutic strategies are available, including surgery of hepatic metastasis, radiofrequency ablation, transarterial hepatic embolization, peptide receptor radiation therapy, chemotherapy, biotherapy with somatostatin analogues, targeted therapy with tyrosine kinase inhibitors. Liver transplantation may be considered in some individuals.

Contrary to the more frequently occurring adenocarcinomas most treatment schedules are not based on prospective controlled trials. Consensus statements regarding diagnosis and treatment of digestive NETs, largely based on expert opinions, were published (3), especially by the European Neuroendocrine Tumour Society (ENETS) (4-10). Although consensus was not reached on a number of specific issues, the ENETS proposed a TNM staging and grading system (11,12) which is a welcome and important development that, however, still needs validation.

In order to define the various approaches to the management of NETs in Belgium and to identify or clarify the remaining questions and problems, a round table discussion was organized with leading Belgian experts in NET in October 2007 near Brussels (*).

This same expert group is responsible for the joint publication of a series of articles that you can read in this issue of *Acta Gastroenterologica Belgica*. Based on the topics discussed during the Round Table, various aspects of NET-management are analysed, including : diagnostic pitfalls, carcinoid heart disease, surgery for pancreatic NETs, locoregional and radioisotopic targeted treatment, the role of cytotoxic chemotherapy, the antiproliferative effect of somatostatin analogues and finally, the promising role of new targeted therapies. An agenda for future research is also proposed.

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