Surgical aspects of neuroendocrine tumours

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Introduction

The name neuroendocrine tumours (NETs), or the synonyme gastroenteropancreatic neuroendocrine tumours (GEP-NETs), is used to depict tumours with origin in neuroendocrine cells within the embryological gut and bronchopulmonary system, and comprise also tumours derived from pancreatic islet cells, as well as neuroendocrine cells at other endodermal sites such as the thyroid (medullary thyroid carcinoma), sympathetic and parasympathetic paraganglia. This contribution presents aspects on the surgical management of a majority group of NETs with origin in the gastrointestinal tract and the pancreas, which due to increased awareness and improved diagnostic methods have been increasingly detected during recent decades. The intestinal NETs, often named carcinoids, account for around two thirds of NETs, whereas pancreatic endocrine tumours (PETs) comprise around one third. The recent World Health Organisation (WHO) classification considers histological appearance, proliferation index, and mitotic index, to categorise the tumours into well and poorly differentiated NETs, and the clinical work-up also includes determination of hormonal excess and possible presence of a clinical syndrome associated with some lesions. Surgical treatment has been important in order to palliate hormonal symptoms and obtain favourable survival in patients with NETs. It has been increasingly evident that the different entities of NETs may have distinctly different requirements of management dependent on widely variable tumour biology, also related to tumour origin. The diagnostic methods with proliferation and genetic markers have proven of value to foresee prognosis and to select patients for surgery, and possibly avoid higher-grade malignant, poorly differentiated NETs, which have appeared to mainly require other forms of treatment, such as chemotherapy.

Carcinoids

Carcinoids occur within the gastrointestinal tract (55%) and the bronchopulmonary system (30%) [1]. The small intestinal carcinoids are the most common gastrointestinal carcinoids (45%), followed by carcinoids of the rectum (20%), appendix (17%), colon (11%), and stomach (7%) [2].

Gastric carcinoids

Type 1 carcinoids

The type 1 carcinoids, accounting for ~75% of gastric carcinoids, occur because of hypergastrinaemia due to absence of gastric acid secretion in patients with autoimmune chronic atrophic gastritis (CAG) (Fig. 1) [3–6]. The tumours are most common in women ~60 years of age and are often associated with vitamin B12 malabsorption (and pernicious anaemia in 50%). These carcinoids rarely cause symptoms and are most often accidentally revealed by endoscopy. The patients generally have multiple, small polyps (usually <1 cm) in the gastric body and fundus, developing in atrophic mucosa together with enterochromaffin-like cell (ECL) hyperplasia and dysplasia. The number of polyps is variable; some can be solitary and difficult to distinguish from adenopolyps, which also occur in CAG patients. Rare larger lesions may be ulcerated or bleeding. The majority of polyps are benign without deeper invasion beyond the submucosa, and have a low proliferation index. The incidence of regional lymph node metastases is low (<5%), distant metastases are exceptional (<2%), and disease-related death is rare.

Annual surveillance may be sufficient for polyps <10 mm [7–9] (Table 1). For larger tumours, endoscopic resection is recommended for up to six polyps, not involving the muscularis propria (investigated by endoscopic ultrasound [EUS]). Surgical excision is recommended for large, invasive tumours. Gastrectomy with lymph node dissection is performed in case of malignant development, serosal infiltration, spread outside the stomach, or recurrence. Antrectomy may cause regression of type 1 carcinoid polyps [9,10].

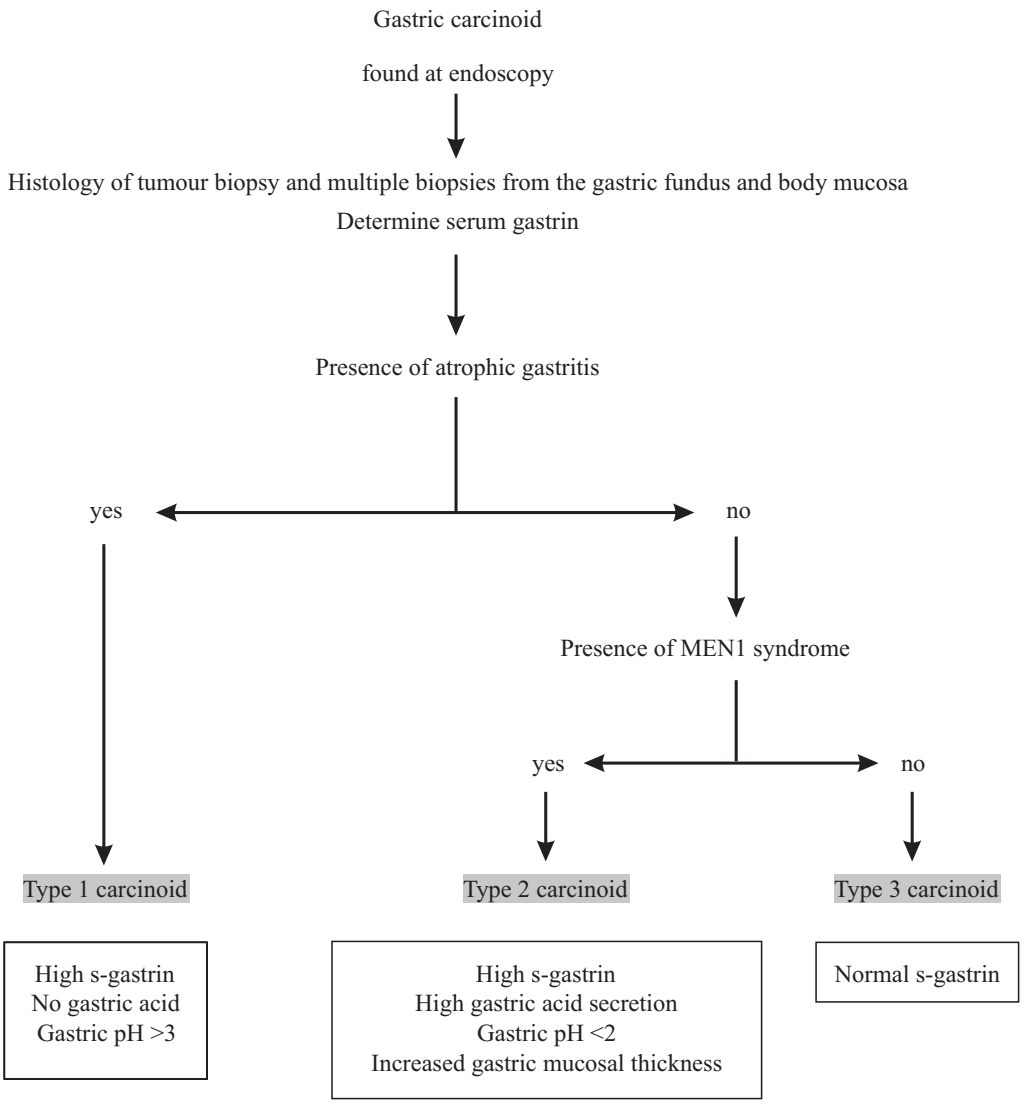

Fig. 1. Diagnosis of a gastric carcinoid found at endoscopy. Demonstration of atrophic gastritis in the gastric body mucosa is a key point, which allows classification as type 1 gastric carcinoid. If atrophic gastritis is not found the patient should undergo screening for the MEN1 syndrome (and ZES) (type 2 gastric carcinoid). If neither CAG nor MEN1 are diagnosed the patient has the more aggressive type 3, sporadic gastric carcinoid (without hypergastrinaemia). Redrawn from Delle Fave G, et al. (2005, Endocrine tumours of the gastrointestinal tract: Part II, Arnold R (ed), Best Pract & Res Clin Gastroenterol, Elsevier, pp. 659–73) with permission.

Follow-up with yearly endoscopy is needed, and treatment with somatostatin analogues may help prevent recurrence [6].

Type 2 gastric carcinoids

Type 2 gastric carcinoids account for ~6% of gastric carcinoids. ECL cell hyperplasia occurs in ~80% of multiple endocrine neoplasia type 1 (MEN1) syndrome patients with the Zollinger–Ellison syndrome (ZES), and 15–30% of MEN1-ZES patients develop carcinoids in the gastric body and fundus, and occasionally in the antrum [3–6,8,9,11]. The patients have increased gastric acid secretion and increased mucosa thickness rather than the atrophy of type 1 lesions (Fig. 1). Sporadic ZES patients may also have ECL cell hyperplasia, but very rarely (<1%) gastric carcinoids.

Type 2 gastric carcinoids are also often multiple and small (<1–2 cm), but more often larger and polypoid than type 1 tumours; occasional tumours may reach sizes of up to 4–5 cm or more [2,8]. Gastric biopsies from the surrounding mucosa show increased mucosal thickness and absence of atrophy. The malignancy rate is higher than in CAG-associated carcinoids, with lymph node metastases in ~30%, and liver metastases

Table 1
Carcinoids – indications for surgery (and recommended procedure) per site

Gastric carcinoids	
Type 1	Polyps <10 mm – surveillance
	Polyps >10 mm ($n=6$) – no invasion at EUS investigation – endoscopic mucosal resection
	Larger, invasive tumours – surgical excision
Type 2	Surgical excision (large/multifocal tumours – partial/total gastrectomy)
Type 3	Gastric resection + lymph node clearance, for tumours >2 cm (or atypical histology) – gastrectomy
Midgut carcinoids	Always consider removal of primary tumour, together with radical removal or debulking of mesenteric metastases, and liver metastases
Appendiceal carcinoids	
<1 cm	appendectomy
1–2 cm	generally appendectomy, if vascular invasion, mesoappendix invasion – consider hemicolectomy*
>2 cm	hemicolectomy
Goblet cell carcinoids	hemicolectomy (+ ooforectomy in females), for locally spread metastatic tumours – add surgical peritonectomy
Colon carcinoids	
(Incidental polyps <1 cm	endoscopic removal)
All other tumours	hemicolectomy/subtotal colectomy + lymph node clearance
Rectal carcinoids	
<1 cm	endoscopic excision (if muscularis invasion is excluded)
1–2 cm	investigate with transanal ultrasound or MRI absence of invasion or lymph node metastases – transanal local excision presence of invasion or metastases – anterior resection + mesorectal excision
>2 cm	anterior resection

*Hemicolectomy is recommended for all tumours located in the appendix base.

in 10–20% of patients [6,9,11,12]. The aggressive tumours with liver metastases have been more frequent with long-standing ZES. Poorly differentiated gastric NETs with local invasion, angio-invasion, and high proliferation rate have occasionally been associated with MEN1.

Surgical treatment aims to remove the source of hypergastrinaemia by excision of duodenal gastrinomas, together with clearance of lymph node metastases (see below) [12–14]. The gastric carcinoids are treated with surgical excision; large, or multifocal tumours may require partial or total gastrectomy with regional lymph gland resection [8,9,13,14] (Table 1). If hypergastrinaemia has not been reversed by surgery for gastrinoma, somatostatin analogue treatment may be used to reduce growth of the gastric carcinoids [6].

Type 3 sporadic gastric carcinoids

The type 3 carcinoids account for ~20% of gastric carcinoids and are most frequent in men aged ~50 years [2–6,8,9]. The tumours occur in patients with normal serum gastrin, in non-atrophic gastric mucosa without ECL-cell proliferation. A family history and determination of serum calcium are helpful in excluding MEN1 (Fig. 1).

The majority of sporadic gastric carcinoids occur in the gastric body and fundus as single, often large tumours, usually >2 cm (Fig. 2); occasional tumours occur in the antral or pre-pyloric region. Most tumours originate in ECL cells, but other cell types (EC cells) may be present and associated with less favourable prognosis. The majority of tumours infiltrate the muscularis layer and 50% invade the gastric wall completely. Regional lymph node metastases occur also with small tumours, altogether in 20–50%, and liver metastases eventually develop in ~75% of the patients [6,8,9,11,15]. The sporadic carcinoids can

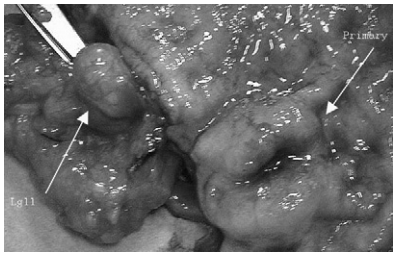

Fig. 2. Sporadic, solitary type 3 gastric carcinoid with lymph node metastasis removed by gastric resection. From Åkerström G, et al. (2006, Endocrine Surgery 3rd edition, Lennard TWJ (ed), Elsevier) with permission.

present with atypical histology, with pleomorphism, high mitosis rate, and high Ki67 index, and are generally larger (mean ~5 cm), more frequently invasive and have a worse survival rate [2,3,16].

The sporadic gastric carcinoids may in 5–10% of patients be associated with an "atypical carcinoid syndrome" [2,3,8,9]. The syndrome typically causes a patchy "geographic" flush, cutaneous oedema, bronchospasm, salivary gland swelling, and lacrimation, and is related to histamine release from the tumour cells. Urinary analysis of the histamine metabolite methylimidazol acetic acid (MelmAA) serves as a tumour marker, and the patients can have minimal elevation of urinary 5-hydroxyindol acetic acid (5-HIAA) values.

The sporadic gastric carcinoids should be treated with gastric resection and regional lymph node clearance [2,8,9,17,18] (Table 1). Tumours >2 cm or those with atypical histology or gastric wall invasion require gastrectomy. The overall 5-year survival has been ~50%, but only 10% in patients with distant metastases [3,5].

Type 4 poorly differentiated gastric NETs

Poorly differentiated gastric carcinoids are similar to small cell carcinomas of the lung, and occur mainly in elderly patients as highly malignant, aggressive tumours with extensive local invasion and generally spread metastases at diagnosis [3]. The tumours are often ulcerating or fungating, and generally large. The prognosis is poor with median survival of ~8 months while few individuals survive longer [6, 17,18]. Chemotherapy is the principal treatment and surgical debulking is only occasionally considered.

Midgut carcinoids

Midgut carcinoids occur most often at ~65 years of age, and are the most common cause of the carcinoid syndrome. The primary tumour is most frequently located in the terminal ileum, as a small, submucosal lesion [2,3,5]. Multiple, small tumours can appear localised in the nearby testine, due to spread within submucosal lymphatics. Mesenteric lymph node metastases are common also with small tumours, and microscopic spread is almost invariably present [19,20]. The mesenteric metastases are often larger than the primary tumour, and often induce marked mesenteric fibrosis, with tendency to contract the mesentery and obstruct the intestine [3,19,20]. Fibrosis around mesenteric metastases may cause fixation of the small intestinal mesentery to the retroperitoneum, with fibrous bands attaching to and ultimately occluding the horizontal duodenum, and with tumours in the lower abdomen occasionally also the ureters with resulting hydronephrosis [21]. More often, tumour growth and fibrosis encase the mesenteric root, and cause venous stasis and incipient ischaemia in segments of the small intestine.

Patients with midgut carcinoids have frequently had episodes of abdominal pain and diarrhoea before diagnosis. In ~30% of patients the diagnosis is revealed by surgery for intestinal obstruction. In other patients the disease is diagnosed by detection of liver metastases, sometimes together with features of the carcinoid syndrome. Extra-abdominal spread occurs to the skeleton, the lungs, as well as to mediastinal and peripheral lymph nodes, ovaries, breast and skin. The carcinoid syndrome develops in ~20% of patients with liver metastases, or occasionally in patients with only extensive retroperitoneal lymphatic spread, or ovarian metastases, where secretory products may by-pass detoxification by the liver. The *carcinoid syndrome* consists of flushing, diarrhoea, carcinoid heart disease due to right-sided valve fibrosis, and occasionally intermittent bronchoconstriction. The heart disease may be diagnosed by echocardiography, and thoracic surgery with valve replacement may sometimes be required before major abdominal surgery is undertaken.

Diagnosis

An increased 24-h urinary level of the serotonin metabolite 5-HIAA is specific for carcinoids, but is only present in patients with advanced disease, generally with liver metastases [21]. Plasma chromogranine A measurements can provide an early diagnosis and can be used to monitor disease progress and evaluate prognosis; however, it may be elevated due to other causes. Contrast-enhanced computed tomography (CT) can visualise mesenteric and retroperitoneal tumour extension, and reveal the relation with the mesenteric artery and vein (Fig. 3), and visualise liver metastases. Octreoscan can show spread to the liver and visualise extra-abdominal metastases.

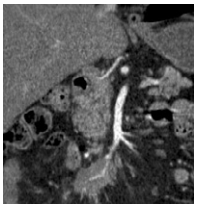

Fig. 3. CT image of mesenteric metastasis from midgut carcinoid growing along the mesenteric vessels.

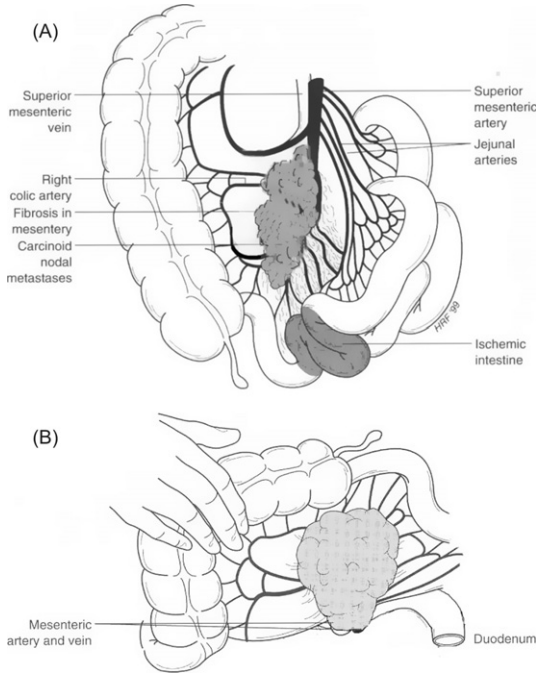

Fig. 4. Resection of midgut carcinoid primary tumour and mesenteric metastasis. (a) Mesenteric tumour may extensively involve the mesenteric root. (b) Mobilisation of caecum, terminal ileum and mesenteric root allows the tumour to be lifted, approached also from the posterior angle, and separated from duodenum, pancreas and main mesenteric vessels with preservation of intestinal vascular supply and intestinal length. From Åkerström G, et al. (2006, Endocrine Surgery 3rd edition, Lennard TWJ (ed), Elsevier) with permission.

Fluorine-18 dihydroxyphenylalanine positron emission tomography (PET) (^{18}F-DOPA-PET), 11C-5-hydroxytryptophan PET (^{11}C-5-HTP-PET) or especially ^{68}Ga-DOTA-octreotide-PET (not requiring in-house-cyclotron) can reveal metastases even more efficiently [21]. Needle biopsy of liver metastases with staining for chromogranine A and synaptophysin is used to diagnose carcinoids, and serotonin reactivity can verify origin in the midgut.

Midgut carcinoids have typical features at laparotomy, with a small ileal tumour and often larger mesenteric tumours surrounded by intense fibrosis [19–22]. The primary tumour should be removed by limited intestinal resection after dissection of lymph node metastases around the mesenteric artery and vein (Fig. 4). After grossly radical tumour removal, patients may be symptom-free for considerable time, but midgut carcinoids are tenacious, and recurrence with liver metastases occurs in a majority (~85%) of patients with long follow-up [22].

Treatment with long-acting somatostatin analogues (and interferon-α) can provide control of the carcinoid syndrome and improve life quality [21]. The mesenteric tumour and fibrosis tend to progress during medical treatment with increased vascular and intestinal entrapment and finally obstruction and compromised intestinal circulation. Some patients develop abdominal pain, weight loss, sometimes severe diarrhoea, and even cachexia due to incipient ischaemia and malabsorption [19–23]. Early prophylactic surgical removal of mesenteric metastases is recommended, since the disease will ultimately later often become inoperable [18] (Table 1). The mesenteric metastases can be dissected from the mesenteric vessels, with preservation of circulation (Fig. 4), and limited intestinal resection to avoid creating a short bowel syndrome.

Repeated surgery may become necessary if mesenteric metastases progress or were not removed at the primary surgery. Due to fibrosis between intestines, such operations are difficult and may cause fistulisation, intestinal devascularisation, or short bowel syndrome [22]. Patients with inoperable mesenteric metastases and symptoms of abdominal pain and malabsorption as a result of mesenteric vascular occlusion have, in our unit, occasionally been palliated by vascular intervention with stenting to restore blood flow in mainly the mesenteric vein.

Anaesthesia, surgery or other invasive procedures may trigger a carcinoid crisis in patients with the carcinoid syndrome, with resulting hypo- or hypertension, cardiac arrhythmia, excessive flushing, hyperthermia, or severe bronchospasm. This is prevented by routine preoperative administration of an intravenous somatostatin analogue (octreotide, 500 μg in 500 ml saline, 50 μg/h) [24].

Surgical removal of the primary tumour and mesenteric metastases can relieve abdominal symptoms, and reduce the risk for severe abdominal complications, and increase survival [22,23,25]. Survival depends on the extent of disease, with presence of liver metastases and carcinoid heart disease recognised as the most significant adverse prognostic factors [21,23, 25]. Patients with unresectable liver metastases (see below) have had ~50% 5-year survival, and survival has been ~40% with inoperable liver and mesenteric tumours.

Appendiceal carcinoids

Although found with decreasing incidence the appendiceal carcinoid is still the most prevalent appendix tumour [3–5,26–28]. Patients tend to be younger than patients with other carcinoids, and children may also

be affected. The mean age has been ~40 years, with female preponderance. Most tumours are located in the distal tip of the appendix (70%), and have rarely caused appendicitis; <10% are situated in the appendix base.

The majority (~90%) of appendiceal carcinoids measure <1 cm in diameter and are not situated in the appendiceal base. They are invariably cured by appendectomy (Table 1).

Right-sided hemicolectomy and ileocaecal lymph node clearance is done if regional lymph node metastases are revealed, and for all tumours >2 cm in diameter. For tumours measuring 1–2 cm a strict evidence base for management is still lacking, but for the majority of patients appendectomy is sufficient. Hemicolectomy should be liberally done for all tumours in the appendix base, since the location may confer higher risk for local recurrence. Invasion of the serosa is not related to lymph node metastases. Meso-appendiceal invasion >3 mm has been related to a 4% risk, and vascular invasion to a 30% risk for lymph node metastases, and is also an indication for hemicolectomy for tumours <2 cm [26–28].

Higher proliferative activity (Ki67 index) or high mitotic activity have not been demonstrated as prognostic indicators.

Appendiceal carcinoids metastasise to regional lymph nodes more often than to the liver. Metastatic disease has not been reported with tumours <1 cm, in 10% with tumour diameter of 1–2 cm, and in 31% of patients with tumours >2 cm. In the presence of massive liver or retroperitoneal metastases the patients may occasionally present with a carcinoid syndrome. Reported 5-year survival has been ~85% for regional disease, and 30% with distant metastases.

The **goblet cell carcinoid** or **adenocarcinoid** occurs at a higher age, ~50 years, and accounts for ~5% of appendiceal carcinoids. It has mixed endocrine and exocrine features [3,26–28]. The tumours are most often located in the mid-third of the appendix, and often present with a diffusely inflamed appendix. The tumours are aggressive; 10% of patients have ovarian or peritoneal metastases at diagnosis, sometimes appearing as mucinous adenocarcinoma. Secondary colonic cancer is not uncommon. The goblet cell carcinoids do not express somatostatin receptors, and cannot be visualised by Octreoscan. The tumour entity should be treated with right-sided hemicolectomy, and bilateral salpingo-oophorectomy is recommended in women (Table 1). For metastatic tumours, aggressive surgical peritonectomy and intraperitoneal chemotherapy (Sugarbaker procedure) may be required according to recent guidelines for colorectal carcinomas. The 10-year survival of goblet cell carcinoid has been ~60% [26].

Colon carcinoids

Colon carcinoids affect older persons, ~65 years of age [3,5,29–31]. The majority of tumours (50%) occur in the caecum, as large (mean diameter ~5 cm), exophytic tumours with general malignant symptoms (as colon adenocarcinoma), anaemia, or a palpable abdominal mass. Many tumours are aggressive with high proliferation rate, and regional lymph node metastases, as well as liver metastases, are common. Occasional tumours of the mid- or left colon may present with obstruction. Uncommon (<5%) right-sided tumours produce serotonin, and may cause raised urinary 5-HIAA values, and infrequently cause the carcinoid syndrome, rarely encountered with distal colorectal tumours. Only occasional tumours are positive on Octreoscan. Although attempts should be made to obtain radical resection by hemicolectomy/subtotal colectomy, and lymph node clearance, only debulking is generally possible (Table 1). Small polyps (<1 cm), which are incidentally found and removed on routine endoscopy, do not metastasise [31]. Overall 5-year survival has been ~40%, and has been slightly worse than for colon adenocarcinoma, and mainly related to tumour stage.

Poorly differentiated (small cell) neuroendocrine carcinoma occurs in the right colon, and has often been associated with synchronous adenoma or adenocarcinoma [5]. These tumours have generally metastasised at diagnosis and are mainly treated with chemotherapy. Palliative surgery has only occasionally been possible, and survival has been poor.

Rectal carcinoids

Rectal carcinoids occur most often at ~55 years of age and are rising in incidence, most likely due to increased detection [3–5,29,30]. The tumours are most often found on the anterior or lateral rectal walls above the dentate line. The majority (~60%) appear as small, solitary, yellowish submucosal polyps <1 cm in diameter, which are most often discovered incidentally by endoscopy in asymptomatic patients. Tumours <1 cm rarely have nodal metastases (>3%), and no distant spread; tumours of 1–2 cm in diameter have local and distant metastases in 10–15%; tumours >2 cm show local and distant metastases in 60–80% [31]. Muscularis layer invasion is more common with larger tumours, and correlates to metastatic spread to lymph nodes and the liver. Larger tumours may be ulcerated

and bleed, or appear with scarring of the mucosa and advanced local infiltration, and even peri-rectal fixation like adenocarcinoma. The large tumours may also be the cause of pain, tenesmus, changes in bowel habits, constipation and weight loss. The carcinoid syndrome is exceedingly rare with rectal carcinoids. Octreoscan is only occasionally positive in rectal carcinoids due to the common lack of somatostatin receptors. Chromogranine A may be elevated in some rectal carcinoids and may then reflect the tumour burden. Carcino-embryonic antigen (CEA) levels are raised in 25%, and prostate-specific antigen (PSA) in 80% of rectal carcinoids.

Rectal carcinoids <1 cm can be endoscopically resected, and excised specimens should be histologically examined to exclude muscularis layer invasion [3,31–34] (Table 1). Tumours between 1 and 2 cm should be investigated by transanal endosonography or magnetic resonance imaging (MRI), and can be treated with transanal local excision in absence of muscularis invasion or regional metastases. Presence of invasion or metastases supports aggressive excision, generally by anterior rectal resection with total mesorectal excision and regional lymph node clearance. Anterior resection is also recommended in cases with tumours >2 cm without general dissemination. For patients with metastatic tumours >2 cm resection may be indicated in patients with threatening obstruction, but without obvious survival benefit [31]. The prognosis has generally been poor in patients with distant metastases with an overall 5-year survival of around 30%.

Pancreatic endocrine tumours (PETs)

Insulinomas

Insulinomas are the most common functioning PETs (accounting for ~25%) and are often diagnosed at ~40–60 years of age [35]. The majority are sporadic and 5–10% are associated with the hereditary MEN1 syndrome. Symptoms occur during fasting or exercise, with sympathetic response (sweating, weakness, anxiety, tachycardia and hunger) and neuroglucopenic symptoms (anxiety, behavioural change, epileptic seizures, confusion, coma, sometimes visual disturbance, speech difficulties, and pareses). Patients learn to avoid hypoglycaemia by eating nightly meals but then tend to become obese.

Biochemical diagnosis is based on demonstration of hypoglycaemia (serum glucose concentrations <45 mg/dl, or <2.5 mM), and concomitant serum insulin >6 μU/ml (18 pmol/L), C-peptide >200 pmol/L, and pro-insulin >5 pmol/L. The diagnosis is verified by a fasting test revealing symptomatic hypoglycaemia and failure of appropriate insulin suppression, substantiating an autonomously secreting insulinoma [36–38].

Insulinomas are generally benign, small tumours, measuring from 6 mm to a mean of ~1.5 cm; 90% are smaller than 2 cm. Ectopic tumours have rarely (<1%) been found in the peri-pancreatic area. Spiral CT with contrast is used routinely to exclude liver metastases, and to reveal unusually large (>4 cm), possibly malignant, tumours, but has a low sensitivity for the typical small insulinomas. EUS is the most efficient preoperative localisation method with nearly 90% sensitivity for visualisation of insulinomas; only some iso-echogenic (6%) or pedunculated tumours fail to be visualised [39,40]. EUS can reveal relationships to the pancreatic or bile duct, and can also visualise the uncinate process if introduced in the horizontal duodenum. A selective arterial stimulation (SAS) test can regionalise an insulinoma to the head, body or tail of the pancreas by calcium injection into the major pancreatic feeding arteries, and concomitant insulin sampling in the hepatic vein [41]. The SAS test is now often proposed before primary operation when other localisation studies are negative, and is essential in case of re-intervention surgery. Insulin secretion from multiple areas of the pancreas revealed by the SAS test may indicate presence of multiple insulinoma or nesidioblastosis [42]. Angiography routinely performed in conjunction with the SAS test may sometimes reveal a characteristic vascular blush of an insulinoma. Intraoperative ultrasound (IOUS) is, together with complete pancreatic exploration and palpation at surgery, considered a necessary prerequisite for insulinoma surgery, and should be carried out by an experienced investigator (Fig. 5) [35,42]. The IOUS can visualise tumours larger than ~3 mm and guide the approach for safe dissection from the pancreatic and bile duct. It may also reveal a possible tumour bi-lobation, which is important to recognise at enucleation.

Combination of IOUS and palpation will, during surgery, detect nearly all insulinomas. The pancreatic tail and corpus is mobilised to allow bi-digital palpation, visual inspection, and IOUS investigation from both dorsal and ventral surfaces. The Kocher manoeuvre is used to explore the head of the pancreas, and the uncinate process is dissected towards the porto-mesenteric vein. Tumours centrally located in the pancreatic head or in the uncinate process may be difficult to palpate, and any tumour can be difficult to find in patients with previous pancreatitis. Most

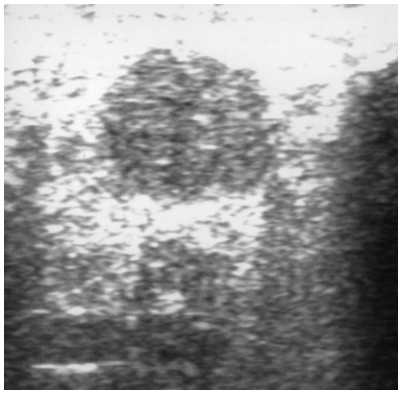

Fig. 5. IOUS revealing typical hypo-echogenic image of insulinoma. From Åkerström G, Hellman P. (2007, Neuroendocrine tumours, Öberg K, Eriksson B (eds), Best Pract & Res Clin Endocrinol & Metabol, Elsevier, pp. 87–109) with permission.

insulinomas in the head of the pancreas can be safely enucleated with cautious ligation of ductal structures. Some pancreatic head tumours adjacent to the pancreatic or bile duct may be safer enucleated towards a catheter introduced in the pancreatic duct via endoscopic retrograde choleducopancreaticography (ERCP) or duodenotomy, or in the bile duct after cholecystectomy. Pancreatico-duodenectomy is only seldomly needed for large or suspiciously malignant tumours. Also, pancreatic tail tumours may be enucleated, but distal resection is often chosen for distal tumours adjacent to the duct to minimise the risk of pancreatic effusion. Distal pancreatic resection can be made spleen-preserving for benign tumours, but this should be avoided with large or suspiciously malignant tumours, since the splenic hilum is often a common site of metastases.

Recently, laparoscopic removal of insulinoma with enucleation or more often tail resection, with confirmation of insulinoma localisation with EUS, has been increasingly performed in many centres. The operation may improve patient comfort and reduce the hospital stay, but with increased risk of pancreatic effusion (20–40%), and should be done for carefully selected lesions and be performed by expert laparoscopists [42].

If no insulinoma is found, blind distal pancreatic resection should not be undertaken, but the abdomen should be closed, and the patient subjected to further investigation to verify the biochemical diagnosis. Before reoperation, more extensive localisation procedures are applied, including the SAS arterial stimulation test, and, in Uppsala, 5-HTP-PET investigation, which also has a high sensitivity for the small insulinomas [35].

Adult nesidioblastosis

Adult nesidioblastosis due to diffuse beta-cell proliferation may cause symptomatic hypoglycaemia, with symptoms typically occurring 2 to 4 h after eating a meal rather than being related to fasting [42,43]. A meal test confirms the diagnosis by causing hypoglycaemia and inappropriate insulin and C-peptide levels, and is supported by a SAS test showing insulin secretion from multiple areas of the pancreas. Nesidioblastosis has been reported in patients previously subjected to bariatric surgery. The hypoglycaemia may be reversed by gradient guided 60–90% subtotal pancreatic resection, and a preoperative treatment period with diazoxide has been proposed to help determine the extent of the required pancreatic resection, and if surgery is necessary [44]. Cure has not been universal and is, apparently, sometimes less efficient in women; also, some patients may be palliated by medical treatment with calcium blockers.

Malignant insulinomas

Patients with endogenous hypoglycaemia may in ~5–10% have malignant insulinomas, with typically large primary tumours (>4 cm), and often metastases at diagnosis [35,38,42]. The patients may have severe hypoglycaemia and require continuous glucose infusion. Attempts at resection and even palliative debulking should be considered, since this may yield palliation and survival benefit. However, the majority of patients present with metastases to lymph nodes, liver, and lungs, and are scarcely available for tumour reduction, with survival depending on response to chemotherapy. Occasional patients have large, malignant insulinomas, with only slight insulin hypersecretion and less severe hypoglycaemia. These patients, especially, can be helped by surgical removal of the pancreatic tumour, and can in absence of metastases experience long-term survival or cure. The 10-year survival in patients with metastatic malignant insulinoma is ~30%.

Gastrinomas – Zollinger–Ellison syndrome (ZES)

Gastrinomas account for ~20% of functioning PETs. Most gastrinomas are sporadic, but ~25% occur in patients with the MEN1 syndrome [35,37,45]. ZES typically causes severe peptic ulcer disease with recurrent, atypically located, multiple and complicated ulcers, sometimes concomitant diarrhoea, and/or oesophagitis, and in 20% only diarrhoea. Fasting gastrin levels tend to be markedly raised, together with increased basal acid output (BAO) and low gastric pH.

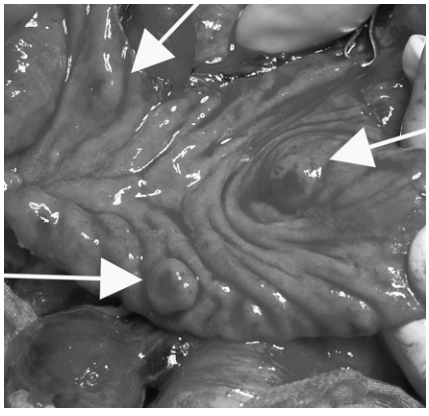

Fig. 6. Multiple duodenal gastrinomas in MEN1 patient.

Serum gastrin >1000 pg/ml and gastric pH < 2 is diagnostic of ZES. In patients with lower gastrin, a secretin test is required and is diagnostic with paradoxical rise in gastrin, >150 pg/ml over baseline, but 15% of ZES patients have a negative test [37]. The patients have to be off proton pump inhibitor therapy for this test. Atrophic gastritis is the important differential diagnosis causing high gastrin without gastric acid (gastric pH > 3 excludes ZES) [37,45].

Two decades ago, gastrinomas were recognised as large (often ~4 cm), malignant endocrine pancreatic tumours with early lymph node metastases (~45%) or liver metastases (~60%) and rapid progression. After 1989, duodenal gastrinomas have been recognised to be more common, causing ~70% of sporadic ZES and ~90% of MEN1-associated ZES (often with multiple tumours) (Fig. 6). The pancreatic gastrinomas are equally distributed in the entire pancreas. Duodenal gastrinomas are typically small submucosal tumours (often ⩽0.5–1 cm), most often found in the first and second part of the duodenum. The duodenal gastrinomas frequently develop lymph node metastases (~45%), while liver metastases occur late and in a minority of patients (~10%), providing a favourable interval for successful surgical removal. This tumour entity is likely to represent the primary tumour in patients with "primary lymph node gastrinoma", reported in up to 10% of patients with ZES, where the small primary tumour is not detected.

In patients with ZES, an investigation with CT (or MRI) is performed to visualise lymph node and liver metastases [35]. Octreoscan will often reveal lymph node and liver metastases from gastrinoma (in ~80%), and occasional large primary tumours. The small duodenal tumours are often not detected, and instead larger lymph node metastases around the pancreatic head may be mistaken to represent the primary tumour. EUS can reveal pancreatic and few larger duodenal gastrinomas, and often lymph node metastases, but not the smaller duodenal tumours. The SAS arterial stimulation test (or Imamura test) was first developed for visualisation of gastrinoma (with injection of pentagastrin), and can regionalise the tumour, and reveal possible liver metastases [46]. Even if diagnosis of the primary localisation is not possible, the ZES patients should be liberally submitted to surgery, since these patients will often have resectable duodenal gastrinomas, which require duodenotomy for visualisation. Occasional gastrinomas occur in the stomach, liver, bile duct or ovary [37].

After recognition that the majority of gastrinomas occur in the duodenum, the surgical cure rate in ZES patients has markedly increased [47]. The duodenal gastrinomas are best visualised at surgery by longitudinal duodenotomy with inversion of the lumen allowing careful palpation of virtually the entire duodenum (Fig. 6). The smallest duodenal submucosal tumours can be removed by mucosal dissection; larger tumours (>5 mm) require full thickness duodenal wall excision. Pancreatico-duodenectomy may be needed for pancreatic head gastrinomas and occasional larger or multiple duodenal tumours. Surgery should include clearance of peri-pancreatic lymph node metastases, and should also aim to remove resectable liver metastases [47,48].

Gastrinomas should always be considered malignant. Survival has been favourable in patients with duodenal gastrinomas and lymph node metastases, and removal of these metastases appears to limit further spread. Few patients with duodenal gastrinomas develop liver metastases (~10%) [47,48]. Less favourable prognosis is encountered in the presence of large pancreatic gastrinomas, liver or bone metastases, and very high serum gastrin. The small duodenal gastrinomas are slowly progressive with ~90% 10-year survival, whereas pancreatic gastrinomas have a poorer prognosis with 10-year survival rates of ~60%.

Glucagonomas

Glucagonomas are rare, accounting for ~10% of functioning PETs, and occur most frequently at ~50 years of age [35,49]. The patients have a typical pruritic skin rash, migratory necrolytic erythema, starting in the groin, with a tendency to migrate to extremities. They have high incidence of diabetes, and a marked risk of developing deep vein thrombosis and thrombophlebitis, and may also at an advanced stage develop severe cachexia. Diagnosis is often delayed, even in the presence of a typical skin lesion, and is settled by demonstration of raised plasma glucagon.

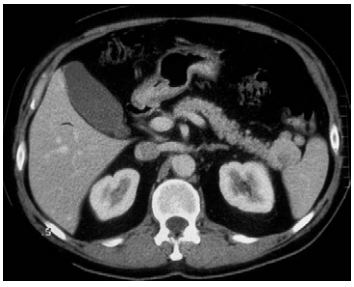

Fig. 7. CT image showing glucagonoma in pancreatic tail surrounded by lymph node metastases in the splenic hilum (easily misinterpreted to represent the primary tumour). From Åkerström G, Hellman P. (2007, Neuroendocrine tumours, Öberg K, Eriksson B (eds), Best Pract & Res Clin Endocrinol & Metabol, Elsevier, pp. 87–109) with permission.

Palliation and even healing of the skin lesion may be obtained by nutritional supplements and treatment with a somatostatin analogue. The patients require antithrombotic medication because of the high risk of thrombosis and pulmonary embolism during surgery.

Glucagonomas are typically slow-growing, distal pancreatic tumours, generally large in size due to late detection, often measuring between 4 and 10 cm (Fig. 7). The tumours are, in ~80% of cases, associated with regional lymph node metastases, sometimes mistaken to be the primary tumour. The patients are treated with distal subtotal pancreatic resection and clearance of regional lymph gland metastases. Disease progression is often slow even in the presence of metastases, and the patients may need sequential excision of lymph node or liver metastases during a long disease course, with often 5 years or more between recurrent lesions. The reported 10-year survival is ~50%.

Vipomas

Pancreatic vipomas occur most often in females ~50 years of age. Children may have vipomas of neurogenic origin, otherwise extra-pancreatic vipomas are exceedingly rare but may occur in the intestine, oesophagus, and the kidney [37,49]. The tumours secrete vaso-active intestinal polypeptide (VIP) causing the WDHA (watery diarrhoea, hypokalaemia, achlorhydria) or Werner–Morrison syndrome, characterised by severe secretory diarrhoea, acidosis and dehydration. Flushing may be present due to the vasodilatory effect of VIP, and some patients have hypercalcaemia.

The diagnosis is based on demonstration of raised serum VIP values. The patients risk severe dehydration and need intensive treatment with a somatostatin analogue and intravenous fluid- and electrolyte resuscitation. The tumours are frequently large and most often located in the pancreatic tail; 50% have metastases at diagnosis.

Attempts at surgical excision, with subtotal pancreatectomy, and resection or ablation of liver metastases, or even resection of lung metastases, are recommended. Routine cholecystectomy is often done to facilitate somatostatin analogue treatment.

The 5-year survival has been ~90% in absence of metastases, and ~60% with metastases.

Non-functioning endocrine pancreatic tumours

The non-functioning PETs have absent or low hormone secretion, or release hormone without symptoms [35,50–54].The majority has increased serum chromogranine A, or pancreatic polypeptide (PP) (revealed in 50–70%), fewer have raised calcitonin values, or even low serum values of insulin/pro-insulin, or glucagon without symptoms [35,53]. Non-functioning tumours are increasing in incidence and constitute ~60% of PETs. Although accounting for a minority of pancreatic tumours (3–5%), they are important to recognise because of markedly more favourable survival than pancreatic adenocarcinoma. The non-functioning PETs are most common at ~50–60 years of age. They may also be discovered as unusually large tumours in younger individuals without the malignant cachexia typical of pancreatic carcinoma [35,51,52].

Diagnosis is obtained by demonstration of vascular blush on contrast-enhanced CT, and positive Octreoscan, raised serum levels of chromogranine A or serum PP, or by ultrasound-guided fine or semi-fine needle biopsy stained with chromogranine A or synaptophysin.

The non-functioning PETs are most common in the pancreatic head (60%), but may also be found in the entire pancreas. The patients may have jaundice, or pain due to local growth or pancreatitis, though jaundice can also be absent with large pancreatic head tumours. Local invasion may affect the ventricle, or the duodenum, causing obstruction or bleeding, and ultimately the mesenteric vein may be occluded by tumour or thrombosis with resulting portal hypertension and an increased tendency to gastrointestinal bleeding. Also, the celiac, the hepatic, and the mesenteric artery may be involved by the tumour [51,52].

The majority of non-functioning PETs represent well differentiated endocrine carcinoma (WDEC) with generally slow growth and low proliferation index (<5%), and often late spread with metastases [53].

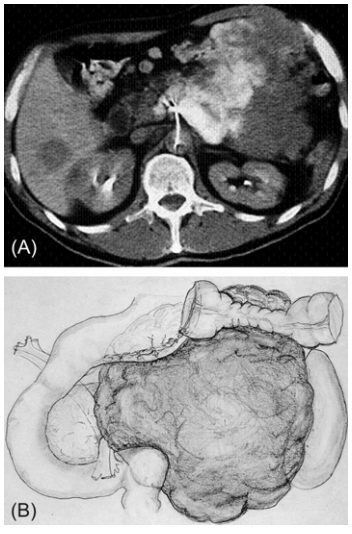

Fig. 8. (a) CT image and (b) drawing of non-functioning pancreatic head tumour with growth in transverse colon. The coeliac-hepatic artery, mesenteric artery, and porto-mesenteric vein could be dissected from the tumour capsule. From *World J Surg* **24**, Hellman P et al., Surgical strategy for large or malignant endocrine pancreatic tumors, p. 1353–7, © 2000 Springer Science and Business Media, with kind permission.

A minority (10–15%) have poorly differentiated carcinomas (PDEC), with high Ki67 proliferation and mitoses rates, and often rapid progression with lymph node and liver metastases.

Surgical removal of the tumours is recommended to reduce the risk for gastric outlet obstruction and portal vein involvement, and to facilitate chemotherapy. Surgery may also be undertaken in the presence of low volume liver metastases. Also, large PETs can be removed but may sometimes, in the presence of portal vein involvement, require use of a vein graft (from internal jugular, saphenous, or splenic vein) to restore porto-mesenteric vein patency [51,52,54]. Tumour growth involving the larger mesenteric or coeliac axis arteries is most often a contraindication for surgery, but central axis arteries can sometimes be free-dissected (Fig. 8). However, extensive mesenteric artery dissection may denervate intestinal plexa and cause severe diarrhoea, with great impairment of the patient's general condition.

The rate of metastases varies from 60–90%. Results of surgery for large non-functioning tumours have reported 5-year survival of up to 80%, and 10-year survival of ~50% [51–54]. Survival advantage has been evident in absence of liver metastases or if metastases have been resected, whereas only debulking surgery with the remaining tumour has been associated with poor survival. The operative mortality of aggressive surgery has varied from 0–15%, with higher risks in patients with involvement of mesenteric or celiac axis arteries [51]. Patients with poorly differentiated PDEC lesions tend to have huge, disseminated tumours and rarely benefit from surgery.

Pancreatic endocrine tumours associated with MEN1

Clinical pancreatic involvement occurs in 30–75% of MEN1 patients, and the syndrome is present in ~25% of ZES, and in ~5% of insulinoma patients [35,53,55]. Non-functioning PETs occur in ~50% of MEN1 patients. Tumour disease accounts for the majority of deaths in MEN1 patients with pancreatic malignancy as the major death cause [56,57]. The MEN1 pancreas appears with numerous micro-adenomas but only a few will grow to clinically relevant tumours [55,58].

Surgery is invariably recommended for MEN1 insulinomas, as well as rare vipomas or glucagonomas [55,58], but has been controversial with MEN1 ZES due to rare long-term cure [45,59]. However, the high risk of metastases in the presence of ZES supports surgery for prevention of malignancy [58]. Non-functioning PET may be diagnosed earlier by biochemical markers (pancreatic hormones and chromogranine A), and surgery is proposed before development of a hormonal syndrome, and in our opinion when EUS [60,61] reveals non-functioning tumours larger than ~10 mm, since tumours larger than this have been associated with a significantly increased metastasis rate [55,61–63]. The active management is supported by an apparently reduced death risk and metastasis rate in operated patients, but entails a risk of causing diabetes, and evidence for effect on survival is lacking [64–68]. Liberally applied pancreatic surgery has to have minimal morbidity, since long survival may also be obtained without surgery.

MEN1 patients are generally subjected to distal subtotal ~80% pancreatectomy together with enucleation of tumours in the pancreatic head (Fig. 9) [55, 58,62]. Duodonotomy is carried out in patients with raised gastrin or ZES to identify and remove duodenal gastrinomas (Fig. 9). Pancreatico-duodenectomy may be required in MEN1 patients with large pancreatic head or duodenal tumours, and has sometime been proposed for efficient eradication of MEN1 ZES [66]. However, pancreatico-duodenectomy is not routinely recommended for MEN1 ZES because of higher operative risks with this procedure and subsequent difficulties in treating tumour recurrence. An increased risk of ascending infection via the hepatico-jejunostomy in

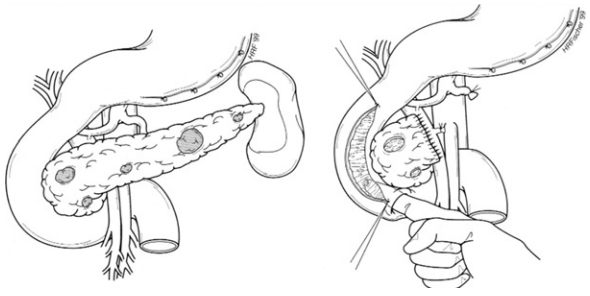

Fig. 9. The commonly applied (80%) subtotal distal pancreatectomy in MEN1 patients (N Thompson procedure), combined with enucleation of tumours in the pancreatic head. Duodenotomy is undertaken in patients with raised serum-gastrin. From Skogseid B, et al. (2001, Surgical Endocrinology, Doherty GM, Skogseid B (eds), Philadelphia: Lippincott Williams & Wilkins, pp. 511–25) with permission.

patients subjected to pancreatico-duodenectomy may later be an obstacle to embolisation and ablation of liver metastases.

Reoperation for new pancreatic tumours may be required during follow-up of MEN1 patients and has, in our experience, been uneventful. Total pancreatectomy may occasionally be needed for large malignant tumours, but has only rarely been needed in our MEN1 patients.

Liver surgery

Liver metastases in patients with carcinoids or PETs should be evaluated for surgical resection or local ablation to reduce the tumour burden, palliate hormonal symptoms, and to increase survival [25,67–74]. A majority of patients have multiple, bilaterally spread liver metastases and, altogether, only ~10% have dominant, apparently solitary metastases which are candidates for radical resection.

Formal lobectomy or segmental resections should be liberally performed for solitary or larger metastases and can be combined with wedge resection or enucleation of concomitant lesions. In 2-stage liver resections, portal embolisation (or portal vein ligation) can be used to trigger liver regeneration, or hepatectomies can be done sequentially, to reduce the risk of liver failure [73]. Radiofrequency ablation (RFA) can be performed concomitantly with the intestinal operation, or percutaneously-guided by ultrasound, and can support liver surgery in patients with bilateral metastases. However, only a limited number of metastases (~5–10) can be treated in such a way [35,75]. The complication rate of RFA has been ~5% with the highest risk being injury to the central bile ducts caused by ablation close to the hepatic hilum [75]. Longer symptom palliation and reduction of tumour markers can be achieved after removal of large, dominant liver metastases if ~90% of the tumour volume can be excised [73]. Best results of liver surgery are obtained in patients with limited (50–75%) liver involvement, but virtually every patient will recur with new tumours after liver resection or ablative therapy, if follow-up time is long enough. When liver surgery is not possible, embolisation and treatment with lutetium-labelled somatostatin analogues may be an option, and smaller metastases remaining after liver surgery may benefit from chemotherapy [53].

Conflict of interest statement

None declared.

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