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.

Cytoreductive Therapy

Research on cytoreductive therapy in endocrine duodenal tumours is sparse but should be performed in accordance with principles applied in other endocrine gastrointestinal tumours. Ablative therapy may be considered.

Medical Therapy

1. Biotherapy

1.1. Somatostatin analogues: somatostatin analogues can be used in patients with hormonal symptoms. Experience is limited.

1.2. Interferon: Interferon can be attempted in patients with disseminated disease. However, experience is limited.

2. Systemic Chemotherapy

Chemotherapy should only be used in metastatic disease (depending on tumour proliferation). The combination of STZ and 5-FU/doxorubicin is recommended in tumours with low to moderate proliferation and cisplatin/carboplatin plus etoposide in poorly differentiated tumours.

In gastrin-producing tumours, proton pump inhibitors should be used to control acid-related symptoms.

Endocrine Tumours of the Pancreas

Epidemiology

The incidence of clinically detected tumours has been reported to be 4–12 per million inhabitants, which is much lower than what is reported from autopsy series (about 1%) [5, 13].

Clinicopathological Staging [12, 14, 15]

Well-differentiated tumours are the large majority of which the two largest fractions are insulinomas (about 40% of cases) and non-functioning tumours (30–35%). When confined to the pancreas, non-angioinvasive, <2 cm in size, with <2 mitoses per 10 high-power field and <2% Ki-67 proliferation index these tumours are classified as of benign behaviour (WHO group 1) and, with the notable exception of insulinomas, are non-functioning.

Tumours confined to the pancreas but >2 cm in size, with angioinvasion and/or perineural space invasion, or >2 cm in size, >2 mitoses per 20 high-power field or >2% Ki-67 proliferation index, either non-functioning or functioning (gastrinoma, insulinoma, glucagonoma, somastatinoma or with ectopic syndromes, such as Cush-

ing, hyperkalaemia or acromegaly) still belong to the WHO group 1 but are classified as tumours with uncertain behaviour. The presence of unquestionable signs of malignancy like metastases or invasion of nearby structures identifies low-grade malignant carcinomas (WHO group 2).

Poorly differentiated, small-cell carcinomas are rare high-grade malignant carcinomas (WHO group 3), presenting with distant metastases, and display solid structure with necrosis, high mitotic/Ki-67 proliferation index and frequent hyperexpression/accumulation of p53.

Prognosis/Survival

The 5-year survival rate was reported to be 60–100% for localized disease, 40% for regional disease, 29% for distant metastases, and 80% for all stages [5, 13]. In a publication from 1993 [16], the 5-year survival rate for advanced EPT approached 60 months from diagnosis.

Clinical Presentation

Endocrine pancreatic tumours are classified according to clinical symptoms into functioning and non-functioning tumours. The non-functioning tumours [17], i.e. the hormonally silent tumours, constitute the largest group, about 50%. Next in incidence are the insulinomas [18, 19] and gastrinomas [20, 21], constituting about 25 and 15%, respectively. VIPomas [22, 23], glucagonomas [24, 25], somatostatinomas [26, 27] constitute the remaining 15%. Patients with malignant tumours may present with mixed syndromes, or the tumours may change clinically over time (for details, see references).

Endocrine pancreatic tumours can occur at any age with an equal sex distribution. About 15–30% of patients have MEN-1. In MEN-1 patients, multiple tumours occur syn- or metachronously [1]. MEN-1 pancreatic tumours are usually non-functioning in early ages and then after the age of 40 may turn into gastrinomas or other functioning tumours. In von Hippel-Lindau's disease the endocrine pancreatic tumours are usually non-functioning.

Diagnostic Procedures

1. Tumour Imaging

Ultrasonography, EUS, contrast-enhanced CT or MRT of the abdomen, MR-angiography for surgical decision-making, octreotide scintigraphy.

Comments

EUS combined with biopsies in experienced hands is the most sensitive method to detect pancreatico-duodenal tumours [28]. US, CT and MRI can also be used to

detect the primary tumours and metastases [29]. Octreotide scintigraphy is a routine investigation for both primary tumours and metastases [30, 31]. However, smaller tumours, especially insulinomas, can be difficult to visualize with this method and intraoperative ultrasonography is still the most sensitive method [32].

According to Gibril and Jensen [31], US can detect 9%, CT 31%, MRI 30%, angiography 28%, and octreotide scintigraphy 58% of possible primary gastrinomas. The sensitivities for detection of histopathologically proven liver metastases with the different methods are the following: US 46%, CT 42%, MRI 71%, angiography 62%, and octreotide scintigraphy 92%, respectively. (For detection of intra- and extrahepatic lesions: US 19%, CT 38%, MRI 45%, angiography 40%, and octreotide scintigraphy 70%.) In conclusion, octreotide scintigraphy has a sensitivity that exceeds the combination of the others. PET with 5-HTP or *L*-dopa can be an option for detection of small tumours [33].

2. Biochemistry

Chromogranin A, insulin, C-peptide, pro-insulin, gastrin, VIP, glucagon, calcitonin, somatostatin.

Comments

Chromogranin A is a general tumour marker, which is increased in almost all different types of endocrine pancreatic tumours [13]. Another general tumour marker is PP, which can be elevated in non-functioning tumours but also in functioning tumours. For each tumour type, characteristic clinical symptoms should lead to measurement of specific markers such as gastrin, insulin, VIP, glucagon, and somatostatin [13]. To establish the diagnosis of insulinoma a 12- to 72-hour fast is recommended; a glucagon test may also be informative [18, 19]. For the diagnosis of gastrinoma, measurement of basal and maximal gastric acid output is recommended to exclude secondary hypergastrinaemia [20, 34]. A secretin test may support the diagnosis. Determination of pituitary hormones, ionized calcium and PTH is included in MEN-1 screening [35]. For early detection of pancreatic involvement in MEN-1, a meal stimulation test with measurements of PP and gastrin can be performed. For genetic testing, see Introduction.

3. Histopathology [14, 36, 37]

Haematoxylin and eosin, chromogranin A, synaptophysin, specific hormones (insulin, gastrin, etc.), Ki-67.

Comments
See previous chapter.

Surgical Therapy

1.1. Curative Surgical Therapy of Primary Tumours

The indications for surgery depend on clinical symptoms, tumour size and location, malignancy and metastatic spread. There is a general consensus that curative surgery should be aimed for also in metastatic disease, including 'localized' metastatic disease to the liver [10]. Preoperative procedures should include exploration of the whole abdominal cavity, intraoperative ultrasonography of pancreas and liver, and transillumination of the duodenum in ZES [10, 38–40]. The type of surgical procedure depends on the location of the tumour: pancreatico-duodenal resection (Whipple's operation), distal pancreatic resection, tumour enucleation, enucleation in combination with resection. If malignancy is suspected, lymph node dissection is mandatory.

Comments

Since the vast majority of insulinomas are benign, patients with insulinomas can undergo surgery. Most patients are cured by enucleation or pancreatic resection. Similarly, surgery is the only treatment that can cure gastrinomas. With the knowledge, that most gastrinomas are localized in the pancreatic head or duodenum, radical operation may be feasible (Whipple's procedure and lymph node dissection). In the other tumour types, radical surgery is the only treatment for cure, although it is rarely possible at the time of diagnosis [10, 38–40].

The indications for surgery in MEN-1 patients are more controversial, since these patients have tumours in other endocrine organs and multiple tumours syn- and/or metachronously in the pancreatico-duodenal area. These patients are very rarely cured for their pancreatico-duodenal tumour by surgery. Surgery is advocated to avoid later development of malignancy (tumours >2 cm) in both functioning and non-functioning cases [41]. Tumours in the head of the pancreas should be enucleated if possible, distal pancreatic resection for caudally-located tumours and duodenotomy for diagnosis and resection of duodenal gastrinoma.

1.2. Curative Surgery of Liver Metastases [42]

Resection of liver metastases should always be considered both in functioning and non-functioning tumours, since progression of tumour disease can be delayed. Complete resection should be aimed for. The type of surgery depends on the location of the metastases. The following procedures can be chosen: enucleation, one or more segmental resections, hemihepatectomy or extended hemi-

hepatectomy. Intraoperative ultrasonography should be performed for detection of all liver metastases.

Comments

Metastatic disease should be confined to the liver. Surgery should be undertaken only if 90% of the tumour's mass can be successfully removed. Liver surgery can be done concomitantly with surgery of the primary tumour or on a separate occasion. Specific anaesthesiological procedures and perioperative somatostatin analogue infusion are indicated to avoid hormonal crises. If feasible, cholecystectomy should be performed synchronously, to prevent gallstone formation during future somatostatin analogue therapy or complications after liver embolization.

2. Palliative Surgery of Primary Tumours and/or Liver Metastases [42]

The indications for palliative/debulking resections of primary tumours and liver metastases have been broadened. Severe hormonal symptoms that cannot be controlled by medical treatment are indications for palliative resections. These procedures have to be individually designed for each patient.

Cytoreductive Therapy

1. Selective Embolization Alone or in Combination with Systemic Chemotherapy

Selective embolization alone or in combination with intra-arterial chemotherapy (chemoembolization) is an established procedure to reduce hormonal symptoms, as well as liver metastases [43, 44]. Selective embolization of peripheral arteries is usually preferred, which induces temporary ischemia and can be repeated. The objective response rates vary between 30 and 70% and the duration of response is between 10 and 30 months. At chemoembolization, cytotoxic drugs are injected intra-arterially together with embolization material. The cytotoxic drugs most often used are 5-FU, doxorubicin and mitomycin C. It has not been established whether chemoembolization is more efficient than embolization alone.

Comments

The procedure is accompanied by a mortality rate of 5–10% and there is significant morbidity. Minor side effects (postembolization syndrome) are fever, right upper quadrant pain, nausea, elevation of liver enzymes and a decrease in albumin and platelet count. Major side effects are gallbladder necrosis, hepatorenal syndrome, pancreatitis, and liver abscess. To prevent hormonal crises, in-travenous infusion of somatostatin analogues is indicated. Forced diuresis to prevent hepatorenal syndrome is recommended.

2. Radiofrequency Ablation

Radiofrequency ablation can be used to reduce the tumour mass in the liver and thereby reduce hormonal symptoms [45, 46].

Comments

The patient should not have more than 8–10 lesions in the liver. The largest diameter should be 4 cm. The morbidity rate is low, if not too many lesions are treated at the same time. Ablative surgery and RF can be combined.

Liver Transplantation

Liver transplantation may be considered in patients with no extrahepatic metastases [47–49]. However, experience is limited. Most patients had recurrences within months to years, possibly because of postoperative immunosuppressive treatment. Hence, improved methods for the detection of extrahepatic metastases are necessary before liver transplantations can be used or recommended.

Comments

Liver transplantation may be indicated for patients with tumours causing life-threatening hormonal symptoms and for patients who do not respond to medical therapy or who do not have access to other surgical interventions. Patients who have undergone Whipple's procedure or have aggressive carcinomas should be excluded.

Medical Therapy

1. Biotherapy

1.1. Somatostatin analogues: Somatostatin analogues are the primary treatment for patients with hormonal symptoms of endocrine tumours [11, 50]. About 80–90% of VIPoma and glucagonoma patients improve very promptly, overcoming diarrhoea and skin rash, and 60–80% have a reduction in VIP and glucagon levels. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. Somatostatin analogues can also be used in malignant gastrinomas and insulinomas, if they are somatostatin receptor scintigraphy positive. Caution has to be taken in insulinomas, since hypoglycaemia may worsen due to a more profound suppression of GH and glucagon than tu-

mour-produced insulin. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily. A significant reduction in tumour size has been seen in <10% of patients, but stabilization of tumour growth, documented by CT, occurs in 30–50% of patients [51].

Comments

To test the tolerability in an individual patient, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 μg s.c. 2–3 times) for 1–2 days, then the patient can be transferred to slow-release Lanreotide-SR i.m., lanreotide autogel s.c. or Sandostatin-LAR i.m. (every 4 weeks) [52]. Octreotide and lanreotide are equally effective. If one preparation is not effective or tolerated, the other can be attempted. Side effects, including abdominal discomfort and flatulence, are usually mild and subside within a few weeks. Long-term side effects include the formation of sludge and gallstones, but very few patients will develop symptoms. Some patients with long-lasting diarrhoea can develop severe hypocalcaemia.

1.2. Interferon: The cytokine α-interferon exerts direct effects on tumour cells by inhibiting protein and hormone synthesis, blocking the tumour cells' cycles in the G1/S phase, and it also indirectly stimulates the immune system. It has been shown to reduce circulating hormone levels in 30–60% of patients with endocrine gastrointestinal tumours, thereby improving symptoms [53–56]. Significant tumour reduction is seen in 10–15% of patients, but tumour stabilization is achieved in 40–60% of patients. Combination of α-interferon and somatostatin analogues can be given [57, 58].

Comments

The usual dose is 3–5 million units 3–5 times per week subcutaneously. There are new long-acting formulations of pegylated α-interferon. The exact doses have not been established yet. The most severe and dose-limiting toxicities are chronic fatigue, mental depression and autoimmune phenomena (SLE, myositis, vasculitis), which may necessitate withdrawal of treatment. Most patients will have a reduction in blood counts and an increase in liver enzymes, but these side effects can be handled by dose adjustments.

2. Systemic Chemotherapy

Systemic chemotherapy is indicated in patients with metastatic endocrine pancreatic tumours and streptozotocin (STZ) in combination with 5-FU or doxorubicin is still first-line treatment [59, 60]. Biochemical responses are seen in >50% of patients with a median duration of more than 2 years. Significant tumour shrinkage (>50%) is seen in 20–35%. All types of EPT respond.

Comments

At initiation STZ plus 5-FU/doxorubicin may induce a hormonal crisis. For example, in VIPoma patients, somatostatin analogues should be administered for protection. The major side effects, nausea and vomiting, can be avoided by 5-HT$_3$ receptor blockers. The dose-limiting toxicity is nephrotoxicity and hydration is important to protect the kidneys. In poorly differentiated neuroendocrine tumours (Ki-67 >15–20%), the combination of cisplatin/carboplatin plus etoposide can induce objective remission in 55–80% of patients [61–63]. Median duration of responses has been reported to be 8–11 months.

Comments

This regimen can also induce hormonal crises in the patients. The toxicity is significant with alopecia, bone-marrow depression, nephrotoxocity and neuropathy being major side effects. Nausea and vomiting can be handled by 5-HT$_3$ receptor blockers.

Follow-Up during/after Treatment
1. Patients with Liver Metastases

Ultrasonography or MR/CT and biochemical markers, including those initially elevated every 3 months. Diagnosis of bone metastases (if clinical signs are present) by Octreoscan and/or bone scan and MR.

2. Patients without Liver Metastases

Long-term follow-up because of the possibility of late recurrences. If curative surgery has been performed, Octreoscan or PET should be done after 6 months.

Comments

Poorly differentiated tumours (all locations): close follow-up every 2–3 months with US/CT/MRT or other radiological methods depending on affected organs. In other cases – check-up at least once per year with clinical examination, efficacy of symptomatic treatment, measurement of initially elevated markers, including chromogranin A, US, CT, MRT of liver/pancreas. If hereditary disease, special follow-up is recommended.

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Neuroendocrine Midgut Tumours

Part 1: Epidemiology, Histopathology and Diagnosis

R. Arnold

Introduction

Endocrine tumours are well-differentiated solid tumours with the characteristics of membrane-bound secretory granules upon ultrastructural examination. These tumours are rarely poorly differentiated. They share features of the neuroendocrine cell system with simultaneous expression of marker proteins: cytosolic proteins; small vesicle-associated markers; dense-core secretory granule-associated markers, and cell-type specific hormonal products [1]. Endocrine midgut tumours include those originating in the distal jejunum, ileum, appendix, and right-sided colon.

From a clinical viewpoint, endocrine midgut tumours can be divided into clinically non-functioning and clinically functioning tumours with hormonal hypersecretion-related symptoms which are responsible for the carcinoid syndrome [1, 2]. Most endocrine midgut tumours are well differentiated and grow slowly. Few tumours are poorly differentiated small-cell neuroendocrine tumours that grow rapidly and have a poor prognosis [2]. Endocrine midgut tumours are only rarely part of a familial genetic disease, i.e. MEN-1 or von Hippel-Lindau syndrome.

Epidemiology

The incidence of endocrine midgut tumours is much higher than those arising in the oesophagus, stomach and duodenum (foregut) and those arising in the hindgut (left-sided colon, rectum) [3–7]. Incidence rates of 0.28–0.8 per 100,000 population per year have been reported. Tumours of the lower jejunum and ileum account for 23–28% of all gastrointestinal endocrine tumours and are more frequent than those of the appendix [3, 6]. Midgut endocrine tumours occur in equal proportion in males and females with an age peak in the 6th and 7th decade [3]. Endocrine midgut tumours (carcinoids) are often multicentric and in 15% are associated with metasynchronous malignancies as gastrointestinal adenocarcinoma, breast cancer and others [3]. The majority of

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tumours are located in the terminal ileum close to the ileocaecal valve.

The incidence rates of appendiceal endocrine tumours account for 0.075 new cases per 100,000 population per year [3–7]. 19% of all gastrointestinal endocrine tumours have been reported to be localised in the appendix. They more often present in the 4th and 5th decade of life and are more common in females.

Prognosis

Endocrine Tumours of Distal Small Intestine
The prognosis of tumours arising in the distal small intestine is generally unfavourable if compared to that of duodenal, gastric (ECL cell carcinoids) and rectal endocrine tumours, since they frequently lead to metastases of the adjacent lymph nodes and later to the liver and elsewhere [8, 9]. Ten-year survival is approximately 60% in the absence of liver metastases at diagnosis, 15–25% in the presence of liver metastases and, according to a retrospective study, more favourable if the primary tumour is removed.

Survival of endocrine midgut tumours correlates closely with the stage of the disease at presentation with a 5-year survival of 65% in patients with localized or regional disease and 36% in those with distant metastases [3, 8–10]. Patients with slow-growing well-differentiated tumours and those with a low Ki-67 live longer than those with more rapidly growing well-differentiated tumours and those with a high Ki-67 [11].

Endocrine Tumours (Carcinoids) of the Appendix
Most patients with appendiceal carcinoids have a favourable prognosis. Carcinoids of <2 cm in size, confined to the appendiceal wall and not angio-invasive are completely cured by appendectomy [12–14]. Invasion of the mesoappendix, a size of >2 cm and angio-invasion carry an uncertain malignant potential as do tumours at the base of the appendix with involvement of the surgical margin or of the caecum [15]. Five-year survival of patients with an appendiceal carcinoid is 95% for localized disease, 85% for those with regional disease and 34% for those with distant metastases [12–14].

Goblet cell carcinoids are more aggressive tumours, but they are not as malignant as adenocarcinomas of the appendix. They are characterised by a predominant submucosal growth and are composed of signet ring-like cells and an endocrine component.

Histology and Clinicopathological Staging

Endocrine Tumours of the Distal Jejunum and Ileum
Endocrine midgut tumours are EC (enterochromaffin) cell tumours containing serotonin. A minority of tumours consist of cells containing enteroglucagon, and/or pancreatic polypeptide, tachykinin or peptide YY [15].

Clinicopathological Staging [15]
1. Well-differentiated endocrine tumour (carcinoid): Benign behaviour: confined to the mucosa-submucosa, non-angioinvasive, <1 cm in size
   1.1. Serotonin-producing tumour
   1.2. Enteroglucagon-producing tumour
2. Uncertain behaviour: non-functioning, confined to mucosa-submucosa, >1 cm in size, or angioinvasive
   2.1. Serotonin-producing tumour
   2.2. Enteroglucagon-producing tumour
3. Well-differentiated endocrine carcinoma (malignant carcinoid), low-grade malignant, deeply invasive (muscularis propria or beyond), or with metastases
   3.1. Serotonin-producing tumour with or without carcinoid syndrome
   3.2. Enteroglucagon-producing carcinoma
4. Poorly differentiated endocrine carcinoma (small-cell carcinoma), high-grade malignant
5. Mixed exocrine-endocrine carcinoma – moderate to high-grade malignant

Endocrine Tumours of the Appendix
Clinicopathological staging [15]
1. Well-differentiated endocrine tumour (carcinoid), benign behaviour, non-functioning, confined to appendiceal wall, non-angioinvasive
   1.1. Serotonin-producing tumour
   1.2. Enteroglucagon-producing tumour – uncertain behaviour, non-functioning, confined to subserosa, >2 cm in size, or angioinvasive tumour
2. Well-differentiated endocrine carcinoma (malignant carcinoid), low-grade malignant, invading the mesoappendix or beyond, and/or with metastases
   2.1. Serotonin-producing endocrine tumour with or without carcinoid syndrome
3. Mixed exocrine-endocrine carcinoma
4. Low-grade, malignant, goblet cell carcinoid

Clinical Presentation

Non-Functioning Tumours

Asymptomatic small endocrine tumours of the distal small intestine are discovered while searching for a primary in patients with newly discovered liver metastases originating from an endocrine tumour or incidentally during colonoscopy and intubation of the terminal ileum. Tumours of >1 cm in diameter are mostly malignant with metastases to regional lymph nodes and later to the liver and elsewhere [15]. Leading symptoms are intermittent abdominal discomfort existing sometimes for years and frequently misinterpreted as a functional disorder. Later, complaints worsen and can lead to intermittent intestinal obstruction due to angulation of the small bowel resulting from a desmoplastic reaction of the mesenterium and not due to the size of the tumour.

Appendiceal carcinoids are mostly detected incidentally during appendectomy. By obstructing the lumen they can produce appendicitis.

Functioning Tumours

Leading Symptoms: 4–10% of patients with liver metastases due to an endocrine tumour of the distal small bowel present with carcinoid syndrome [5, 8]. Signs and symptoms of carcinoid syndrome can include one or any of the following: flushing, diarrhoea, carcinoid heart disease, intermittent bronchoconstriction.

Associated Symptoms: Abdominal pain due to desmoplastic reaction of the mesenterium as a consequence of growth factors secreted by the primary and its lymph node metastases. Pellagra-like skin reactions (very rare).

Carcinoid Crisis: A rare but frequently fatal exacerbation of symptoms mostly during anaesthesia or surgery if patients are not under continuous somatostatin treatment. It includes severe and long-lasting flushing, hyper- and hypotension, severe bronchospasm and cardiac arrhythmias.

Diagnostic Procedures

Imaging and Staging

Abdominal ultrasound, contrast-enhanced CT or MRI of the upper and lower abdomen, octreotide scintigraphy (Octreoscan®), endoscopy, echocardiography, bone scan or spine MRI to prove bone metastases if Octreoscan® is negative.

Comments

No accepted TNM classification of endocrine midgut tumours exists. Once an endocrine midgut tumour is assumed by suspicious symptoms and/or the presence of liver metastases, the tumour load should be assessed before specific therapeutic measures are discussed.

Abdominal ultrasound is in most patients the initial imaging procedure showing either liver metastases or lesions previously misinterpreted as haemangiomas or focal nodular hyperplasia with a specificity and sensitivity of ~95%. If lesions are growing, correct diagnosis will be made by additional contrast enhanced CT or MRI followed by fine-needle biopsy. CT and MRI are complementary procedures with a similar sensitivity in detecting endocrine tumour lesions in the abdomen and their metastases [16–18]. Whereas liver metastases are easily detectable by ultrasound, CT and/or MRI, localisation of the primary within the distal small bowel and the presence of enlarged mesenterial lymph nodes with and without a desmoplastic reaction can be more difficult and requires experience.

After confirming the histological diagnosis by fine-needle biopsy, the next diagnostic procedure is ^{111}In-pentetreotide (Octreoscan®) which is positive in 80–90% of the patients with midgut endocrine tumours [19]. It eventually unmasks the primary and its regional lymph node metastases and additional tumour manifestations within lung, skin, breast, brain and other locations. Limitation of the technique is related to the size of the lesion (<0.5 cm) and the receptor density. In 10–15%, midgut endocrine tumours do not express somatostatin receptors. Additional CT scans or MRI of the positive areas should follow to estimate the size of the lesions. CT or MRI of the lower abdomen can visualize mesenteric lymph node metastases and desmoplastic reaction of the mesentery in the neighbourhood of the primary. Staging is important to judge the respectability of the primary.

In case of an unknown primary suspected to be present in the midgut, colonoscopy can identify a primary in the distal ileum, at the ileocaecal valve or in the right-sided colon. Small bowel enteroclysis is an established technique for the detection of midgut endocrine tumours [20]. CT and MRI enteroclysis [21, 22], capsule endoscopy or double balloon enteroscopy are promising new methods for identifying a primary in the distal small intestine, but their significance, specificity and sensitivity have not been evaluated so far. More importantly, it is unsettled whether or not localization of an non-symptomatic primary at these locations has therapeutic consequences if distant metastases are present. Surgeons argue that early

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removal of a primary (or of multiple small endocrine tumours) can prevent later occurring obstruction through slowly growing primaries or later occurring desmoplastic reactions. ^{18}F-dopa whole-body PET is a promising imaging procedure but can presently not be recommended as a routine diagnostic procedure since its sensitivity and specificity have not been investigated [23]. If spine and/or bone metastases are indicated by Octreoscan®, MRI is recommended to estimate the true tumour mass within the respective skeleton and to prove or disprove the risk of fracture. If Octreoscan® is negative, bone scan can be performed to exclude bone metastases but it is less sensitive than MRI. Echocardiography is mandatory in patients with carcinoid syndrome to confirm or to exclude coexisting carcinoid heart disease and to judge the severity of the manifestation.

Concerning the time interval of restaging investigations in patients with metastatic endocrine midgut tumours, accepted recommendations do not exist. Time intervals depend mainly on the growth characteristics of the tumour and should be longer (every half year) in slowly growing tumours. For economic reasons and outside prospective trials, ultrasound is frequently the method of choice to judge tumour load and to follow tumour growth.

Specific Biochemical Diagnosis
Chromogranin A, 5-HIAA in 24-hour urine.

Comments
Chromogranin A, a regulator of secretory granule biogenesis, serves as a sensitive but non-specific tumour marker in non-functioning and in functioning endocrine midgut tumours. Excessively elevated levels (>1,000 pg/ml) indicate an unfavourable prognosis [24]. 5-HIAA is an excretory product of serotonin. It serves as a sensitive tumour marker for diagnosis and follow-up in patients with carcinoid syndrome and should be estimated in two 24-hour urine collections. In patients with carcinoid syndrome treated with long-acting somatostatin analogues, a decrease in chromogranin A and urinary 5-HIAA mirror relief of symptoms as flushing and diarrhoea. Available assays for the estimation of chromogranin A may differ due to different antibody specificities [25]. This should be kept in mind if levels originating from different laboratories are compared. There is a slight increase in circulating chromogranin A in patients taking proton pump inhibitors and a marked increase in patients with type-A gastritis [26].

Falsely elevated 5-HIAA urine levels can be caused by foods such as avocado, pineapple, banana, kiwi, melon, plum, walnuts and by drugs such as acetaminophenol, coumarin, reserpine, nicotine, caffeine, melphalane, paracetamol, phenacetin, phenobarbital. Falsely low levels can be caused by ethanol, aspirin, MAO inhibitors, ranitidine and others.

Serotonin should not be used as a marker for endocrine tumours due to difficulties in reliable measurement [24].

Histopathology [27]
EC cell tumours are characteristically formed by rounded nests of closely packed tumour cells, often with peripheral palisading (type A). Tumour nests may reveal rosette type and/or glandular-like structures [called such because of a mixed insular plus glandular structure (type A plus C)] and have a more favourable prognosis. Abundant desmoplastic reaction is frequently observed. Mesenteric arteries and veins located near the tumour may be thickened and their lumen narrowed or occluded by elastic sclerosis leading to ischaemic lesions in the intestine. Most tumour cells are argyrophilic and react with chromogranin A antibodies. 30% of tumour cells are reactive for prostatic acid phosphatase. Identification as EC cell tumours is ascertained by staining for serotonin. In addition, some tumours contain PP/PYY-reactive cells and can be positive for glucagon/enteroglucagon. Most endocrine tumours of the appendix are serotonin-positive, a minority are glucagon-like peptide and PP/PYY-producing tumours.

Goblet cell tumours are characterised by a predominant submucosal growth. The mucosa is characteristically spared. Tumours are composed of small, rounded nests of signet ring-like cells resembling intestinal goblet cells expressing CEA. The endocrine component reacts with antibodies against serotonin, chromogranin A, enteroglucagon, somatostatin, and PP.

High Ki-67 and mitotic counts serve as a parameter for poor prognosis. In the absence of defined limits, Ki-67 >10% and mitotic counts ≥ 10/HPF may be used as indicative of aggressive endocrine carcinoma.

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Neuroendocrine Midgut Tumours

Part 2: Therapy

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Surgical Therapy

Curative Surgical Therapy

Surgery of Localized Disease in Midgut and Appendiceal Carcinoids

Midgut Carcinoids. Curative surgery should be intended for patients with midgut tumours and localised disease. The size of the primary does not correspond to the metastatic propensity. As microscopic tumour spread to lymph nodes and metastatic liver disease are seen even in patients with small (<1 cm) primary lesions at diagnosis, surgery of the primary should adhere to oncological principles. The surgical treatment of primary neuroendocrine carcinoids and loco-regional disease is not controversial [1–6].

Appendiceal Carcinoids. Appendiceal carcinoids can be cured by appendectomy if the tumour is located at the tip of the appendix *and* the tumour diameter is <1 cm. Right hemicolectomy is indicated if any of the following is present: tumour diameter >2 cm; angio- or neural invasion; location of the tumour at the base of the appendix; histopathological classification of the tumour as goblet cell carcinoid or mixed endocrine-exocrine (compound) tumour; a tumour between 1 and 2 cm in size *with* meso-appendiceal involvement and/or positive margins [6–8].

Surgery with Curative Intent of Midgut Carcinoids Metastatic to the Liver

Surgery is the only therapy with curative potential. Curative tumour resection, i.e., removal of the primary, regional lymph nodes, and resectable liver metastases, is possible in up to 20% of the patients [3, 9, 10]. Peri-operative mortality is <3% in most reports and post-operative 5-year survival rate is 61% and even higher in some

Table 1. Results of surgical therapy

Evaluation interval	Patient No.	Midgut tumours	Complete resection	Operative mortality, %	Operative morbidity, %	Median survival months	5-year survival	Reference
1984–1992	74	41/74	n.i.	2.7	24	not yet reached	54 (73%)[a]	12
1977–1998	170	90/170	75 (44%)	1.2	14	81	103 (61%)	13
1992–1998	34	12/34	15 (54%)	n.i.	6	not yet reached	25 (76%)	14
1983–1996	31	17/31	15 (75%)	0	30	n.i.	16 (80%)	15
1960–1989	64	64/64	21 (33%)	n.i.	n.i.	139	n.i.	16
	373	224/373 (60%)	126/224 (56%)				198 (53%)	

Most series give results for neuroendocrine tumours of different locations. The number of midgut tumours in each investigation is indicated, while results refer to all operated tumours. n.i. = Not indicated.

[a] 4-year survival.

centres (table 1) [9–16]. Surgical results depend on the experience of the centre [13].

Comments

Historical data indicate a survival rate of 8 years after the onset of symptoms [17–19]. In contrast, in patients with midgut carcinoids and liver metastases without surgical therapy, recent publications give a 5-year survival rate of 30% (range 13–54%), with a median survival of 3–4 years [9, 10, 14, 17, 18, 20, 21]. In interpreting the data, it has to be kept in mind that most published studies were retrospective analyses of pooled data from neuroendocrine tumours of foregut and midgut origin. In the reports cited, hindgut or appendiceal tumours are a negligible minority. In addition, published data are based mostly on single-institution experience, compared to historical controls [13]. No prospective randomized studies comparing medical therapy with surgery alone are available [9].

Curative intent in these studies was defined as the possibility of complete tumour resection (R0 or R1). As randomised prospective studies are not feasible in these rare tumours, selection bias may well improve the reported outcome [3]. Preoperative imaging may underestimate the number of hepatic lesions and, due to intra-operative findings, the initial curative intent results are changed to palliative surgery. As a prerequisite for these extended procedures, mortality should be <5% and morbidity <30%. In metastasized non-functional midgut tumours, distant metastases other than liver metastases should preclude liver surgery [9, 10, 16–27].

Palliative Surgery in Endocrine Midgut Tumours with Liver Metastases

Cyto-reductive surgery can be considered in all patients in whom 90% of the tumour can be safely removed [12, 14, 16, 28]. Surgical intervention can be divided into resection of the primary with loco-regional metastases or intra-abdominal debulking, resection of liver metastases alone or synchronous resection of primary and liver metastases. Compared to non-functional midgut tumours, survival is reduced in patients with functional midgut tumours, i.e. the carcinoid syndrome. However, such a difference is no longer evident after palliative surgery [13].

Intra-Abdominal Tumour Resection, Excluding Liver Metastases

Removal of the primary according to oncological criteria is indicated to prevent intestinal obstruction or ischaemic complications due to a fibrotic reaction of the mesenterium or compression of the mesenteric vein due to the tumour mass. As symptoms correlate with tumour mass, a reduction of tumour mass provides symptomatic relief in 70–100% of the patients. Intra-abdominal tumour resection (liver excluded) increased survival significantly from 69 (no treatment) to 139 months [16, 28].

Comments

Before transferring these surgical study data into practical recommendations it is worthwhile to consider some inherent problems of these investigations. In most studies reporting on palliative surgery in neuroendocrine tu-

mours, surgery is only one part of a multimodal approach and may be combined or followed by other means of cytoreductive therapy, biotherapy or systemic/regional chemotherapy. Thus, the effect of surgery alone is difficult to estimate. Furthermore, most reports give univariate survival analyses, which may be potentially misleading. Surgery is mostly done in patients with less extensive disease and thus prolonged survival of patients undergoing debulking procedures may be an aspect due to the stage of the tumour [10].

Surgery for Liver Metastases

If functional symptoms of the carcinoid syndrome cannot be managed by medical therapy alone, debulking of the hepatic tumour mass may be a life-saving procedure. Symptomatic response to hepatic resection is seen in up to 90% of the patients [11–13, 29], with a median duration of 19.3–45.5 months [11]. Most tumours progress/recur after palliative surgery (probability of progression/recurrence 84–91% at 5 years) [11, 13]. The median time to progression varies between 20 and 16 months [13] depending on the type of surgical intervention (complete or palliative resection). While historical data give a 5-year survival of 30% [17], 5- and 10-year survival after surgical intervention is 39–76 and 35–60%, respectively [10, 11, 13, 14, 19, 20, 26, 27], there is an indication that surgery can delay tumour progression [13, 27]. In addition, the reduction of functionally active tumour volume may increase the efficacy of adjuvant medical therapy [19]. As no difference has been observed in the outcome of functioning and non-functioning midgut tumours with liver metastases [13], resection of liver metastases should be considered for both tumour types.

Comments

Surgery should only be undertaken if at least 90% of the tumour mass can be removed successfully [3, 24, 26, 28]. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection [26, 29]. If the criteria for extensive hepatic surgery are fulfilled, mortality of palliative hepatic surgery should not be higher than 3–5% and morbidity about 30% [3, 19]. For palliation, metastatic disease should be confined to the liver [9, 24, 26]. It is unclear whether hepatic surgery should be performed only after prior surgery of the primary, synchronous with surgery of the primary or even in cases of non-resectable primaries [9]. With multiple liver tumours a two-stage liver resection strategy is an option [29]. Cholecystectomy should be undertaken synchronously during hepatic surgery to prevent the formation of gallstones during somatostatin analogue therapy and ischaemic complications of the gallbladder subsequent to chemo-embolisation [24].

As carcinoid heart disease has a profound effect on survival, it should be excluded or, if significant, treated surgically before tumour debulking is undertaken [10, 20, 24]. Specific anaesthesiological procedures and peri-operative somatostatin analogue infusion are indicated to prevent a peri-operative carcinoid crisis in patients with functional tumours [3, 24].

Synchronous versus Metachronous Surgery of Primary Tumour and Liver Metastases

There are no studies specifically comparing the effect of synchronous versus metachronous surgery of the primary tumour and liver metastases. Analyses of subgroups thus far indicate a better prognosis for patients with hepatic surgery after resection of the primary. However, the effect may well be due to selection bias, owing to a better prognosis in those diagnosed with localized disease [26].

Liver Transplantation

Liver transplantation may be an option in patients with metastases confined to the liver. Possible indications for liver transplantation: tumours not accessible by curative surgical therapy or major cytoreductive therapy; tumours not responding to medical therapy, and tumours that cause life-threatening hormonal symptoms. Aggressive, rapidly proliferating carcinomas should be excluded [12, 18, 30–37].

Comments

Experience with liver transplantation is restricted. Liver transplantation is fraught with a high peri-operative mortality and a high rate of recurrent disease. Improved methods for the detection of extrahepatic metastases are necessary before liver transplantation can be used, more frequently for patients with a large bi-lobar tumour burden. The timing of transplantation is not well-defined (i.e. whether patients with bulky, but stable liver metastases should be operated on or, preferably, when the disease is slowly progressive). Up to now, liver transplantation cannot be considered a routine therapeutic option.

Loco-Regional Ablative Therapy

Hepatic artery occlusion is directed at interrupting the arterial supply of highly vascularised neuroendocrine hepatic metastases. Initially ischaemia has been achieved by surgical ligation of the hepatic artery alone or in combination with intra-arterial chemotherapy. Due to the substantial peri-operative risk, mortality and rapid revascularisation with collateral formation and surgical hepatic artery occlusion is no longer recommended. The following options are available.

Selective (Chemo)-Embolisation

Selective embolisation of peripheral arteries induces temporary, but complete ischaemia. The procedure can be performed repeatedly. Survival rates in patients treated with arterial embolisation are between 59 and 64 months after the occurrence of the first symptoms of the carcinoid syndrome [38]. For chemo-embolisation the cytotoxic agent most often used is doxorubicin [39–44]. Indication: If surgery is not feasible, (chemo)-embolisation as an anti-proliferative treatment modality is an option. The combination of peripheral hepatic artery embolisation with local cytotoxic chemotherapy effectively reduces symptoms of an otherwise untreatable hypersecretion syndrome as well as symptoms caused by extensive tumour burden.

Comments

Complete or partial responses for symptoms, tumour markers and imaging occurred in 73–100, 57–91 and 33–35% of the patients, respectively [39–42]. The duration of symptomatic response and mean survival time were 14–22 and 24–32 months, respectively [39–42]. Whether survival is prolonged following chemo-embolisation has yet to be demonstrated.

All the results given include repeated chemo-embolisation procedures as deemed necessary or possible in an individual patient. Doxorubicin is the cytotoxic drug most often used [39–46]. Due to its hepatic clearance, doxorubicin-specific systemic side effects are decreased. However, toxic effects on the endothelium may reduce the feasibility of repeated chemo-embolisation.

Mortality (0–3.3%) of the procedure is low in experienced hands [39–44, 46]. As significant morbidity may result from this procedure, chemo-embolisation should be performed only in experienced centres.

Minor side effects such as nausea and vomiting (50–70%), right upper quadrant pain (50–60%), fever (30–60%), and elevation of transaminases (100%) are common [45]. This post-embolisation syndrome is often observed. Major observable side effects include: gallbladder necrosis; hepato-renal syndrome; pancreatitis; liver abscess, and formation of aneurysms. The procedure is contraindicated in patients with complete portal vein thrombosis and hepatic insufficiency [3, 39–44]. The following points remain unclear: whether chemo-embolisation is preferable to embolisation alone; timing of sequential (chemo)-embolisations, and choice of cytotoxic agents (e.g., doxorubicin vs. streptozotocin).

The only study which compared the results of hepatic resection with chemo-embolisation demonstrated prolonged survival in the former. However, selection bias may have influenced the outcome towards hepatic surgery [11].

Local Ablative Therapy

Radiofrequency ablation is now preferred to cryotherapy in most centres. There are no published data on laser-induced thermal therapy in neuroendocrine tumours.

Radiofrequency Ablation

Indication: Radiofrequency ablation is effective in reducing hepatic (or even extrahepatic) tumour mass in functioning and non-functioning midgut carcinoids. Depending on the tumour location radiofrequency ablation can be performed laparoscopically or percutaneously [47–49]. However, intra-operative ultrasonography is essential for staging [50].

Comments

Radiofrequency ablation can be used repeatedly within one metastasis [47]. Depending on the technique, tumour volume and tumour numbers are limiting factors. Symptomatic improvement could be achieved in 95% of the patients, a partial or significant decrease in tumour markers was observed in 65%, and median survival was 1.6 years after radiofrequency ablation in the largest series so far (34 patients with 234 neuroendocrine metastases). During a median follow-up of 1.6 years, 41% of the patients showed no disease progression [51]. In experienced hands mortality and morbidity are low (5%) [51]. The method can be used as an adjunct to surgical therapy [47–52]. No data exist on whether tumour volume reduc-

tion by radiofrequency ablation has any effect on survival.

Cryotherapy

Cryotherapy has been performed as an adjunct to open surgery but is now replaced by radiofrequency ablation in most centres. Few data on this technique in the treatment of neuroendocrine tumours are available [53–56]. A combination of radiofrequency ablation and cryosurgery may reduce the morbidity (coagulopathy and thrombocytopenia) of cryosurgery. Lesions of >3 cm may be treated more effectively by cryosurgery than by radiofrequency ablation [56].

Hepatic Radioembolisation

Radioembolisation is an experimental approach for hepatic metastases. Microspheres labelled with radioactive isotopes are used for hepatic embolisation and simultaneous local irradiation (brachyradio therapy) [58].

Alcohol Injection

Alcohol injection into liver metastases has been used for metastases of different tumours. Experience with midgut carcinoids is small [49].

Medical Therapy

Biotherapy

Somatostatin Analogues

Somatostatin analogues effectively improve symptoms in patients with the carcinoid syndrome. This antisecretory effect results in a reduction of biochemical markers in up to 40% [59–65] and in symptomatic improvement in 40–80% [66–72] of the patients. The duration of remission can be limited due to desensitisation or tachyphylaxis. The anti-proliferative effect of somatostatin analogues is unknown, and partial and complete response can be observed in fewer than 10% of the patients. Overall 30 patients with partial tumour regression have been reported so far. Stabilization of tumour growth occurs in 24–57% of patients with documented tumour progress before somatostatin analogue therapy [62, 63, 70, 73, 74].

Indication: Somatostatin analogues are clearly indicated for symptomatic therapy in functioning midgut carcinoids. Whether somatostatin analogues inhibit tumour growth or induce tumour reduction has still to be demonstrated.

Comments

Generalised conclusions should be interpreted with caution as most studies report on a mixed tumour cohort. Demonstration of progressive disease before initializing somatostatin analogue therapy has been a prerequisite in only a small number of studies. No placebo group was included in any of the studies. Most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials. Standardized schemes for evaluating therapeutic efficacy have not been universally employed and sufficient information on spontaneous tumour growth is lacking. Despite these shortfalls a consistent pattern of the efficacy of somatostatin analogues on symptom control can be demonstrated.

Tolerance to somatostatin analogues (nausea, newly developed diarrhoea, abdominal pain) and efficacy in an individual patient should be tested, by initiating therapy with short-acting analogues (e.g. octreotide). Thereafter, depot formulations, usually lanreotide-SR i.m. (every 2 weeks), lanreotide autogel s.c. or octreotide-LAR i.m. (every 4 weeks), are effective in suppressing symptoms. The dose for symptomatic treatment should be individually titrated. The efficacy of lanreotide and octreotide is comparable [65, 66, 70].

Minor, initial side effects, usually subsiding within a few weeks, are abdominal discomfort, bloating and sometimes steatorrhoea [61, 66, 67, 75]. In patients with steatorrhoea, pancreatic enzyme supplementation may be of help. Major side effects are the development of gallstones (about 50%, rarely symptomatic), and in a few cases persistent steatorrhoea resulting in malabsorption [75, 76]. To prevent carcinoid crisis, somatostatin analogues should be given during an interventional procedure in patients with carcinoid syndrome.

Serotonin antagonists and morphine analogues can influence diarrhoea due to the hypersecretion syndrome. As diarrhoea may be due to several different mechanisms (bile acid loss, bacterial overgrowth after abdominal surgery), additional treatment options, such as cholestyramine and antibiotics, should be kept in mind.

Interferon

Interferon is given for the same indications as somatostatin analogues, with the exception of carcinoid crisis. Control of symptoms, though with a delayed response, is comparable to somatostatin analogues. Thirteen trials (1986–2003) report data on 302 patients, 92% with midgut tumours. Ninety-five (287/302) percent of the patients were evaluable for tumour response to interferon

Table 2. Results of interferon therapy

Dose of interferon	Number of patients	Number of evaluated patients	CR	PR	SD	PD	Year	Reference
$3–6 \times 10^6$ U/day	29	29	–	3 (10%)	25 (86%)	1 (4%)	1986	76
$4.5–21 \times 10^3$ U/week	6	6	–	1 (16%)	2 (33%)	3 (50%)	1991	77
$10.5–28 \times 10^3$ U/week	8	8	–	–	6 (75%)	2 (25%)	1992	78
2×10^3 U/day	10	10	–	–	10 (100%)	n.i.	1996	79
$12–24 \times 10^3$ U/m^2/3/week	27	20	–	4 (20%)	n.i.	n.i.	1989	80
3×10^3 U/m^2/3/week	12	12	–	2 (17%)	9 (75%)	1 (8%)	1992	81
5.9×10^3 U/3/week	20	17	–	–	16 (94%)	1 (6%)	2003	82
$2–10 \times 10^3$ U/m^2/3/week	14	14	–	–	n.i.	n.i.	1987	83
3×10^3 U/3/week	24	20	–	–	15 (75%)	5 (25%)	1991	84
5×10^3 U/day	25	25	–	–	16 (64%)	9 (36%)	1995	85
$5–10 \times 10^3$ U/day	16	15	–	3 (20%)	12 (80%)	1 (7%)	1991	86
$15–30 \times 10^3$ U/week	111*	111	–	16 (15%)	74 (66%)	21 (19%)	1991	87
	302	287/302 (95%)	–	29/287 (10%)	185/253 (73%)	44/243 (18%)		

Number of patients with midgut tumours not indicated. CR = Complete regression; PR = partial regression; SD = stable disease; PD = progressive disease; n.i. = not indicated.

therapy (table 2) [76–87]. A biochemical and symptomatic response could be noted in up to 50% of patients, whereas partial remission of tumour volume could only be demonstrated in about 10% of the patients. Time to progression from start of therapy was a median of 12 months, while median survival ranged from 44 to 80 months in the 5 studies where these parameters were indicated. Due to a larger range of side effects, interferon is generally used as a second-line therapy for symptomatic control.

Comments

As with somatostatin therapy, generalized conclusions should be interpreted with caution as most studies report on a mixed tumour cohort. The demonstration of progressive disease before initializing somatostatin analogue therapy has been a prerequisite in only a small number of studies and sufficient information on spontaneous tumour growth is lacking. Furthermore, no placebo group was included in any of the studies. Most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials, and standardized schemes for evaluating therapeutic efficacy have not been used throughout.

There are no studies using a randomised, prospective, multi-centre approach including only tumours with demonstrated progress. Most trials used secondary endpoints such as tumour shrinkage or a decrease in tumour markers for the evaluation of drug efficacy. Endpoint analysis, i.e., time to progression or overall survival, was reported in only 5/14 trials. Despite these shortfalls a consistent pattern of the efficacy of interferon on symptom control can be demonstrated.

Pegylated interferon, i.e. a long-acting formulation of interferon, is available but still not registered. Comparative studies with subcutaneous interferon are required. Minor side effects are a flu-like syndrome, easily relieved by paracetamol, anorexia with weight loss and fatigue. Major side effects are hepatotoxicity, autoimmune reactions, depression and mental disturbances. Severe bone marrow depression is rare. Whether the combination of somatostatin analogues and interferon-α does increase therapeutic efficacy is still a matter of discussion [70, 89–91].

Systemic Chemotherapy

Results with systemic chemotherapy have been poor in patients with metastatic midgut carcinoids with response rates below 10% [92–96]. Therefore it is generally not indicated in patients with well-differentiated metastatic endocrine midgut tumours. Single-agent therapy with either adriamycin or 5-fluorouracil (5-FU) gave response rates of >20% [95], while dacarbazine was even less effective [97]. Furthermore, in these early studies,

reports of tumour therapy referred to less strict criteria than are used today and thus probably overestimated therapeutic efficacy. Results of polychemotherapy (5-FU, dacarbazine and epiadriamycin) have been reported by Bajetta et al. [98] with 50% partial remission, 25% stabilisation and 3% progressive disease in 12 patients with midgut tumours. In contrast, Ollivier et al. [99] achieved a poor response rate (1 of 9 carcinoid patients) with the combination of 5-FU, dacarbazine and leucoverin. The efficacy of systemic chemotherapy is best in fast-growing or poorly differentiated tumours. In fast-growing tumours cisplatin plus etoposide have proven to be effective [100–102]. The number of treated patients with midgut tumours is low and the overall 2-year survival in this aggressive subgroup of neuroendocrine tumours is still below 20%. High-dose paclitaxel recently has been used in patients with advanced neuroendocrine tumours with significant toxicity and lack of anti-tumour activity [103].

Somatostatin Receptor Radionuclide Therapy

Most endocrine midgut tumours express somatostatin receptors, especially its subtype 2 (sst2), on their cell membrane [104, 105]. Targeting these receptors with radio-labelled somatostatin analogues may be used not only for imaging but also for radiotherapy [106–110]. Since 1992, different analogues have been investigated for somatostatin receptor radionuclide therapy (SRRT) [111–119]. For metastatic disease with clear-cut tumour expression of sst2 proven by octreotide scintigraphy, two still unapproved analogues for SRRT show very promising results: [90Y-DOTA-Tyr3]octreotide [120–131] and [177Lu-DOTA-Tyr3]octreotate [132–135].

Treatment with these analogues in the context of phase-1 and -2 trials results in improvement in quality of life which is partly due to anti-secretory effects (many patients were refractory to therapy with non-radioactive somatostatin analogues). Partial and minor responses and stabilisation in patients with progressive disease at the start of SRRT occur in 12–34, 12–14, and 28–56%, respectively. SRRT yielded a median time to progression and median overall survival of 30 and >59 months, respectively, for [90Y-DOTA-Tyr3]octreotide treatment, and >30 months for a median time to progression and overall survival for [177Lu-DOTA-Tyr3]octreotate. However, the results for the latter are for much shorter follow-up periods. Thus, SRRT is indicated in metastatic endocrine midgut tumours with a positive octreoscan.

Comments

These radiopharmaceuticals are still under investigation and only available in a few centres. Treatment has to be in collaboration with nuclear medicine units since radiation protection and dosimetry are necessary. Side effects are minimal as long as limits for radiation doses to the kidneys and bone marrow are applied; the use of kidney protection by co-infusion of amino acids (lysine and arginine) allows the administration of higher therapeutic doses (within the same kidney limits), resulting in much higher tumour radiation doses [129, 130].

It is likely that combination therapy with the radionuclides 90Y and 177Lu will lead to better SRRT results for metastasised disease as has been shown in animal trials [134]. This is based on the complementary physical characteristics of these radionuclides resulting in a more effective treatment in case of small- and large-sized tumours combined.

Carcinoid Heart Disease

Screening for carcinoid heart disease should be performed on a regular basis [135–140]. If it develops, heart failure rather than metastatic disease may limit life expectancy [141, 142]. Medical therapy for heart failure should be introduced when necessary and cardiac surgery with valve replacement should be considered for patients with good performance status or before surgery for hepatic metastases [142, 143].

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Introduction

Hindgut neuroendocrine tumours are located beyond the watershed (i.e. middle colic artery) in the transverse colon. The vast majority of these are in the rectum with most being localised and thus having a good prognosis. The rarer more advanced neuroendocrine tumours of the rectum are usually aggressive and have a poor prognosis. Colonic neuroendocrine tumours of hindgut origin, strictly speaking, exclude the caecum, the most common site in the colon. The vast majority of colonic neuroendocrine tumours are diagnosed when the tumours are large in size and already invasive; hence their poor prognosis. Despite new WHO classification systems and nomenclature, the term carcinoid is still applied liberally in publications and histology reports.

Epidemiology

Rectal Tumours

The incidence of carcinoid tumours of the rectum is on the increase in clinical practice. In the latest subset (1992–1999) of SEER data, rectal carcinoids comprised 18.54% of all carcinoid tumours, and 27.44% of all gastrointestinal carcinoids. In the early SEER data subset (1973–1991) rectal carcinoids comprised 9.44% of all carcinoids and 15.33% of all gastrointestinal carcinoids [1]. This apparent increase is probably genuine but may, in part, be due to increased awareness and increased reporting of small polypoid carcinoid lesions removed at endoscopy. Other authors have also reported a higher incidence, which may reflect more aggressive endoscopic surveillance over many years of practice [2]. Rectal carcinoids have a threefold higher incidence in the black population compared to the white population (age and gender adjusted), in the USA [1]. Rectal carcinoids are diagnosed in relatively young patients, on average 56.2 years of age at diagnosis as reported in the SEER data set [1].

Colon Tumours

Colonic carcinoids are particularly rare, totalling 7.84% of all carcinoid tumours in the review by Modlin et al. [1]. Caecal tumours alone made up 3.47% of the late SEER subset, leaving a small number of true hindgut colonic tumours. Non-appendiceal colonic carcinoids have a predominance for a white ethnic background (black:white ratio 0.62 in the USA).

Prognosis

Rectum

The majority of rectal carcinoids are localised at diagnosis (75–85%). Distant metastases at diagnosis are uncommon, between 1.7 and 8.1% in review by Modlin et al. [1]. In the latest subset of SEER (1992–1999) only 1.7% of the 925 tumours had distant metastases, 2.2% had regional metastases (lymph nodes), but 14.4% were classified as unstaged. The shift towards unstaged or purely localised tumours may reflect the common use of en-

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doscopic resection for diagnosis and treatment of early disease.

Rectal carcinoids in the series by Modlin et al. [1] have an overall 5-year survival rate of 75.2–88.3%. If localised at diagnosis, the 5-year survival rate is 84–90.8%. The 5-year survival decreases to 36.3–48.9% with regional disease and 20.6–32.3% with distant disease. The vast majority therefore have a survival expectancy in excess of 80% at 5 years, comparing favourably with the overall survival for all gastrointestinal carcinoids of 67%.

Colon

The clinical picture at presentation and prognosis of colonic carcinoids contrasts greatly with rectal carcinoids. Colon carcinoids have the worst overall 5-year prognosis of any gastrointestinal tract carcinoid tumour, between 33 and 60% depending on specific site. (Small numbers in individual series and definition of colonic sites make good comparisons difficult.) These poor outcomes are best explained by the advanced stage at which the tumours are diagnosed. Only 16% of caecal tumours are localised at diagnosis in the latest SEER subset, although the figures have improved for the other colonic sites. More than 40% of caecal tumours have distant metastatic disease at diagnosis. Survival for sigmoid and other distal colonic tumours is considerably better, and has improved over the last decade, probably due to earlier diagnosis and treatment with easier access to high-quality endoscopy.

Histopathology

General Overview

The histological classification of 'carcinoid' tumours is initially according to differentiation and site. Well-differentiated carcinoid tumours (WHO group 1) are recognised by uniform cells, rare mitotic cells and no mucin production, arranged as submucosal nests and strands with less likely invasion of lymphatics, blood vessels perineum or muscularis propria. A similar histology is observed for well-differentiated endocrine carcinomas or malignant carcinoids (WHO group 2) though with a higher mitotic index, deep wall invasion, lymphoid and angio-invasion. Poorly differentiated small cell endocrine carcinomas (WHO group 3) display a solid structure with abundant central necrosis, severe atypia with high mitotic counts and Ki67 index, deep wall invasion often with evident invasion of blood vessels, lymphatics and perineum [3]. Mucin production may also be observed.

Endocrine tumours of the rectum and distal colon are mainly asymptomatic and thus considered non-functional. However, many produce enteroglucagon or pancreatic polypeptide-related hormones whereas serotonin production is observed infrequently [4, 5].

General Neuroendocrine Phenotyping

The cells may stain positively for neuron-specific enolase and PGP9.5, but the specificity of these markers is not absolute. The staining is diffusely cytosolic and nuclear, and may co-localise. Synaptophysin is associated with the small vesicles, and a sensitive marker for neuroendocrine tumours. Chromogranin A is localised to the secretory granules and is regarded as a powerful universal marker for neuroendocrine tumours [4, 5].

Specific Neuroendocrine Differentiation

As for any other sites of the gastrointestinal tract, endocrine tumours are categorised into well-differentiated and poorly differentiated. Two types of well-differentiated endocrine tumours have been identified in the hindgut, L-cell tumours and EC-cell tumours. Rectal tumours are usually L-cell tumours, producing glicentin-related products and PP-PYY peptides. The tumours may contain subsets of other neuroendocrine cells among the L cells. Argentaffin EC tumours with typical serotonin production are extremely rare in the rectum [4, 5]. Specific markers that should be performed when investigating rectal neuroendocrine tumours are those that identify the L cells. Markers such as glucagon-29, glucagon-37, glicentin, PYY and PP and their precursors are useful. Argentaffin staining and serotonin positivity is rare, but should be excluded [4–6]. Proximal colonic tumours (midgut) on the other hand are usually EC-cell tumours, and may produce serotonin. Metastatic disease may be associated with the carcinoid syndrome in EC-cell tumours. Poorly differentiated small cell carcinomas usually display extensive expression of synaptophysin and cytosol markers of neuroendocrine differentiation like PGP9.5 and neuron-specific enolase.

Other Markers

Prostate-specific acid phosphatase is expressed in 80–100% of rectal carcinoids [7, 8]. β-HCG may be expressed, and may relate to the malignant potential of the lesions [9]. Attempts to identify lesions of high malignant potential should include mitotic indexing and Ki-67 staining to determine the tumour proliferative index [10–12].

Clinico-Pathological Staging and Classification [4, 5]

Well-Differentiated Endocrine Tumour – Carcinoid. Benign non-functioning tumour of small size (<2 cm), within the mucosa or submucosa, without angio-invasion:
– Trabecular enteroglucagon-producing tumours.
– Serotonin-producing tumours usually in the caecum or rarely the colon.

Uncertain behaviour: non-functioning tumour within the mucosa or submucosa, >2 cm or with angio-invasion.
– Trabecular enteroglucagon-producing tumours.
– Serotonin-producing tumours usually in the caecum or colon.

Well-Differentiated Endocrine Carcinoma – Malignant Carcinoid. Low-grade malignant – deeply invasive or with metastasis.
– Enteroglucagon-producing carcinoma.
– Serotonin-producing carcinoma with or without syndrome.

Poorly Differentiated Endocrine Carcinoma – Small Cell Carcinoma. High-grade malignant.

Clinical Presentation

Rectal Tumours

They may present with blood per rectum, incidental findings on sigmoidoscopy or colonoscopy (asymptomatic), change in bowel habit, anorectal symptoms, i.e. tenesmus, discomfort or pain, non-specific complaints for example related to anaemia [8].

Very rarely do rectal tumours present with features of the carcinoid syndrome, as EC tumours with serotonin production are rare. In that unusual scenario the symptoms are similar to carcinoid syndrome of ileal origin.

Malignant metastatic disease may present with generalised symptoms of carcinomatosis, i.e. right upper quadrant abdominal pain, lethargy, wasting, anorexia and hepatomegaly. Bowel obstruction from rectal tumours is rare, but may occur with recto-sigmoid or sigmoid lesions, or advanced intra-abdominal disease.

Colon Tumours

Colonic carcinoids usually present late, being large tumours often with extensive metastatic disease when diagnosis is made. Patients therefore may present with non-specific complaints of malaise, lethargy, vague abdominal pains. More specific complaints may include altered bowel habit, right upper quadrant pain or weight loss. Clini-

cally, anaemia may be the first presenting feature. Hepatomegaly or a palpable abdominal mass may be present. Bowel obstruction is a possible presentation as an emergency. Usually the presumptive diagnosis of colonic adenocarcinoma is made until histology distinguishes the neuroendocrine nature. A tissue diagnosis is often made on colonoscopic biopsy.

Diagnostic and Staging Procedures

Biochemical

Serum chromogranin A is likely to be elevated and levels often reflect tumour burden [4, 5, 13]. For assessment of rectal carcinoid, analysis of pancreatic polypeptide and enteroglucagon may be useful. 24-Hour urinary 5-HIAA is often negative.

Serum acid phosphatase levels may be raised in prostate-specific acid phosphatase-positive tumours [8, 13]. β-HCG levels may be increased [8, 9].

Endoscopy

The majority of lesions in the rectum will be diagnosed endoscopically. Many lesions present as polyps, which are completely removed by snare polypectomy, with the diagnosis being made after histological studies.

Full colonoscopic assessment is required to exclude concomitant colonic disease as part of staging, and the possibility of synchronous carcinoma can be excluded. All other polyps should be removed or biopsied and marked for future surgical/endoscopic removal. The endoscopic features of rectal carcinoid tumours are well described [14], and these findings should be detailed and carefully reported. Central mucosal depression or ulceration suggests high metastatic potential [2].

Barium Enema

Barium enema may demonstrate colonic tumours where endoscopy is not first performed.

Endoanal/Rectal Ultrasound (EUS) [14–18]

EUS is very useful in assessing rectal carcinoid tumours pre-operatively. EUS can accurately assess tumour size, depth of invasion and the presence or absence of pararectal lymph node metastases. In conjunction with other investigative techniques and endoscopy this provides important information with respect to choice of therapy.

Ultrasound of Abdomen. Trans-abdominal ultrasound has low sensitivity for primary and local disease but is

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useful for assessing liver metastases and guiding biopsy of suspected lesions.

Computed Tomography (CT)/Magnetic Resonance Imaging (MRI). These are much more sensitive imaging modalities. Spiral CT is probably the most useful for staging the thorax, abdomen and pelvis, although MRI is probably superior for determining liver metastases [19]. Any lesions with evidence of malignant potential or extension require a pelvic CT/MRI to assess local advancement and involvement of other pelvic structures and respectability.

111-Indium Octreotide Scanning

As hindgut carcinoids are relatively uncommon, the sensitivity of 111-indium octreotide scanning is difficult to determine. However, it is useful for determining metastatic disease. Although detection of the primary tumour especially in the rectum with background activity can be difficult [20]. Additionally the high-grade hindgut lesions are often negative for 111-indium octreotide uptake, and other modalities have to be relied on to detect extra-pelvic disease.

Positron Emission Tomography (PET) Imaging

PET is currently considered experimental but may be of use with labels based on dopa for well-differentiated tumours and FDG for poorly differentiated tumours [21].

Bone Scintigraphy

Bone scintigraphy is important in assessing bone metastases [22].

Therapeutic Management of Hindgut Neuroendocrine Tumours

Surgery
Surgery for Rectal Carcinoid

The only guaranteed curative option is complete resection of a localised lesion. The benefit of radical surgery for more advanced disease is not clear. The size of the tumour provides the simplest way of predicting behaviour, although other features and patient factors should also be taken into consideration. Muscularis propria invasion on histology is an indicator of aggressive behaviour and, combined with size, provides the best prediction of behaviour. Other features of the tumour such as atypia and a high mitotic index are important. Imaging investigations may suggest locally or systemic advanced disease even prior to resection.

Lesions of <1 cm have a low risk of metastatic disease and should be completely resected endoscopically or by another local trans-anal technique [3, 23]. The risk of metastases has been estimated at less than 3% [24] for rectal carcinoids of <1 cm in diameter. Standard polypectomy is commonly performed, but in certain situations considered inadequate as argued by Matsushita et al. [15] especially if there is evidence of local invasion. Band-snare resection [25], aspiration lumpectomy [26] or strip biopsy [16] may be performed endoscopically where appropriate. Trans-anal resection using a variety of techniques and equipment offers the ability to resect higher lesions and a full thickness mucosal-muscular resection [27]. Aggressive surgery, such as anterior resections, carries a higher risk for the small lesions <1 cm than the metastatic potential of the lesion, whereas adequate local resection carries a comparatively low risk.

The outcome of a lesion between 1 and 2 cm is unclear. The metastatic risk is considered to be between 10 and 15% [24]. Some studies demonstrate no benefit with aggressive management [3]. Other authors have reported successful treatment with local or radical surgery, with disease-free survival in several cases [2, 28]. It may be possible to recognise tumours with particular atypia and high mitotic index before embarking on radical surgery. Assessment of tumours endoscopically and by endo-anal ultrasound should also guide treatment [14] in this group of patients.

Lesions of >2 cm have a significantly higher metastatic risk [1, 3, 29], considered to be between 60 and 80% [24]. Invasion of the muscularis propria is common in this group, and indicates a high metastatic potential. Local resection is unlikely to benefit patient survival with metastatic disease, but will provide local symptomatic relief [30]. Loco-regional resection may be argued to control local symptoms and pelvic disease without improving survival [25, 31]. Aggressive surgery has not been shown to improve the survival outcome in this group of patients. Studies are limited and the numbers are invariably small.

Occasionally small lesions may present with peri-rectal lymph nodes on radiology, suggesting a very aggressive metastatic tumour. In young patients aggressive surgery may be a reasonable option, although cure cannot be guaranteed. Multidisciplinary treatment options should be offered in conjunction with a specialist team.

Factors Favouring Metastatic Behaviour. Size >2 cm [19], high grade, poorly differentiated histology [3, 30], muscularis propria invasion [24], lymphatic and vascular invasion [31], angiogenesis [32], neural invasion, increased tumour proliferative index – mitotic index [12],

Ki-67 [10], endoscopic features [2, 15], endo-anal ultrasound features [14].

Effect of Surgery on Outcome. Any metastatic disease at diagnosis dictates prognosis. Survival is not altered by offering aggressive therapy to the primary lesion in these cases [3, 29, 30]. Surgery may improve symptom control of local complications associated with an advanced rectal tumour mass [30]. In patients with factors favouring metastatic disease, but no evidence of metastatic disease at diagnosis, the survival advantage of surgery is unknown. However, individual cases with high metastatic risk, but where subsequently metastatic disease was not evident, have been cured by aggressive surgery [30]. This is a difficult judgement which calls for further studies on predictors of metastatic risk. In patients with rectal carcinoids with low metastatic potential, aggressive surgical intervention carries significant risk, both in morbidity and mortality, and local resection alone is advocated.

Surgery for Colonic (Hindgut) Carcinoid Tumours

Carcinoid tumours of the colon present and are treated in a fashion similar to adenocarcinoma of the colon. Since the vast majority of tumours are in fact invasive through the muscularis propria and >2 cm, a localised colectomy with oncological resection of the lymph drainage is appropriate. These lesions may well be obstructive, and treatment is advised in most cases even if only palliative in nature. Advanced disease may, however, be considered different to adenocarcinomas, although the evidence is limited. Often patients will require surgical resection of the primary tumour because of the obstructive features, and the metastatic disease is treated as per protocol (see below). It is likely that more tumours may be diagnosed at an earlier stage by endoscopy. No particular evidence is available, but it should be advised that any invasive disease be resected surgically as is practiced with adenocarcinoma.

The Treatment of Advanced Metastatic Disease *(Amended from Midgut Experience)*

Surgical
Intra-Abdominal Debulking, Excluding Liver Metastases
Removal of non-functioning or functioning primary according to oncological criteria may be indicated to prevent intestinal obstruction or ischaemic complications due to tumour mass. Desmoplastic reaction is not as evident in hindgut carcinoid as compared with midgut carcinoid.

Surgery of Liver Metastases
Hindgut tumours rarely have functional symptoms hence resection for a hormonal syndrome is unlikely. There is no evidence for debulking resection for hindgut tumours; however, for bi-lobar liver metastases a two-stage liver resection strategy is an option. As for midgut carcinoid, most tumours recur after palliative surgery; however, there may be a delay of progressive tumour disease.

Surgery should only be undertaken if at least 90% of the tumour mass can be removed successfully. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection. If criteria for extensive hepatic surgery are fulfilled, mortality of palliative hepatic surgery should not be higher than 3–5% and morbidity about 30%. Metastatic disease should be confined to the liver.

It is unclear whether hepatic surgery should be performed only after prior surgery of the primary, synchronous with surgery of the primary or even in the case of a non-resectable primary. Cholecystectomy should be undertaken synchronously with hepatic surgery to prevent the formation of gallstones in patients requiring somatostatin analogue therapy and ischaemic complications of the gallbladder subsequent to chemo-embolisation.

Cytoreductive Therapy

Cytoreductive therapy of liver metastases may be indicated in patients with the carcinoid syndrome (rare for hindgut tumours) and insufficient symptomatic relief by medical therapy or symptoms due to rapid tumour progression. The symptomatic relief from hormonal hypersecretion correlates with the reduction in tumour mass. Cytoreductive strategies other than surgical therapy are indicated in patients with metastases not amenable to surgical resection and symptoms related to progressive liver disease. The following options are available:

Hepatic Artery Occlusion – Embolization. Treatment is directed at interrupting the arterial supply of highly vascularised neuroendocrine hepatic metastases. Hepatic artery occlusion may be indicated in patients with non-resectable bi-lobar hepatic metastases or in patients with untreatable hormonal hyper-secretion syndrome. Ischaemia can be achieved by hepatic artery ligation, alone or in combination with subsequent systemic chemotherapy or by selective embolisation alone or combined with intra-arterial chemotherapy (chemo-embolisation). There is no evidence to suggest benefit of chemo-embolisation alone vs. particle embolisation.

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Cryotherapy. Cryotherapy effectively reduces tumour mass in patients with intractable hyper-secretion syndrome. It can be performed repeatedly and does not preclude subsequent surgical debulking. Cryotherapy is mostly performed as an adjunct to open surgery. No data exist showing whether tumour volume reduction by cryoablation has any affect on survival [23].

Radiofrequency Ablation. Radiofrequency ablation is effective in reducing hepatic tumour mass in functioning intestinal carcinoids. Radiofrequency ablation can be used repeatedly. For tumours >4 cm diameter and more than 6 tumours, radiofrequency ablation is not recommended. The method can be used as an adjunct to surgical therapy. No data exist on whether tumour volume reduction by radiofrequency ablation has any affect on survival [33].

Hepatic Radio-Embolisation

Radio-embolisation is an experimental approach for hepatic metastases. Microspheres labelled with radioactive isotopes are used for hepatic embolisation and simultaneous local irradiation (brachy-radiotherapy).

Alcohol Injection

Alcohol injection into liver metastases has no evidence base for neuroendocrine tumours but may be useful for tumours <3 cm in size.

Liver Transplantation

Liver transplantation may be an option in patients with metastases confined to the liver. There would need to be robust determination that there is extra-hepatic disease. Consideration would be on an individual patient basis [34, 35].

Medical Therapy

Biotherapy
Somatostatin Analogues

Carcinoid syndrome is uncommon in patients with hindgut carcinoid tumours. As per midgut tumours, somatostatin analogues improve symptoms effectively in patients with the carcinoid syndrome. There is currently no evidence to suggest use of a somatostatin analogue as an anti-tumour agent for non-functioning hindgut tumours.

Interferon

Interferon may be tried within a prospective trial protocol for anti-tumour effect in patients with metastatic hindgut carcinoid, but there is no evidence base for current recommendation. Anecdotal evidence suggests there may be benefit of interferon in patients with tumours of low proliferative index.

Systemic Chemotherapy

Systemic chemotherapy is rarely indicated in slow-growing carcinoids. When used for progressive disease streptozotocin in combination with 5-fluorouracil or doxorubicin is most often used, but the response rate is <25%. The efficacy of systemic chemotherapy is best in fast-growing or poorly differentiated tumours. In these tumours cisplatin plus etoposide have proven to be effective [23].

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