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Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours

A Consensus Statement on Behalf of the European Neuroendocrine Tumour Society (ENETS)

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Introduction

G. Rindi

The endocrine tumours of the gastrointestinal tract have been attracting the attention of clinicians since their very first identification, which paralleled the identification of gut endocrine cells.

The history of enteroendocrine cells and derived tumours begins with the early development of histology and histochemistry, dating back to the end of the 19th century. Unusual cells of gastric [1] and intestinal mucosa [2–4] attracted the attention of scientists and, due to their chromium salt affinity [4], were named enterochromaffin cells [5]. Cells with similar properties were observed in other sites of the body [6] and were suggested to be part of a complex system exerting a local, 'paracrine', action via production and secretion of peptides or amines [7]. This concept was further revived and supported in the 1960s by the identification in some of these cells of the property of taking up amine precursors which are then transformed into amines by intracellular decarboxylation [8].

At the same time, a non-conventional, epithelial slow-growing tumour was identified and defined as 'karzinoide' (carcinoid, i.e. carcinoma-like) by Öberendorfer [9]. Some of these tumours were then shown to display argentaffin properties [10], thus establishing a relationship with enterochromaffin cells [11].

As many as 15 highly specialized epithelial cells of endodermal origin compose the diffuse endocrine system (DES) of the gut [12] and are considered the source of gut carcinoids and of tumours of the endocrine pancreas.

Gut DES cells and derived tumours express several antigens shared with nerve elements, usually defined as 'neuroendocrine markers' [13]. This phenomenon provides reason for the term 'neuroendocrine' which is widely used to connote DES cells and their tumours. The neuroendocrine markers comprise neuron-specific enolase (NSE) and protein gene product 9.5 (PGP 9.5) [14, 15] located in the cytosol, the chromogranins (A, B and C or secretogranin) associated with electron-dense granules [16, 17] and synaptophysin within small synaptic-like vesicles [18, 19].

The remarkable heterogeneity of the endocrine cells of the gut [20] compose the complexity of derived tumours. Besides neuroendocrine markers, multiple hormones are in fact produced and, in some instances, also released in the bloodstream to determine a hyperfunctional syndrome.

Many attempts have been made in the past few decades to uniformly classify, diagnose and treat gut endocrine tumours. Unfortunately, because of their rarity, no structured practice for diagnosis and therapy has been developed, despite increasing knowledge and awareness of the subject. The recent introduction of a more structured classification of tumours of the diffuse endocrine system by the World Health Organisation [21] inspired an effort to develop common diagnostic and treatment guidelines within Europe. As members of the European Neuroendocrine Tumour Society (ENETS), a group of clinicians became involved in the study of neuroendocrine tumours and in the treatment of affected patients. The following papers are the result of this common effort and represent an organized attempt to give evidence-based information on this subject.

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Management of Endocrine Foregut Tumours

B. Eriksson

I. Introduction

Endocrine foregut tumours include tumours originating in the stomach, duodenum, pancreas, lung and thymus. For practical reasons, lung and thymic tumours are not included in these recommendations.

From a clinical viewpoint, endocrine foregut tumours can be divided into functioning tumours, associated with hormonal symptoms and non-functioning tumours, not associated with any hormonal symptoms. Most endocrine tumours are well-differentiated, non-functioning, and slowly growing. Some tumours are poorly differentiated small cell endocrine carcinomas that are rapidly growing and have a poor prognosis. The possibility of the endocrine tumour being part of a familiar, genetic disease, i.e. multiple endocrine neoplasia type 1 (MEN-1), should be excluded.

Comments: MEN-1 is associated with hyperparathyroid hyperplasia/hyperparathyroidism, pancreatic endocrine tumours, pituitary adenomas, thymic, gastric and bronchial carcinoids, adrenocortical hyperplasia, and also skin fibromas/lipomas. The mean age of clinical diagnosis has been reported to be around 30 years; however, in screened families it is about 15 years. The exact incidence is not known, but a prevalence of 0.2 has been reported; MEN-1 is probably underdiagnosed [1]. A specific deletion on chromosome 11q13 is the genetic background of the disease. The gene encodes a protein called menin, which acts as a tumour suppressor [2, 3].

The most common clinical syndrome associated with MEN-1 and pancreatic or duodenal endocrine tumours is the Zollinger-Ellison syndrome (ZES). Other syndromes include hypoglycaemia, VIPoma, and glucagonoma syndrome. Most tumours are initially non-functioning. Genetic screening for MEN-1 should be offered to family members. Those with genetic lesions should be followed annually for detection of parathyroid disease, pituitary, pancreatic and other tumours [1–4].

Endocrine Tumours of the Stomach

Epidemiology

The yearly age-adjusted incidence of gastric neuroendocrine tumours has been reported to be around 0.2 per 100,000 population [5]. The tumours are probably underdiagnosed.

Clinicopathological Staging

As in other sites of the gastrointestinal tract, neuroendocrine tumours of the stomach are categorized into well- or poorly differentiated tumours [6, 7].

Well-differentiated tumours are the majority. Besides the extremely rare gastrin-producing (G), somatostatin-producing (D), or serotonin-producing (EC) cell tumours, most well-differentiated tumours are mainly, but not exclusively, composed of enterochromaffin-like (ECL) cells and are most frequently located in the acidopeptic mucosa. They are also called ECL-cell carcinoids or ECLomas and three subtypes of well-differentiated ECL cell tumours are recognised [6, 7].

Type 1 is the most common NE neoplasm in the whole stomach with a relative incidence of 70–85%, and is frequently small, polypoid, often multiple and usually benign (WHO group 1). It is secondary to hypergastrinaemia, related to atrophic gastritis (also includes microcarcinoidosis) and is always associated with ECL-cell hyperplasia.

Type 2 is a rare tumour associated with primary hypergastrinaemia as a manifestation of ZES as part of MEN-1. Type 2 tumours appear mostly as multiple benign polyps (WHO group 1), and are only in exceptional cases metastatic (WHO group 2, endocrine carcinoma).

Type 3 is the second most common NE gastric tumour with a relative incidence of 13–20%; it appears sporadically without predisposing factors either local (atrophic gastritis) or genetic (MEN-1: ZES). It is usually solitary and belongs to WHO group 2: Ki-67 >2%, >2 cm in diameter and infiltrative growth with metastases both to regional lymph nodes and the liver. Less than 5% of these tumours can cause the so-called 'atypical carcinoid syndrome' due to histamine production.

Poorly differentiated tumours are highly malignant and belong to WHO group 3, i.e. poorly differentiated, small-cell, endocrine carcinomas (PDEC). They are relatively rare and account for <5% of endocrine tumours. They are probably underestimated since they may resemble undifferentiated carcinomas. A positive staining for synaptophysin may be the only indicator of endocrine differentiation.

Prognosis/Survival

Type 1 occurs most often in women, with no tumour-related death at an overall mean follow-up of 53 months [8]. Among type 2 tumours there was 1 tumour-related death (49 months after diagnosis) and an overall mean survival of 84 months. In the same series, type 3 tumours had a mean survival of 28 months and poorly differentiated only 7 months.

Clinical Presentation

Small gastric carcinoids rarely give rise to symptoms and are diagnosed incidentally or in patients with pernicious anaemia [9]. Larger carcinoids may bleed. Occasionally, patients may complain of flush and present the 'atypical carcinoid syndrome'. The 'atypical carcinoid syndrome' includes severe generalized flushing, swelling, lacrimation, asthma and diarrhoea, caused by histamine production from a gastric endocrine tumour type 3.

Diagnostic Procedures

1. Tumour Imaging

Gastroscopy/endoscopic ultrasonography (EUS), abdominal ultrasound, contrast-enhanced CT or MRT of the abdomen and octreotide scintigraphy.

Comments: Gastroscopy with multiple biopsies from tumour and non-tumour tissue is essential for histopathological diagnosis to distinguish between the different types of gastric tumours and also indicating the size and location of the primary tumour. It is also important to exclude infection with *Helicobacter pylori*. CT/MRT and octreotide scintigraphy are important for staging of the disease in type 3 and poorly differentiated tumours.

2. Biochemical Diagnosis [9]

Chromogranin A, gastrin, histamine metabolites in urine (with appropriate diet). It is also important to determine the presence of parietal cell antibodies. MEN-1 should be excluded by determining ionized calcium, PTH and possibly also pituitary hormones.

Comments: Chromogranin A is the most sensitive marker for detection of gastric endocrine tumours (not in type 1 and 2). Measurement of gastrin will reveal atrophic gastritis and secondary hypergastrinaemia. If the patients present with flush in association with a gastric endocrine tumour (type 3), measurement of urinary histamine metabolites is recommended (elevated in 33% of type 1 and 80% of type 3 gastric carcinoids). MEN-1 should be confirmed in gastric endocrine tumours type 2.

3. Histopathology

Haematoxylin and eosin, chromogranin, synaptophysin, Ki-67.

Comments: If the diagnosis of a well- or poorly differentiated endocrine tumour is established by routine histopathology including the staining for chromogranin A and synaptophysin, additional staining for Ki-67 should always be performed to demonstrate the proliferative capacity of the tumour. High Ki-67 (>15–20%) indicates poor prognosis.

Endoscopic and Surgical Therapy [10]

1.1. Curative Therapy

Type 1 and 2 tumours (atrophic gastritis or MEN-1).

Polyps <1 cm in size: surveillance once per year; 1–6 polyps and >1 cm in size, endoscopic resection after EUS and surveillance; >6 polyps and >1 cm in size, extension to muscularis and/or repeated recurrences: alternatively surgical resection or antrectomy (reduces gastrin stimulation from antral G-cells).

Malignant development or recurrence despite local surgical resection: partial or total gastrectomy with lymph node dissection.

Type 3 and poorly differentiated tumours: partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Cytoreductive Therapy (Type 3 and Poorly Differentiated Tumours)

There are very few reports on the results with liver embolization (not recommended in histamine-producing tumours) and radiofrequency (RF) ablation in gastric endocrine tumours.

Medical Therapy

1. Biotherapy

1.1. Somatostatin analogues: In the case of multiple ECLomas with atrophic gastritis or ZES/MEN-1, somatostatin analogues have been shown to induce regression of gastric tumours, type 1 and 2 [11]. This scheme, however, is not recommended.

1.2. Interferon: Can be tried in disseminated type 2 and 3 tumours. Experience is limited [9].

2. Systemic Chemotherapy

Chemotherapy should only be used in metastatic disease (mainly type 3 and poorly differentiated tumours). The combination of streptozotocin (STZ) plus 5-fluorouracil (5-FU)/doxorubicin is recommended in less aggressive tumours and cisplatin/carboplatin plus etoposide in poorly differentiated tumours. There are few reports in the literature and experience is limited.

Endocrine Tumours of the Duodenum

Epidemiology

The age-adjusted annual incidence is <0.1 per 100,000 individuals [5].

Clinicopathological Staging

According to WHO indications, tumours of the duodenum and upper jejunum are classified together [12].

Well-differentiated tumours – carcinoids – are the majority. Most of them are mainly, but not exclusively, composed of gastrin-producing (G), somatostatin-producing (D) or serotonin-producing (EC) cells. They may be either benign and of uncertain behaviour (WHO group 1), or low-grade malignant (WHO group 2, carcinoma). G-cell tumours are preferentially located in the proximal duodenum when non-functioning. When functioning (gastrinomas) may be found at any site in the duodenum and jejunum and are usually multiple when associated with MEN-1. D-cell tumours are usually non-functioning and may be associated with neurofibromatosis (Recklinghausen's disease). Serotonin cell tumours are rare. Gangliocytic paragangliomas are observed in the ampullary region, are usually benign and only exceptionally low-grade malignant with metastases composed of the epithelial component only. Poorly differentiated carcinomas belonging to WHO group 3 (small-cell, poorly differentiated endocrine carcinomas) are relatively rare, highly malignant carcinomas of the ampullary region.

Prognosis/Survival

Five-year survival rate for localized disease is 66%, regional disease 28%, distant metastases 17%, and all stages 51% [5].

Clinical Presentation

The majority of patients presenting with dyspepsia are diagnosed with duodenal ulcer. In an occasional patient anaemia may be a result of bleeding. Most patients are diagnosed incidentally.

Diagnostic Procedures

1. Tumour Imaging

Endoscopy, EUS, contrast-enhanced CT or MRT of the abdomen, octreotide scintigraphy.

Comments: Endoscopy with biopsy is essential for histopathological diagnosis to distinguish between the different types of duodenal tumours also indicating the size and location of the primary tumour. CT/MRT and octreotide scintigraphy are important for staging.

2. Biochemical Diagnosis

Chromogranin A, further determination according to the clinical picture: gastrin, calcitonin, somatostatin, urinary 5-HIAA twice (24 h) with appropriate diet.

Comments: Chromogranin A is the most reliable tumour marker in endocrine duodenal tumours. The levels of other tumour markers will vary depending on the type of tumour. Patients with suspected Recklinghausen's disease or ZES secondary to MEN-1 should have an extended biochemical work-up.

3. Histopathology

Haematoxylin and eosin, chromogranin A, synaptophysin, S-100 (gangliocytic paragangliomas only), Ki-67, gastrin, somatostatin, serotonin or other hormones, if required by the clinical setting.

Comments: The diagnosis of an endocrine tumour should be demonstrated by routine histopathology including stainings for chromogranin A and synaptophysin. The staining for specific hormones will help to establish the type of duodenal tumour and the determination of Ki-67 the proliferation rate.

Surgical Therapy

2.1. Curative Surgical Therapy

Small duodenal tumours may be locally resected by endoscopy or surgery. Patients with larger tumours should undergo pancreatico-duodenal resection (Whipple's procedure). Tumours located in the distal duodenum should be removed by duodenal resection.

2.2. Palliative Surgery

Similarly as in other types of endocrine tumours, debulking of liver metastases should be considered.

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