OVERVIEW ARTICLE

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Guidelines for the Management of Gastroenteropancreatic Neuroendocrine Tumours (Including Bronchopulmonary and Thymic Neoplasms)

Part II—Specific NE Tumour Types

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Part II of the guidelines contains a description of epidemiology, histopathology, clinical presentation, diagnostic procedure, treatment, and survival for each type of neuroendocrine tumour. We are not only including gastroenteropancreatic tumours but also bronchopulmonary and thymic neuroendocrine tumours. These guidelines essentially cover basic knowledge in the diagnosis and management of the different forms of neuroendocrine tumour. We have, however, tried to give more updated information about the epidemiology and histopathology, which is essential for the clinical management of these tumours.

TUMOUR TYPES

1. Neuroendocrine tumours of the stomach

Epidemiology. The yearly age-adjusted incidence has been reported to be around 0.2 per 100 000 individuals. However, there are reasons to believe that gastric carcinoids are under-diagnosed. The ECL-cell carcinoid transpires to be the most common NE neoplasm in all the GEP organs (1).

Histopathology (2, 3)

Four types of NE neoplasms occur in the gastric mucosa:

- *Type 1:* Well-differentiated NE tumour, more commonly called ECL-cell carcinoid or ECL-oma. It has the characteristic features of a benign neoplasm (PI $<2\%$) (WHO group 1), is usually small and polypoid and restricted to the mucosa/submucosa. Often multiple lesions occur. Type 1 NE tumour is the most common NE neoplasm in the whole stomach; its relative incidence is 70–85%. The aetiology and pathogenesis of the Type 1 NE tumour is secondary to hypergastrinaemia and in humans it is closely related to autoimmune atrophic gastritis and pernicious anaemia.
- *Type 2:* Well-differentiated NE tumour or ECL-cell carcinoid associated with primary hypergastrinaemia as a manifestation of Zollinger–Ellison syndrome (ZES) as part of MEN 1. Mostly these tumours appear as multiple benign polyps. With a size >2 cm, a PI $>2\%$, and invasive growth they can exceptionally metastasize and then belong to WHO group 2.

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– *Type 3:* The second most common of NE gastric tumours; its relative incidence is 13–20%. It is a solitary lesion, appearing sporadically without predisposing factors. Normogastrinaemia is present. The Type 3 gastric tumours belong to WHO group 2, well-differentiated NE carcinomas with a PI >2%, >2 cm in diameter and infiltrative growth. Metastases often occur to both regional lymph nodes and the liver. The tumours consist of a mixture of ECL-, EC-, and gastrin cells. Due to excessive overproduction of histamine, an 'atypical carcinoid syndrome' can occur in association with these tumours.
– *Type 4:* This is a heterogeneous group of NE neoplasms, fortunately very rare, which belong to WHO group 3, poorly differentiated NE carcinomas. They are highly malignant and have often metastasized at the time of diagnosis. The primary tumour is often >4 cm in size, PI >15% and positive staining for synaptophysin may be the only indication of its NE nature.

Clinical presentation (4)

Small gastric carcinoids rarely give rise to symptoms and are detected incidentally or in patients with pernicious anaemia. Larger carcinoids may bleed. Occasional patients may complain of flush.

Diagnostic procedures (4)

Biochemistry. The following marker should be measured in gastric carcinoids: P-CgA, s-gastrin, urinary histamine metabolites, urinary 5-HIAA. Depending on which type of NE tumour is found, the biochemical findings will vary.

Imaging. Gastroscopy with biopsies is crucial in distinguishing between the different types, also indicating size and location of the primary tumour.

CT, EUS and SRS are important in the staging of the disease.

Treatment modalities

Surgery (5). Type 1 and 2 tumours (atrophic gastritis or Z-E/MEN-1):

– Few polyps, <1 cm in size: endoscopic resection and surveillance is recommended.
– Multiple polyps, >1 cm in size, extension to muscularis and/or repeated recurrences: surgical resection or antrectomy (reduces gastrin stimulation from antral G-cells) is recommended with regard to symptoms, function, extension, and histological type of tumour.
– Malignant development or recurrence despite local surgical resection: partial or total gastrectomy with lymph node dissection.

Type 3 and 4 tumours: Partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Somatostatin analogues. In cases of multiple 'ECL-omas' with atrophic gastritis or ZE/MEN 1: somatostatin analogues have been shown to induce regression of gastric tumours, type 1 and 2.

Chemotherapy. Chemotherapy should only be used in metastatic disease (mainly type 3). The combination of STZ plus 5-FU/doxorubicin is recommended in less aggressive tumours and cisplatin/carboplatin plus etoposide in more aggressive tumours.

Interferon. Can be tried in disseminated type 2 and 3 tumours (4).

Survival

The five-year survival rate was reported to be 69% for localized, 38% for regional, 21% for distant tumours, and 63% for all stages (1)

2. Neuroendocrine tumours of the duodenum

Epidemiology. The age-adjusted annual incidence is <0.1 per 100 000 individuals (1).

Histopathology (6, 7)

Five major types of NE tumours are identified in the duodenum:

– *Type 1:* Gastrin-producing tumours are most frequent and occur preferentially in the proximal duodenum. In one third of patients there is an association with ZES and MEN 1.
– *Type 2:* Somatostatin-producing tumours are second most common, have a predilection for the ampulla of Vateri and are often a component of neurofibromatosis. They exhibit psammoma bodies.
– *Type 3:* Gangliocytic paragangliomas are somatostatin- and pancreatic polypeptide-positive and are usually benign. They occur in the ampullary or peri-ampullary region.
– *Type 4:* Serotonin-, calcitonin or pancreatic polypeptide-producing tumours are rare, usually small, and benign and reside outside the ampullar region.
– *Type 5:* Poorly differentiated NE carcinomas are quite rare, highly malignant, and occur in the ampullar region.

Clinical presentation

The majority of patients present with dyspepsia suggesting duodenal ulcer. In occasional patients, anaemia may be a result of bleeding.

Diagnostic procedures

Biochemistry. The following marker should be measured in duodenal NE tumours: gastrin, calcitonin, CgA, U-5-HIAA. Patients with suspected von Recklinghausen's disease or ZES secondary to MEN-1 should have an extended biochemical work-up.

Imaging. Endoscopy with biopsies is crucial in distinguishing between the different types of duodenal carcinoids. CT, EUS, MRI, and SRS are recommended for staging of the disease and detection of metastases.

Treatment modalities

Surgery. Small duodenal NE tumours may be locally resected by endoscopy or surgery with good outcome. Patients with larger tumours should undergo pancreaticoduodenal resection (Whipple's procedure).

Somatostatin analogues. Somatostatin analogues can be used in patients with hormonal symptoms related to the tumour. The experiences are limited.

Chemotherapy. Chemotherapy should only be used in metastatic disease (mainly type III, IV and V) (depending on tumour aggressiveness). The combination of STZ and 5-FU/doxorubicin is recommended in less aggressive tumours and cisplatin/carboplatin plus etoposide in highly proliferative tumours.

Interferon. Can be attempted in disseminated tumours. However, the experience is limited.

Survival

Five-year survival rate for localized disease 66%, regional disease 28%, distant metastases 17%, and all stages 51% (1).

3. Neuroendocrine 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 the actual reported 1% incidence from autopsy series. Most of the 'occult' NE pancreatic tumours are probably so-called non-functioning (8–10).

NE pancreatic tumours are classified according to clinical symptoms into functioning and non-functioning tumours. The non-functioning tumours, i.e. the hormonally silent tumours, constitute the largest group, about 50%. Next in incidence are the insulinomas and gastrinomas, constituting 25% and 15% of the total, respectively; glucagonomas, VIP-omas, somatostatinomas, and serotonin-producing NE pancreatic tumours constitute the remaining 15%. NE pancreatic tumours can occur at all ages (median age at diagnosis 53 years) with an equal sex distribution. The primary tumour can be located in any part of the pancreas. About 15–30% of patients have MEN-1.

Histopathology (8, 11, 12)

The histopathological features are discussed in relation to functionality.

Insulin-producing NE pancreatic tumours. These are typically small, solitary, well-encapsulated tumours, which show no angioinvasion and fulfil the WHO criteria of group 1 well-differentiated NE tumours, which are completely benign. Their PI is close to 0. They show distinct immunoreactivity (IR) for insulin, sometimes IGF-2, and when amyloid deposition is present also islet amyloid polypetide (IAPP)-IR.

About 10–15% of insulin-producing NE pancreatic tumours belong to WHO group 2 and then the tumour size exceeds 2 cm, angioinvasion is present, and possibly also infiltration into neighbouring tissues. These tumours also express insulin-IR but the KI-67 PI is $>2\%$ but not $>15\%$. Amyloid deposition is rare. When metastases occur they first appear in peri-aortic and portal lymph nodes, and then in the liver.

Gastrin-producing NE pancreatic tumours. About 45% of the gastrinomas originate in the pancreas, but as many as 35–40% originates in the duodenum and about 10–15% primarily in periduodeno-pancreatic lymph nodes. They are very often multiple, and simultaneously located in the pancreas, duodenum, and regional lymph nodes. Gastrin-producing tumours can also occur in the stomach, the upper jejunum, the biliary tract, the lung, the liver, and the ovary. In about 50% of patients with ZES no primary tumour is found. A typical gastrin-producing NE pancreatic tumour is well delineated but not encapsulated, and not larger than 4 cm in size. The Ki-67 is often $>2\%$ but not $>15\%$ and the tumour belongs to WHO group 2, i.e. well-differentiated NE carcinomas. They may show IR for gastrin (-17 and -34). About 50% are multihormonal but symptomatically the hypergastrinaemia is predominant. At the time of diagnosis, 60–80% of the tumours have metastasized to regional lymph nodes or to the liver.

In about 25% of patients, the ZES is part of MEN-1. Then the gastrin-producing tumour is frequently found in the duodenum but may additionally also be found in the pancreas in regional lymph nodes.

Glucagon-producing, VIP-producing and somatostatin-producing NE pancreatic tumours. These are usually larger (>5 cm), non-encapsulated tumours, which show angioinvasion and have metastasized at the time of diagnosis. The Ki-67 exceeds 2% but not 15% and thus they belong to WHO group 2, i.e. well-differentiated NE carcinomas. All these tumours produce other hormones, e.g. pancreatic polypeptide, calcitonin etc. In about 10% of VIP-oma patients the source of VIP is outside the pancreas—particularly in children, a ganglioneuroma/ganglioneuroblastoma.

The term *non-functioning NE pancreatic tumours* refer to the fact that the patients do not present any hormone-

related symptoms. At IHC most of these tumours produce NE proteins, such as CgA, synaptophysin, pancreatic polypeptide, calcitonin, and biogenic amines. Ultrastructurally they are equipped with secretory granules and synaptic vesicles. Most of the tumours (60–70%) are large (>5 cm) and show signs of malignancy at the time of diagnosis. The Ki-67 PI can vary from <2% to 10%, rarely >15% and they belong to WHO group 2, i.e. well-differentiated NE carcinomas.

Clinical presentation (10, 13–17)

As mentioned above the tumours can be divided into functioning and non-functioning tumours. In functioning tumours, symptoms may lead to the diagnosis of a specific syndrome, such as insulinoma, gastrinoma, VIP-oma, or glucagonoma. A NE pancreatic tumour may also be found incidentally during surgery or in a surgical specimen, when an adenocarcinoma was suspected. Due to delay in diagnosis, non-functioning tumours are often larger and have metastasized. Patients may present with mixed syndromes, or change clinical syndrome over time. When located in the pancreatic head, jaundice may be present, due to bile obstruction.

Diagnostic procedures (10, 13–19)

Biochemistry. Measurement of the following markers is recommended: p-CgA, s-insulin, c-peptide, pro-insulin, s-gastrin, p-VIP p-glucagon, s-calcitonin., s-pancreatic polypeptide (PP), and p-somatostatin.

To establish the diagnosis of insulinoma a 24–72-hour fast is recommended. For the diagnosis of gastrinoma, measurement of basal and maximal gastric acid output is mandatory to distinguish from secondary hypergastrinaemia. A secretin test may support the diagnosis.

Determination of pituitary hormones, s-calcium and PTH is included in MEN-1 screening. For early detection of pancreatic involvement in MEN-1, a meal stimulation test with measurement of PP and gastrin can be performed.

Imaging and endoscopy (20–24). EUS eventually combined with biopsies is the most sensitive method to detect pancreatico-duodenal tumours. Furthermore, US, CT, and MRI can be used to detect the primary tumour and metastases. SRS is a routine investigation for both primary tumours and metastases. However, smaller lesions, especially insulinomas, can be difficult to visualize with this method. PET with 5-HTP or L-dopa can be an option for detection of small tumours. Portal venous sampling or secretin or calcium stimulated angiography may be used in patients in whom other preoperative procedures have failed.

Intraoperative US is mandatory to find smaller or multiple lesions (MEN-1) in the pancreas as well as liver metastases.

Treatment modalities (5, 9, 25, 26)

Surgery. The indications for surgery depend on symptoms, hormone production, tumour size, multiplicity, potential or manifest malignancy, and dissemination. In addition, surgery may be indicated to improve the therapeutic and symptomatic effect of medical treatment.

Preoperative localization and intraoperative US are of outmost importance for the surgical strategy.

The surgical procedure depends on the localization of the tumour(s): pancreatico-duodenal resection (Whipple's operation), distal pancreatic resection, tumour enucleation, or enucleation in combination with resection. Lymph node dissection is mandatory when malignancy is suspected. Total pancreatectomy should be avoided owing to development of severe diabetes. In most cases open surgery is performed but in selected cases laparoscopic surgery may be optional.

In rare cases where the tumour is not found at operation, blind pancreatic resection should be avoided. Instead, localization procedures should be repeated after a period to identify the tumour(s) before reoperation.

Since 90% of insulinomas are benign, patients with insulinomas should 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 gastrinoma triangle, radical operation may also be feasible (Whipple's procedure and lymph node dissection) in patients with multiple tumours.

In the other tumour types, radical surgery is the only treatment for cure, although it is rarely possible at the time of diagnosis. Palliative resections are indicated to relieve symptoms and facilitate medical therapy.

The indications for surgery in MEN-1 patients are more controversial, since these patients frequently have tumours in other endocrine organs and multiple tumours syn- and/or metachronously in the pancreatico-duodenal area. These patients are only occasionally cured of their pancreatico-duodenal tumours by surgery. However, we advocate more aggressive surgery in these patients, in order to avoid later development of malignancy (tumours >2 cm), to reduce symptoms related to excessive hormone production and to reduce tumour burden.

Chemotherapy (27–31). The combination of STZ plus 5-FU/ doxorubicin is considered as the primary medical treatment. In highly proliferative tumours (PI >20%), cisplatin/carboplatin plus etoposide is recommended.

Interferon (32–34). Alpha-interferon with or without somatostatin analogues can be used in low proliferating tumours after initial cytotoxic treatment.

Somatostatin analogues (35–38). Somatostatin analogues are particularly useful in patients with VIP-omas and glucagonomas, and they may be used in patients with gastrinoma and less aggressive non-functioning tumours.

They can also be attempted in insulinomas but caution has to be exercised, since hypoglycaemia may worsen due to suppression of glucagon and GH.

Symptomatic treatment. Proton pump inhibitors are first-line therapy in gastrinomas and control acid secretion in almost all patients. Diazoxide is used for controlling hypoglycemia in insulinoma or nesidioblastosis. Glucagon and corticosteroids might be used in exceptional cases.

In patients suffering from Cushing's syndrome, ketoconazole and metyrapone as well as bilateral adrenalectomy should be considered in patients not responding to other therapies.

Survival

The five-year survival rate was reported to be 60–100% for localized disease, 40% for regional, 29% for distant tumours, and 80% for all stages (8–10).

4. Neuroendocrine tumours of the ileum (classical carcinoids)

Epidemiology. The annual incidence of clinically overt cases has been reported to be 0.6 to 1.7 per 100 000 individuals. However, several carcinoids may remain 'clinically silent', as Berge & Linell 1976 observed a much higher incidence (8.7/100 000) in autopsy material, where most tumours were found in the terminal ileum (1, 39).

Histopathology (40–42)

As a rule an ileal carcinoid is a solitary, button-like lesion. When still small, it is confined to the mucosa/submucosa and non-ulcerated. Tumour lesions larger than 2 cm are notorious for having already metastasized to the regional lymph nodes in the mesentery at the time of diagnosis. The incidence of multiple ileal carcinoids is high ($>25\%$), and the number of such lesions can be great.

Ileal carcinoids are derived from the serotonin- and tachykinin- producing EC (Kulschitsky) cells. The predominating microscopic growth pattern is usually the insular type, but a mixed insular/glandular type is also quite common. By IHC the tumours are positive for serotonin and tachykinins as well as the common NE markers, notably CgA, Syn, NSE.

Most ileal carcinoids are histopathologically found to belong to the WHO group 2, 'well differentiated NE carcinomas' with a Ki-67 PI around 2%. Small carcinoids, detected incidentally or at an early stage, practically always are 'well differentiated NE tumours' (WHO group 1).

Clinical presentation (40, 41)

The tumours may present with local symptoms or with the carcinoid syndrome (Table 1), which occur with an incidence of about 0.65 per 100 000.

Local growth and metastatic infiltration in the gut wall and abdominal lymph nodes as well as peritumoural fibrosis can cause abdominal discomfort, bowel obstruction, and diarrhoea. The carcinoid syndrome consists of flushing, diarrhoea, bronchial constriction, right-sided heart failure, and elevated urinary 5-HIAA levels in the presence of metastases in the liver. When flushing is the first symptom, the abdominal infiltration and spread of disease may vary considerably at operation and may seem unrelated to the number and size of liver metastases. The tendency to produce fibrosis leads to involvement of cardiac valves, mostly the tricuspid valve, during the course of disease. Quite frequently bone metastases occur, which may give rise to local symptoms such as pain or fractures. More rarely, metastases occur in the lungs, brain, skin and breast.

Table 1

Carcinoid syndrome

Clinical presentation
Vasomotor symptoms (90%)
Flushing (facial and upper part of the thorax)
Telangiectasias
Chronic facial cyanosis
'Rhinitis'
Increased intestinal motility (80%)
Diarrhoea
Borborygmia
Abdominal pain
Heart failure (40%)
Endocardial fibrosis
Right-sided heart insufficiency
Pulmonary stenosis
Bronchial constriction (15%)
Asthma

Diagnostic procedures (40–43)

Biochemistry. The ileal carcinoids often have the most characteristic clinical features, including the carcinoid syndrome caused by overproduction of hormones and biogenic amines from disseminated disease.

P-CgA and urinary 5-HIAA are typically increased. Measurement of plasma/serum serotonin and p-5-HIAA in some centres may be a convenient alternative. Plasma substance-P and neurokinin A might be increased.

Imaging. Somatostatin receptor scintigraphy has become the gold standard for staging. US, CT, and MRI are useful for both diagnosis and follow-up and may reveal the primary tumour and in particular metastases. Small bowel follow-through is of value in patients with signs of intestinal obstruction. Capsule endoscopy might be an option in the future for detecting small primary tumours. PET with C11-5-HTP can be an option in special centres. Bone scan should be performed in patients suspected of having bone metastases. Right-sided valvular heart disease is diagnosed with echo-cardiography.

Treatment modalities

Surgery. The surgical treatment includes resection of jejunum, ileum, or ileocaecal resection. The margin for the resection should be at least 10 cm from the tumour. As the carcinoid tumours may be multiple, it is important that all tumours are included in the intestinal segment removed. Mesenteric resection must include central lymph node dissection and excision of other mesenteric or retroperitoneal tumour deposits. Liver metastases may be resected as well, if possible. Concomitant carcinosis and/or liver metastases do not prohibit intestinal and lymph node resection, as local symptoms may be relieved. Prophylactic cholecystectomy is controversial.

Somatostatin analogues. Somatostatin analogues are the primary medical treatment for most patients with small gut tumours and the carcinoid syndrome.

Interferon. α-IFN can be added to prevent further tumour growth in patients with low proliferating tumours. α-IFN can be the initial therapy, eventually in combination with somatostatin analogues when hormone-related symptoms are present.

Chemotherapy. Cytotoxic agents such as a combination of STZ plus 5-FU/doxorubicin or cisplatin/carboplatin plus etoposide are of limited value in low proliferating tumours, but may be applied in highly proliferative neuroendocrine ileal carcinoids.

Survival

Patients with lymph-node metastases only live for a median of 12 years. Patients with a small number of liver metastases have the same survival, whereas patients with extensive disease and carcinoid syndrome live for a median of 6–8 years after diagnosis. Carcinoid heart disease reduces survival to a median of 4–5 years.

The 5-year survival rate was reported to be 64% for localized, 72% for regional, 50% for distant tumours, and 61% for all stages. The lower figures for localized tumours might be explained by cases with problems related to bowel obstruction.

5. Neuroendocrine tumours of the appendix

Epidemiology. At present, the annual incidence is reported to be around 0.05 per 100 000 individuals. These figures show a marked reduction in incidence from the previously reported figures from 25 years earlier (1969–71), which were between 0.14 and 0.79 (1).

The marked reduction in numbers of 'appendectomia per occasionem' and autopsies performed during the last decade might explain the low detection rate of tumours in the appendix, which mostly have a benign and asymptomatic clinical course of disease. In contrast, tumours of other localizations have shown an increased frequency on the basis of improved diagnostic procedures.

Histopathology (44)

The typical lesion seldom exceeds 0.5–1.0 cm. Vascular invasion, perineural growth, local or distant metastases do not occur. In around 2% tumours >2 cm may metastasize to the regional lymph nodes. The Ki-67 PI is lower than 2%. Thus, the appendiceal carcinoid belongs to the WHO group 1, a 'well differentiated NE tumour'.

Their main NE hormonal products are serotonin and tachykinins but a fraction of their cells can display a distinct IR for the antigen S-100. This is a well-known IHC marker for nerves, Schwann cells, and the sustentacular ('satellite') cells in the adrenal medulla and its NE tumours, such as pheochromocytomas and paragangliomas.

A rare variant of appendix carcinoids is the so-called goblet-cell carcinoid (adenocarcinoid). The NE tumour is mixed with a highly differentiated (mucus-producing), non-NE adenocarcinoma of that type which appear as a primary tumour in other parts of the colo-rectal mucosa. It is controversial as to whether an appendiceal goblet-cell adenocarcinoid originates from the same cells as the usual carcinoid, thus just representing two different phenotypes of one and the same original neoplasm, or whether the lesion should be looked upon as a 'collision tumour', consisting of two histogenetically different neoplasms, which just incidentally happen to grow in the same anatomical structure. When metastases occur, most often in ovaries or peritoneum, they are from the goblet-cell component of the tumour.

Clinical presentation (45, 46)

NE tumours of the appendix are mostly detected incidentally during operation for suspected appendicitis, in a resected specimen, or at autopsy. The minimal risk of metastatic disease increases with the size and basal location of the primary tumour. Local or distant lymph nodes may be noted. Liver metastases are much less frequent than in small gut carcinoids.

Symptoms of goblet-cell carcinoids are mostly as for ordinary appendiceal carcinoids but may present as a disseminated tumour with ovarian metastasis, carcinosis, and ascites.

Diagnostic procedures

The diagnostic procedures are essentially the same as for ileal NE tumours. Lack of hormone secretion and CgA and U-5 HIAA are usually normal. However, serum CEA, CA 19-9 might be elevated.

'Goblet cell carcinoids' are mostly negative concerning NE markers and on Octreoscan®.

Treatment modalities (45, 46)

Surgery. The surgical treatment depends on tumour size, localization, histological aggressiveness, and presence of regional lymph node metastases.

Appendectomy is sufficient for:

- carcinoid tumours <2 cm located in the appendix tip without histological evidence of aggressiveness and without external serosal invasion or lymph node metastases.

Right-sided hemicolectomy with lymph node dissection is advocated in the presence of:

- carcinoid tumours >2 cm;
- tumours located at the appendix base;
- macroscopic local invasion;
- regional lymph node metastases;
- uncertain resection line according to the pathology report;
- histopathological features of aggressiveness (high PI, local invasion, adenocarcinoids).

When only appendectomy is performed at the initial operation, a right-sided hemicolectomy has to be performed at a second operation, if one of the criteria mentioned above is fulfilled.

Adenocarcinoid tumours (goblet-cell carcinoids) of the appendix are more malignant than ordinary appendix carcinoids. Therefore, right-sided hemicolectomy and lymph node dissection is indicated in all cases. Ovarian metastases can occur and require oophorectomy and resection of the omentum majus.

Medical treatment. Disseminated appendiceal tumours should be treated in the same way as ordinary small gut NE tumours with somatostain analogues as the primary medical treatment. Adenocarcinoid tumours should be treated similarly to colorectal carcinomas with cytotoxic agents.

Follow-up

Patients who have undergone appendectomy only need no follow-up (see surgical criteria). After hemicolectomy for carcinoids or goblet-cell carcinoids, patients should be followed-up annually for five years in the same way as radically operated small gut tumours.

Survival

The 5-year survival of metastasizing appendiceal carcinoids has been reported to be 81% for localized, 88% for regional, 31% for distant tumours, and 83% for all stages (1)

6. Neuroendocrine tumours of the colon

Epidemiology. The annual incidence is around 0.15 per 100 000 individuals (1).

Histopathology (47)

Most of the rare NE tumours arising in the colon are usually of the small-cell-carcinoma type. They are highly malignant, belonging to the WHO group 3, 'Poorly differentiated NE carcinomas' and behave like colonic adenocarcinomas. They may display the common NE markers (CgA, NSE, and in particular synaptophysin) but rarely any specific hormones. Instead—like their counterparts in the lung—they can overexpress the c-kit proto-oncogene, a tyrosine kinase, thus having some IHC features in common with gastrointestinal-stromal tumours (GIST). At the time of diagnosis, most have widespread metastases.

Clinical presentation (48)

The majority of colonic NE tumours present with similar symptoms to adenocarcinomas with obstruction and bleeding.

Diagnostic procedures

Biochemistry. P-CgA is increased especially in metastatic disease with liver involvement.

S-serotonin and urinary 5-HIAA are usually not elevated, except in the case of carcinoid tumours in the caecum.

Imaging. Colonoscopy with biopsy is the most reliable method to diagnose the primary tumour. US, CT, and MRI as well as somatostatin scintigraphy are useful in diagnosing liver metastases and larger primary tumours.

Treatment modalities (48)

Surgery. Carcinoids and poorly differentiated NE carcinomas in the colon are treated surgically like conventional colonic adenocarcinomas.

Somatostatin analogues. Somatostatin analogues can be used for a patient with progressive disease even in the absence of hormonal symptoms. Experience is limited.

Chemotherapy. Experience in this patient group is limited.

Interferon. Can be used in low proliferating disseminated tumours, but experience is limited.

Follow-up

After colonic resection, annual clinical follow-up is needed with colonoscopy, CT, and biochemistry.

Survival

The 5-year survival rate was reported to be 80% for localized, 50% for regional, 5% for distant tumours, and 60% for all stages.

7. Neuroendocrine tumours of the rectum

Epidemiology. The annual incidence for Caucasians is 0.35 per 100 000 individuals, and 1.2 per 100 000 for Afro-Americans (1).

Histopathology (49)

A typical rectal carcinoid is a small (often less than 1 cm in diameter), button-like, slightly protruding mucosal/submucosal lesion, not uncommonly discovered incidentally on rectal palpation during a routine health control. Histopathologically, the most common growth pattern variant is the trabecular one. Vascular invasion and/or perineural infiltration does not occur. A broad spectrum of neurohormonal substances are produced and includes serotonin, somatostatin, members of the glucagon-, tachykinin- and PP-families, as well as endorphins/encephalins. Clinical signs and symptoms of a release to the blood of all these NE message substances are rare or virtually absent. The Ki-67 pi is mostly below 2%. Thus, a typical rectal carcinoid belongs to the WHO group 1, a 'well differentiated NE tumour'. Metastases to regional lymph nodes, liver, lungs, and bones are extremely rare but the incidence increases with the size of the primary tumour and local infiltration.

Clinical presentation (50)

Half of the rectal NE tumours give local symptoms such as pain or bleeding. The remaining tumours/polyps are found (at routine examination, manually or) by endoscopy performed for other reasons.

Diagnostic procedures (50)

Biochemistry. P-CgA is usually normal, but may be increased in metastatic disease with liver involvement. P-serotonin and urinary 5-HIAA are usually not elevated.

Endoscopy and imaging. Endoscopy is the most reliable method to find the primary tumour. Staging of the primary tumour may be performed with rectal US or MRI. CT and somatostatin scintigraphy are useful to diagnose distant metastases.

Treatment modalities

Surgery. Small, benign tumours (<1–2 cm) may be removed by endoscopy or transanal endoscopic mucosectomy (TEM), and rarely recur if radically resected. Larger and/or malignant tumours are surgically treated as rectal adenocarcinomas. All patients are followed up by endoscopic surveillance.

Somatostatin analogues. Somatostatin analogues can be used for a patient with progressive disease even in the absence of hormonal symptoms. Experience is limited.

Chemotherapy. There is limited experience in this patient group. The same treatment should be advocated as given for rectal adenocarcinomas.

Interferon. There is limited experience in this patient group.

Follow-up

After colonic resection, there should be annual clinical follow-up with colonoscopy, CT, and biochemistry.

Survival

The 5-year survival rate was reported to be 91% for localized, 49% for regional, 32% for distant tumours, and 88% for all stages.

8. Neuroendocrine tumours of the thymus

Epidemiology. The overall age-adjusted incidence is 0.01 per 100 000 individuals with a male preponderance (1).

Histopathology (51)

Thymic NE tumours can show a continuous spectrum of differentiation, from a typical, well-differentiated carcinoid to a small-cell NE carcinoma. The proliferation capacity varies and is closely linked to the degree of differentiation. Thymic NE tumours are prone to invade surrounding tissues and to metastasize to mediastinal lymph nodes and also to distant organs, such as the liver and skeleton.

Clinical presentation (51, 52)

In one study, 71% were asymptomatic at diagnosis when detected as part of MEN-1. In another series, 30–40% were asymptomatic at diagnosis. In sporadic thymic NE tumours the carcinoid syndrome is very uncommon, whereas ectopic Cushing's syndrome can be present.

Diagnostic procedures (51, 52)

Biochemistry. Elevated levels of p-CgA, calcitonin, and PP can be found. In the case of suspected Cushing's syndrome, P-ACTH and urinary cortisol should be measured.

Imaging. Contrast-enhanced CT, MRI, and SRS can be used to detect the tumour and metastases. PET with C11-5-HTP is the most sensitive method in detecting small thymic tumours including ACTH-secreting tumours.

Treatment modalities (51, 52)

Surgery. Aggressive surgical treatment, including complete surgical excision with local lymph node dissection and postoperative irradiation, offers the best chance for prolonged survival. MEN-1 thymic NE tumours should be managed in the same way as sporadic tumours. Prophylactic thymectomy should be performed in association with parathyroidectomy, which may prevent the risk of later thymic NE malignancy.

Radiation therapy. External radiotherapy (RT) should be considered after non-radical surgery.

Somatostatin analogues. Somatostatin analogues should be used in patients with hormonal symptoms although the carcinoid syndrome is extremely rare ($<1\%$). Patients with

ectopic Cushing's syndrome may benefit from this treatment.

Chemotherapy. Depending on the proliferation index the combinations of STZ plus 5-FU/doxorubicin or cisplatin/carboplatin plus etoposide can be considered.

Interferon. Interferon alone or in combination with somatostatin analogues can be used in tumours with low proliferation.

Treatment of Cushing's syndrome. Ketoconazole and metyrapone as well as bilateral adrenalectomy should be considered in patients whose symptoms cannot be controlled by other therapies.

Survival

The 5-year survival rate was reported to be 60–100% for localized, 40% for regional, 29% for distant metastases, and 80% for all stages.

9. Neuroendocrine tumours of the bronchopulmonary system

Epidemiology. The annual incidence for typical and atypical carcinoids has been reported to be 0.6 per 100 000 individuals (1).

Histopathology and tumour biology (53, 54)

- *Typical carcinoid (TC):* The tumour is characterized by a highly organized 'carcinoid' architecture. Mitoses are rare (<2 per 10 HPF). The neoplastic cells express the retinoblastoma gene (Rb) product and normal p53 protein and show little loss of heterozygosity. More than 20% of the patients have second cancers before or after TC, indicating a genetic abnormality. TCs are not related to smoking.
- *Atypical carcinoid (AC*): Is similar to a typical carcinoid but with a lesser degree of architectural organization and cellular uniformity, shows greater mitotic activity (<10 per 10 HPF) and exhibits focal, discrete necrosis. About 20% of ACs lack the expression of the Rb gene product, about 25% express mutant p53 protein, and they show occasional LOH. Secondary malignancies are common.
- *Large-cell NE carcinoma (LCNEC)*: These may be difficult to differ from ACs but they have a greater mitotic activity (>10 per HPF). Necroses are more widespread and confluent. Often the 'carcinoid' structure is lost and they appear to be histopathologically malignant. LCNEC may be difficult to separate not only from SCLC, but also from poorly differentiated squamous and adenocarcinomas. Immunohistopathological NE markers are often weakly expressed. The Rb gene product is rarely present and most express mutant p53 protein. LOH is prevalent.
- *Small-cell lung carcinoma (SCLC)*: They are the most poorly differentiated of the NE tumours of the lung, and recognized as the classical oat-cell carcinoma. The mitotic activity is high (>80 per 10 HPF), and necrosis is widespread. Almost none express the Rb gene product, most express mutant p53 protein and LOH is frequent.

Clinical presentation (55)

About 50–70% of patients do have symptoms at the time of diagnosis. Symptoms are mostly one or more of the following: coughing, pneumonia, haemoptysis, and dyspnoea. The primary tumours with a peripheral location are more likely to be discovered incidentally. A 'bronchial wheeze', caused by incomplete obstruction of a bronchus, is reported to be the first sign in some cases. Some patients may present with Cushing's syndrome, acromegaly, or carcinoid syndrome.

Diagnostic procedures (56)

Biochemistry. The biochemical findings are dependent on the histological type of bronchial carcinoid. If a typical carcinoid is found, an increased value of the following tumour markers can be seen: p-CgA, s-serotonin, U-5-HIAA. If hormone-related symptoms are present, p-ACTH, U-cortisol, GHRH, GH, IGF-1, or histamine metabolites should be measured.

Imaging and endoscopy. Conventional X-ray of the chest may lead to diagnosis but CT and bronchoscopy are the best procedures to detect an abnormal mass in the chest. Since 80% of the typical bronchial carcinoids express somatostatin receptors, SRS may be informative. EUS with biopsies can be performed to demonstrate the primary tumour and mediastinal lymph node metastases. PET with 5-HTP or L-dopa can be used to detect small tumours.

Treatment modalities

All these medical treatment modalities can be applied in both TC and AC. Medical treatment of LCNEC and SCLC is not discussed in these guidelines.

Surgery. Surgery is the primary treatment for bronchial typical and atypical carcinoids. Some patients with stage 1 TC may be resected by broncho- or thoracoscopy, as these tumours have a benign behaviour. However, in all other cases lobectomy or pulmectomy with hilar and mediastinal lymph node dissection is required. Palliative resections, in particular in patients with hormonal symptoms, should be considered.

Radiation therapy. External radiotherapy (RT) can be considered after non-radical surgery in AC, and in metastatic disease in both AC and TC.

Somatostatin analogues. Somatostatin analogues can be used for symptomatic treatment in combination with cytotoxic agents and/or α-IFN. They can be especially useful in patients with Cushing's syndrome. Furthermore, they can be used as second-line treatment after cytotoxic

therapy in low proliferative tumours for tumour stabilization.

Chemotherapy. The combination of STZ plus 5-FU/doxorubicin is recommended in less aggressive tumours. In more aggressive tumours cisplatin/paraplatin plus etoposide is recommended.

Interferon. In patients with low proliferating tumours, α-IFN can be used alone or in combination with somatostatin analogues, or as second-line medical therapy after cytotoxic therapy for tumour stabilization.

Metastatic pattern and survival (1, 56)

TC: are indolent tumours with a low rate of recurrence. Metastases after adequate resection are rare (7%). Five-, 10- and 20-year disease-specific survival rates have been found to be 79%, 63%, and 39%, respectively.

AC: Distant metastases occur in 23%. Patients suffering from AC have been found to have 5-, 10- and 20-year disease-specific survival rates of 60%, 37%, and 28%, respectively.

Both LCNEC and SCLC show the classical metastatic pattern for malignant bronchial carcinomas, namely mediastinal lymph nodes, liver, adrenal glands, brain, and skeleton. Patients with LCNEC and SCLC show a bad prognosis with a 5-year survival rate of $<10\%$.

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