Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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Chapter 1

DIAGNOSTIC, SURGICAL AND MEDICAL ASPECTS OF THE MIDGUT CARCINOIDS

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Abstract

This review covers the incidence, prognosis, diagnosis and treatment of midgut carcinoids with emphasis on the surgical and peri-operative aspects.

Midgut carcinoids are rare neuro-endocrine tumours which become manifest once they have metastasized to the liver. Treatment of metastatic disease can aim at radical resection but is usually palliative. The tumour grows relatively slow. Besides the biochemical effects resulting in the carcinoid syndrome, patients can suffer from mechanical mass effects of the tumour. Medical treatment can alleviate the biochemical effects of the tumour, but has a limited effect on tumour growth. Especially the use of octreotide was a milestone in palliation of these symptoms and has lead to more aggressive treatment protocols.

Treatment aimed at cytoreduction of hepatic metastasis and diminished secretion of bioactive amines can achieve good palliation. Cytoreduction can be performed by means of surgery, hepatic arterial ligation, (chemo)embolization, cryosurgery, radio-frequency ablation, internal radiation or even liver transplantation. The role of these options will be discussed in this review.

Introduction

Carcinoid tumours are rare, slowly growing, neuroendocrine neoplasms. In 1907 Obendorfer was the first to use the term carcinoid (Karzinoide).[1] He described an ileal tumour with a much slower progression than expected from adenocarcinomas.

The traditional classification of the carcinoids according to their embryonal site of origin was introduced in 1963.[2] It comprises foregut- (in the lung, thymus, stomach, pancreas and proximal duodenum) midgut- (from the distal duodenum to proximal colon) and hindgut carcinoids (origin in the distal colon en rectum). This classification corresponds consequently to their vascular (i.e. embryonic) supply, respectively: the celiac axis, superior mesenteric artery and inferior mesenteric artery.

The midgut carcinoids are usually referred to as the "classical" carcinoids. They arise from cells of Kultschitzky in the intestinal crypts and display, when producing serotonin, both an argentaffin and argyrophilic silverstaining reaction.[3] In general the tumour can develop in almost all organs arising from the primitive entoderm as well as the ovary and retroperitoneum. The goal of this article is to review the literature with emphasis on the diagnostic, surgical and medical aspects of the midgut carcinoid

Incidence, prognostic factors and survival

Incidence

In 1997 Modlin performed a comprehensive study of 8305 carcinoid tumours using 3 databases from the National Cancer Institute in the United States, each covering a different era.[4] The incidence varied according to site, sex and age. The male:female incidence of appendiceal carcinoid was 0.25 vs. 0.79, in the small intestine 0.48 versus 0.28 and 0.14 versus 0.15 in rectum/rectosigmoid. The average age at diagnosis of appendiceal carcinoids was 42 years, small intestine: 65 years and rectum/rectosigmoid: 58 years. The malignant carcinoids predominantly metastasize to regional lymph nodes and liver. At the time of diagnosis the carcinoids of the small intestine were localised in 25% of the cases, whereas 39% had regional metastases and 31 % presented with distant metastases. A secondary co-malignancy (non-carcinoid malignant tumours) was often registered and expressed as percentage of the number of carcinoids in a specific site: small intestine 16.6%, appendix 14.6% and rectum 9.2%. An explanation for this high rate of co-malignancy can not be given at present. There are speculations concerning the role of growth factors produced by the carcinoid influencing the growth of normal tissue.[5] Gertsle *et al* found as much as 46% second malignancies in a group of 69 carcinoid patients.[6] These data were collected from patients diagnosed to have a carcinoid during

life and not from post-mortem studies. In contrast Westergaard et al calculated from population based data of the Danish Cancer Registration (1978-1989) in 1029 identified carcinoid patients, an overall relative risk of only 1.1% (95 CI: 0.8-1.6).[7]
Carcinoids can grow very slowly and therefore remain often subclinical; post-mortem analysis in Malmö by Berge and Linell (1976) concerning 16.294 subjects revealed a carcinoid incidence of 8.4 which is far exceeding the clinical incidence.[8] Ninety percent of these carcinoids were accidentally found post mortem, the vast majority originating from the gastro-intestinal tract.

Prognostic factors
McDermott *et al* studied 188 carcinoid patients with a median follow up of 72 months. On univariate analysis the variables of prognostic significance were: sex, women having a better prognosis ($P < 0.01$), the site of the primary tumour with a good survival of appendiceal carcinoids and poor survival of carcinoids of the small intestine ($P < 0.01$), depth of invasion ($P < 0.001$), tumour size ($P < 0.005$), presence of lymph node metastasis ($P < 0.001$), hepatic metastases ($P < 0.001$) and the mode of discovery, with accidentally diagnosed carcinoids having a far better prognosis ($P < 0.001$). On multivariate analysis, gender and presence of metastases at the time of diagnosis were independent prognostic variables of death from disease.[9]
Janson *et al* published in 1997 a series of 301 consecutive carcinoid patients (256 midgut, 39 foregut and 6 hindgut). Poor prognostic factors for midgut carcinoid patients were multiple hepatic metastases, presence of carcinoid syndrome and high levels of 5-HIAA. The only independent predictors of a poor prognosis were advanced age and the plasma chromogranin A level exceeding 5000 μg/l. Thus, chromogranin A may prove to be a prognostic marker for patients with carcinoid tumours.

Survival
Survival is determined by the stage of the disease at the time of diagnosis and the therapeutic interventions. Table 1 shows the 5-year survival (%) of carcinoid tumours by site and stage, from the SEER database from the National Cancer Institute USA (Surveillance Epidemiology and End Results, 1973-1991) comprising 5468 patients as modified from Modlin & Sandor[4]. Zakariai (1975) reviewed 107 patients with a carcinoid tumour of the gastro-intestinal tract and found that carcinoids, which were still intramural, were usually asymptomatic and patients remained well after segmental resection (85% 5-year overall survival). Carcinoids which had invaded the serosa and/or beyond were usually symptomatic, and had poor results, only 5% overall 5-year survival, despite

radical surgery with or without palliative radiotherapy and/or chemotherapy. However, 23% of these patients, namely the older patients, died within 5 years without evidence of disease.[10]

Site of primary tumor	Localized	Regional	Distant
Small intestine	65	66	36
Appendix	94	85	34
Colon	71	44	21
Rectum	81	47	18

Table 1: 15-year survival (%) of carcinoid tumours and site of origin, the SEER database (1973-1991; 5468 patients) Modified from Modlin and Sandor [4]

Norheim *et al* described a series of 103 patients (86 % midgut carcinoids) of a referral hospital, showing that the estimated median survival from the time of histological diagnosis was 14 years, but from the time of a manifest carcinoid syndrome, merely 8 years.[11]

Clinical presentation of midgut carcinoids

The primary tumour can remain subclinical for many years, being deeply embedded in the crypts and discreetly invading the intestinal wall without interference with the bowel function. Progressive growth of the tumour usually causes only vague abdominal complaints varying from mild discomfort to intermittent obstruction. These vague complaints may be the cause of a considerable patients and doctors' delay. Frequently the diagnosis of a midgut carcinoid becomes evident only after the appearance of hepatic metastases and the "carcinoid syndrome". The interval between the initial symptoms and diagnosis varies from 1-5 years.[12,13] Occasionally the primary tumour can cause (intermittent) intussusception with the carcinoid as 'leading point'.[14,15] Soreide *et al* registered the symptoms in 75 patients with a midgut carcinoid scheduled for operation in an uncontrolled study without a case-control group.[16] Predominant findings were flushing (68%), diarrhea (62%) and abdominal pain (52%) followed by weight loss (44%) and classic carcinoid syndrome (35%).

As the tumour grows, it invades the bowel wall and spreads to regional lymph nodes. There is no agreement in the literature (appendiceal carcinoids excluded) regarding the relationship between tumour size and lymphatic spread.[10,17] Burke *et al.* found no correlation between tumour size or invasion depth and lymph node metastasis in jejunoileal carcinoids. Twenty-one percent of the ileal carcinoids smaller than 1 cm had spread to the regional lymph nodes. Tumours confined to the submucosa had concomitant lymphatic spread in 17 % of the cases. In case of invasion of the muscularis propria or transmural penetration the incidence of lymphatic metastases was respectively 23% and 34%.[18]

Makridis *et al* related lymph node metastasis to tumour size. Sixty-nine percent of the patients with a tumour smaller than 0.5 cm had lymph node metastases, 94% between 0.5 - 1 cm and 100% between 1 - 2 cm and larger.[19] These data are biased, since all these patients required surgery. Patients subjected to surgery to relieve abdominal complaints usually have at least mesenteric lymph node metastases.[20] However, many primary carcinoids are only identified during post-mortem examination.[16,21,22] Characteristic for extensive carcinoid growth is the fibrotic and retracted mesentery, causing kinking of the small intestine in an accordion like fashion and (intermittent) obstruction. Another characteristic feature is vascular elastosis, a thickening of the vessel wall, resulting in ischemic changes of the gut.[23,24] Both mesenteric fibrosis/retraction and vascular elastosis can cause abdominal angina, which is a symptom reflecting extensive disease. The diagnostic use of sublingual nitroglycerin can help to differentiate between mechanical obstruction and abdominal angina. This drug causes endothelium independent vasodilatation, which can result in a remarkable and instantaneous relief of symptoms.[25] The exact aetiology of vascular elastosis is still a matter of debate. Intestinal ischemia is only seen in midgut carcinoids. One hypothesis is that the fibrosis results from serotonin release, which causes shortening and kinking of the mesentery and narrowing of the vessels by means of elastic vascular sclerosis. The mechanical effect of bulky metastatic nodes compressing the vessels in the mesentery may add to the effect of the fibrosis. Anthony and Drury suggested that local secretions arising from tumour in the mesentery are responsible for the ischemia.[26] Other authors postulate a direct effect of serotonin on smooth muscle cells and the fibroblasts of the vessel wall. They agree that this ischemia is only seen with residual metastatic disease in the mesentery, suggesting a locoregional biochemical effect. Recent findings that acidic fibroblast growth factor and transforming growth factor alpha are expressed in carcinoid tumours as well as the presence of their respective receptors on the stromal fibroblasts might be a step towards elucidating this local factor.[27]

During progression of the disease, the carcinoid frequently metastasises to the liver. Fifty-eight percent of the patients with a primary tumour diameter exceeding 1 cm had hepatic metastasis whereas in 22% hepatic metastases were present with tumours smaller than 1 cm.[12] Literature however is not univocal with respect to the relation of tumour size and metastases. Once hepatic metastases have developed, the patient with a classical midgut carcinoid usually shows the "carcinoid syndrome". This syndrome will be discussed in detail below

Carcinoid Syndrome

The carcinoid syndrome in midgut carcinoid has a variety of symptoms. Patients seldom have all these symptoms. Eating, alcohol and stress (surgery and anaesthesia) can provoke the symptoms, particularly flushes and alteration of blood pressure. The carcinoid syndrome is caused by tumour derived substances and their metabolites in the systemic circulation, amongst others: serotonin, bradykinin, prostaglandin, catecholamines, and substance P.[28-30] The liver and lung will metabolise some of these substances, which prevents their release into the systemic circulation. Therefore, development of the carcinoid syndrome generally requires the presence of pulmonary or hepatic metastases. The carcinoid syndrome can also be caused by carcinoid tumour or metastatic foci draining directly into the caval vein bypassing the liver, but this is a rare situation.[31-33] Very often the ileal carcinoid is only detected after appearance of the carcinoid syndrome and hepatic metastases. Elevation of urinary levels of 5-hydroxy-indol-acetic-acid (5-HIAA) or high platelet serotonin is diagnostic.

The aetiology of flushing remains uncertain. Gustafsen *et al* reported raised serum levels of histamine during flushes[34], whereas Kema *et al* found urinary histamine excretion to be of no importance in hepatic metastases.[30] Matuschansky *et al* measured serotonin and norepinephrine during flushes. Both agents were markedly elevated during facial flush but whether this surge is causal can not be concluded from presented data especially while norepinephrine causes vasoconstriction.[35] Bradykinin seems to play no role in the genesis of flushing.[36] Diarrhoea occurs almost as often as the flushes and may have several causes. It is not clear which of the substances secreted by the carcinoid tumour is responsible for the diarrhoea. There is however growing evidence that serotonin plays an important role both direct and indirect on the bowel movement and secretory processes.[37-41] Furthermore, even a small ileal resection can cause mild diarrhoea (although not attacks) due to reduced bile salt absorption. Short bowel syndrome due to repeated bowel resections can cause diarrhoea. Ischemie caused by vascular obstruction due to large metastases in the mesentery and/or vascular elastosis can result in incapacitating diarrhoea. Several other humoral factors may also play a role, presumably tachykinins, motilin, substance P produced by the tumour (metastases) as well as local paracrine mechanisms producing prostaglandins.[42,43]

Right-sided valvular heart disease is a relatively late complication because it will occur only following long-standing serotonin overproduction by hepatic metastases.[44] Direct action of serotonin in particular is held responsible for fibrotic alterations, i.e. shrinkage and thickening, of the tricuspid and pulmonary valve. Usually only the right side of the heart is affected, because the pulmonary tissue harbours enzymes, which completely metabolise serotonin.

When these enzymes are saturated or in the presence of extensive pulmonary metastases, left sided heart disease can also occur.
Moyssakis *et al* performed a study among 87 patients with the carcinoid syndrome. Of these patients, 45% had cardiac involvement with thickened and shortened tricuspid-leaflets causing tricuspid valve insufficiency and/or pulmonary stenosis resulting in right-sided heart failure. The consequences of tricuspid insufficiency may be impressive but seldom is the direct cause of death. Pulmonary stenosis and hypertension however, can be fatal.[45]

Diagnostic tools
The diagnostic strategy in case of a (suspected) metastatic carcinoid is determined by the clinical presentation.

History
The diagnosis of a carcinoid ought to be based on a thorough history. This interview should consist of specific questions regarding intermittent abdominal pain or discomfort and triggering factors resulting in the well-known paroxysmal diarrhoea and the flushes. Patients, when asked, frequently report intolerance for alcohol. Intermittent bowel obstruction and/or heart failure in combination with flushes can be a lead to the diagnosis.

Biochemistry
Midgut carcinoids characteristically produce large quantities of serotonin, reflected in raised levels of platelet serotonin and a high urinary 5-HIAA excretion. Platelet serotonin appeared to be more sensitive in carcinoids with relatively low serotonin production compared to urinary excretion of 5-HIAA.[46] The demonstration of elevated levels of platelet serotonin and 5-HIAA is highly specific for the presence of a carcinoid tumour.
The urinary 5-HIAA excretion and serotonin in platelets have limited sensitivity in hindgut carcinoids, because they seldom produce serotonin. The foregut carcinoids may produce only limited amounts of serotonin, since they sometimes lack the enzyme to convert 5-hydroxytryptophan (5-HTP) to serotonin.[11] The kidney however does contain this enzyme. Both urinary serotonin and platelet serotonin but not 5-HIAA have been found to be elevated in foregut carcinoids.[30] Chromogranin A (a marker representing the presence of neuroendocrine cells) is a protein constituent of granules in neuroendocrine cells. It therefore is not specific for carcinoids but can be a helpful marker in detecting a neuroendocrine tumour in the absence of specific neuroendocrine features.[47,48] However, chromogranin A is not obligatory in the analysis of a patient with suspected carcinoid disease. In the course of an in onset curative

treatment of the carcinoid disease, chromogranin A appears to be a sensitive marker of relapse.[49]

Conventional radiology
The primary tumour of a midgut carcinoid sometimes can be detected by means of a small bowel study.[50,51] However, often the carcinoid only causes discrete stenosis undetectable by small bowel study. A plain abdominal film of a patient suffering from bowel ischemia or mechanical obstruction can reveal a distended small bowel loop and or a thickened bowel wall.

Ultrasonography
Ultrasound can detect hepatic metastasis and is therefore a useful tool in screening.[52] The benefit of intra-operative ultrasonography to detect hepatic metastases during hemi-hepatectomy is well established. Yoshikan *et al* used a endoscopic ultrasound to visualise gastric and rectal carcinoids enabling loco-regional staging. The series in literature however, are too small (7-15 patients) to define its precise diagnostic value.[53]

Computed tomography (CT)
In 60-70 % of the patients with a biochemical diagnosis of carcinoid disease, CT scans will show hepatic metastases. The sensitivity for detecting the primary tumour is low, ranging from rare to 20%. The CT is helpful in evaluating the extent of the tumour spread before surgical exploration.[54,55] The presence of punctate or radiating mesenteric densities, when combined with rounded mesenteric masses or liver metastases is highly suggestive of hepatic metastases of a carcinoid tumour.[56]

Magnetic resonance imaging (MRI)
The MRI is a more recent diagnostic tool in evaluating hepatic metastasis. Shi *et al* found MRI in staging of carcinoids to be superior over CT.[57] There are however no specific reports regarding the use of MRI in carcinoid disease in general. Like CT, the MRI will probably only be suitable for targeted areas.

Angiography
Angiography can be used for diagnostic or therapeutic purposes (e.g. (chemo) embolization). In case of abdominal angina, angiography may show the affected branches of the vascular tree but the significance of the radiological finding is matter of debate. Rose *et al* evaluated angiography in 11 with intra abdominal metastatic carcinoid tumour.[58] They concluded that the radiological finding correlates with tumour invasion and vascular elastosis, but showed

poor correlation with ischemia (five of the eight patients without ischemia had a abnormal angiogram) In addition, Makridis *et al* concluded that a normal angiogram does not exclude intestinal ischemia because the angiogram only shows relatively large vessels whereas vascular elastosis and ischemia can express itself in smaller vessels that are not visualized by angiography.[19]

Octreotide Scan

Reubi *et al* in 1987 demonstrated somatostatin receptor expression in a mediastinal carcinoid.[59] In 1990 the same group demonstrated somatostatin receptor expression in 45 out of 62 histological samples of carcinoid tumours.[60] Binding a somatostatin analogue to a radioisotope made it possible to visualise the tumour.[61] Carcinoids with elevated urinary 5-HIAA excretion appeared to express somatostatin receptors more often than the non-secreting carcinoids. Furthermore, pre-treatment with somatostatin analogs appeared to enhance the tumour/background ratio resulting in enhanced sensitivity.[62,63] Anthony *et al* using octreo-scintigraphy found additional metastases influencing the surgical strategy in 36 of 60 patients when compared to "conventional" investigations.[64] Single photon emission computed tomography (SPECT) appears to be more sensitive than planar scintigraphy.[65] However, Ohrvall *et al* stated that the clinical significance of a scintigram or SPECT in patients planned for surgical resection was limited, because all the tumours which were not detected by conventional investigations were palpable at surgery.[66] This imaging technique did not alter the surgical procedure in any case. Kisker *et al* published that somatostatin scintigraphy was not superior to CT or ultrasound in detecting a primary tumour larger than 2 cm or hepatic metastases. Yet scintigraphy was superior in detecting extra-abdominal metastases in the pre-operative work up of a planned radical (intentional curative) resection of hepatic metastases.[67]

I^{131} metaiodobenzylguanidine scintigraphy (MIBG)

MIBG is taken up in the cell where it accumulates in the argentaffin granules. In contrast, octreotide is attached to cell surface receptors. Fischer *et al* reported the diagnostic use of MIBG in carcinoids in 1984.[68] The sensitivity of MIBG scans varied from 60-85% in selected patients.[68-71] The combination of MIBG and the somatostatin analogue In^{111}-pentetreotide scans attained a sensitivity of 95%.[71]

ECG, echocardiography

Patients scheduled for surgery should be submitted to careful cardiac evaluation, standard ECG and echocardiography. As mentioned before, approximately 45% of these patients have manifest right-sided valvular heart disease requiring careful perioperative hemodynamic monitoring.[45]

Medical treatment of metastatic carcinoid tumours

Diarrhoea and flushing are the prominent and sometimes debilitating symptoms of the carcinoid syndrome. As mentioned earlier, the carcinoid syndrome is usually caused by amine secreting hepatic metastases. The presence of a carcinoid syndrome is synonymous with extensive disease and incurability in the vast majority of the cases. Nevertheless, staging of the disease is important in order to identify those patients suitable for resections of the metastases e.g. unilobar hepatic metastases in the absence of further spread. Other patients might be candidates for procedures aiming at the debulking of the hepatic metastases. However in this situation medical treatment in the absence of urgent surgical indications can achieve good palliation.

Symptom relief

The advent of somatostatin analogs provided the physician with an effective tool to alleviate the hormone-induced symptoms. Octreotide can improve or even prevent flushes and diarrhoea.[72-74] Recently, long acting analogs have become available requiring less frequent injections.[75] Some symptoms however resulting from extensive disease like unremitting abdominal cramps caused by obstruction or ischemia generally can only be relieved by surgery. Somatostatin analogs can interfere with endo- and exocrine pancreas function. This may cause, although rare and transient, diarrhoea, steatorrhoea, flatulence, nausea, vomiting and mild hyperglycaemia. Trendle *et al* observed 44 patients receiving octreotide. Approximately half of the patients developed cholelithiasis, in three patients requiring emergency cholecystectomy.[76] Apart from symptomatic treatment, at present, the peri-operative use of octreotide is strongly advised (see below).

Control of tumour growth

Somatostatin analogs:

Saltz (1993) performed a study in 34 patients, elucidating the anti-proliferative role of octreotide.[77] No evident regression of the tumour was observed. Fifty percent of the patients showed stable disease which lasted for a median five months (range 0-27 months). Compared to a historical group, there was a tendency towards a longer survival. Similar results were found by the German Sandostatin Study Group investigating 115 gastro-entero-pancreatic tumours, 53 of which were carcinoids.[78]

Interferon-alpha

In 1991 Oberg *et al* published a prospective study concerning the effects of interferon alpha. Forty-seven out of 111 patients (42%) treated with interferon alpha demonstrated a biochemical response but this agreed with a tumour size

reduction of 50% in only 17 patients. In another 39% stabilisation of the carcinoid disease was noted, whereas 19% showed progressive disease. The median duration of the biochemical response was 34 months. Subjective responses with improvement of diarrhoea, flush and/or bronchoconstriction were noticed in 68%.
The adverse reactions to interferon alpha treatment were dose-dependent and include, mainly, flu-like symptoms, fatigue, and weight loss. Autoimmune reactions were noted in 20% of the patients. Some patients treated with recombinant interferon alpha developed neutralising antibodies (6-27 percent), which abolished the anti-tumour effect. The anti-tumour effect of interferon alpha in neuroendocrine tumours included apoptosis, cell differentiation, and cytostatic effects.[79,80] Interferon alpha 2b did not augment these neutralizing antibodies.[81] Four percent of the patients developed antibodies directed against carcinoid tumour cells.[82]

Chemotherapy
Moertel *et al* published in 1979 a study of 118 patients with a metastatic carcinoid who were randomly subjected to treatment with streptozotocin combined with cyclophosphamide or with 5-fluorouracil. Biochemical response rates among patients with a primary tumour originating in the small bowel, treated with the 5-fluorouracil combination, was 44% and with the cyclophosphamide combination 37%. There was no difference in patient survival between the two treatment arms. The median survival from time of diagnosis was 28.4 months. Common side effects were nausea, vomiting, leukopenia, thrombocytopenia, and nephrotoxicity.[83]
The Southwest Oncology Group conducted a non-randomised phase II trial of combination chemotherapy in 56 patients with metastatic carcinoid tumours. The therapy included 5-fluorouracil, doxorubicin, cyclophosphamide, and streptozotocin (FDC-S) or the same combination without doxorubicin (FC-S) in patients with pre-existent heart disease. Fifty-six patients received FDC-S, and nine received FC-S. The median survival of all patients was 10.8 months. They concluded that the FDC-S combination can produce objective responses in patients with metastatic carcinoid tumours, but these are generally partial and brief.[84] In 1989 Oberg *et al* published the results of a small randomised study of 20 patients with malignant carcinoid tumours of which ten patients received streptozocin plus 5-fluorouracil for 6 months and another ten human leukocyte interferon alpha. After 6 months of treatment, a biochemical response (5-HIAA) was noted in five of the patients treated with interferon alpha (50%) but in none of the patients on chemotherapy. Only two patients also showed a reduction in tumour size. Subjective improvement was noted in 72%

of patients treated with interferon alpha, but only in 9% of those treated with streptozocin plus 5-fluorouracil. The results of these small studies suggest that interferon alpha treatment is superior to the combination of streptozocin plus 5- fluorouracil regarding quality of life.[85]

Iodine-131 metaiodobenzylguanidine (I^{131}-MIBG)
Radiolabelled MIBG at first was used for imaging of carcinoids or neuroendocrine cells in general.[68,69,86-88] After a few years the treatment potential of MIBG for carcinoids was evaluated by Hoefnagel *et al.*[89] Both "cold" MIBG and radioactive MIBG alleviated symptoms of the carcinoid syndrome in approximately 60% of 30 patients, although the effect seemed to last somewhat longer when using radioactive MIBG (median duration 4.5 versus 8 months, n.s.).[90]

The rate of progression of the tumour cannot be predicted in individual patients. Many of the above mentioned studies deal with small groups of patients, making it difficult to asses the value of treatment. Pooling data of centres will therefore be crucial.

Surgery

General
The primary objective of surgery should be to carry out a curative resection i.e. radical resection of the primary tumour. In case of metastatic disease a potentially curative resection, if possible, should be carried out, taking into account the risk of damage to surrounding tissue. In the vast majority of cases however, the resections can only aim for palliation. The metastatic mass in mesentery and liver are usually larger than the primary tumour. In the last decade many authors advocate, in case of irresectable metastatic disease, a palliative resection of the primary tumour(s) in order to maintain passage of the bowels.[16,19,91,92] Although there is no controlled study proving the alleged advantage, these authors state that the life expectancy and or quality of life will benefit from a palliative resection. The peri-operative use of octreotide allows surgery even in advanced stages of the disease. Before the advent of octreotide, the operative hazards of a carcinoid crisis and a relatively short life expectancy made surgeons reluctant to perform major surgery.[19] The decision to perform a palliative resection in a patient with a disseminated midgut carcinoid should be based on the balance between the risks and the prospects of relieving the intestinal symptoms. It has been established that surgery can palliate symptoms due to intestinal obstruction or ischaemia.[19] Many authors therefore advocate liberal indications for surgery.[16,92-95]

Soreide *et al* (1992) found a better survival for those patients with midgut lesion subjected to resection of primary tumour and mesenteric metastases; median survival was 139 months versus 69 months without debulking. For patients with hepatic metastases the median survival after surgical intervention was 216 months and 48 months without such treatment ($p<0.001$).[16] Although the authors admit the bias of selection, as some large or diffuse hepatic metastases simply can not be resected, resulting in worse survival, the difference in survival is striking. Intestinal ischemia can result from compression of the main mesenteric vessels by tumour, fibrosis of the mesentery or elastic vascular sclerosis. Cautious dissection can free the larger vessels from tumour resulting in prolonged symptom free intervals up to several years. Ohrvall e.a. described a technique in which they mobilize and release the right colon and mesenteric root from posterior adhesions, identifying the mesenteric artery below the pancreas, and free-dissecting this artery on the tumor capsule in the mobilized mesentery.[19,96]
Up tot 40% of the patients with midgut carcinoids had multiple primary tumours (up to 11) usually in the region of the predominant tumour.[16,19,97,98]

Jejunum / ileum
The aforementioned general guidelines are applicable to carcinoids of the jejunum and ileum. Primary tumours without spread to mesentery and/or liver are rare and are usually detected by accident during abdominal surgery for another condition. Most patients undergo a laparotomy to relieve symptoms of (intermittent) bowel obstruction caused by fibrosis and shrinkage of the mesentery. Abdominal angina can be another indication for laparotomy.[23,99] As mentioned earlier, there is no agreement in the literature regarding the size of the primary tumour and the chance of distant spread. Thorough pre-operative assessment for distant spread therefore is essential. In the absence of hepatic metastases, the tumour must be resected meticulously because resection constitutes the only chance for long-term survival.

Appendix
Appendiceal carcinoids have by far the highest incidence and are found by coincidence at appendectomy carried out for a presumed appendicitis. The prognosis of appendiceal carcinoids smaller than 2 cm is good (see below). Why this prognosis is so much better than other primaries remains uncertain. Several authors were able to identify features distinguishing the appendiceal carcinoids. They appear to arise from sub-epithelial cells whereas other midgut carcinoids arise from mucosal endocrine (enterochromaffin) cells in the crypts of the bowel wall.[100] Moertel and co-workers performed a survey amongst 150

unselected patients with appendiceal carcinoids. There were no metastases observed in 127 patients with tumours smaller than 2 cm. Three out of 14 patients with the tumour size between 2 – 3 cm had lymph node metastases and 4 out of 9 with tumour sizes larger than 3 cm. Moertel concluded that patients with a carcinoid smaller than 2 cm can be adequately treated by simple appendectomy. In case of a larger mass, a right hemicolectomy should be performed.[101] There are however reports of lymphatic spread of tumours smaller than 2 cm.[102] It can be concluded that in case of an appendiceal tumour smaller than 1 cm a simple appendectomy is satisfactory. Tumours between 1 – 2 cm in size remain the challenging ones. In case of involvement of the appendiceal mesentery the need for radical hemicolectomy is obvious.

Colon carcinoids

Ballantyne surveyed the Connecticut Cancer Registry Database and found 54 patients with a carcinoid of the colon (0.31/100.000). Forty-eight% was localized in the cecum; 16%, ascending colon; 6%, transverse colon; 11%, descending colon; 13%, sigmoid colon; and 6%, not assigned. In general, the abovementioned general guidelines for the surgical management of carcinoids are applicable in case of colon carcinoids.[103]

Treatment of hepatic metastases

Surgical resection.

Radical resection is the treatment of choice in unilobar disease, as in treatment of the primary tumour. Unfortunately, most hepatic metastases are bilobar or diffuse. Wangberg *et al* published a series of 64 patients, 61 of whom had hepatic metastasis. Fourteen of these patients were treated by surgery alone resulting in clinical and biochemical complete remission.[95] McEntee *et al* reported a series of 37 patients (24 carcinoid, 13 islet cell tumours). Ten patients with a carcinoid underwent a radical liver resection. At time of investigation, five patients were alive 6 – 34 months after resection with no evidence of disease, 3 were alive with disease 52 – 92 months after surgery and two died 49 and 60 months postoperatively. Patients who underwent a palliative resection benefited from this procedure reducing the invalidating symptoms of the carcinoid syndrome.[104] Even long-term survivors with no detectable evidence of disease in advanced stages are reported.[105] Although the data are promising, it should be kept in mind that the reports mentioned here describe uncontrolled studies. Moreover there are no trials in which different treatment modalities are compared regarding survival, symptom relief and morbidity.

Dearterialisation of hepatic metastases

In view of the indolent nature of carcinoid hepatic metastases and the lack of a curative therapy for advanced hepatic metastases, the optimal moment for dearterialisation has yet to be determined. Some authors treat lesions only when they are symptomatic and no longer controlled by somatostatin analogs, whereas others recommend an earlier approach.

The blood supply of metastases in the liver is predominantly arterial, whereas the hepatic tissue has a double blood supply consisting of both hepatic artery and portal vein. The normal hepatic parenchyma receives 20-25% of its blood supply from the hepatic artery and 75-80% from the portal vein.[106,107] The obstruction of the arterial blood flow will cause ischemia and necrosis of the metastases but will affect normal parenchyma to a lesser extent. Patency of the portal vein however should be proven prior to the dearterialisation procedure. There are several ways to interfere with the arterial circulation of the liver. The first reports mention ligation of one of the hepatic arterial branches causing ischemia followed by regeneration of the parenchyma within 6 weeks.[108,109] The disadvantage of this procedure is the need for a laparotomy. This has led to the development of non-operative embolization of the hepatic artery by radiological intervention. The first one to describe this procedure for carcinoid metastases was Allison in 1977.[110] Some authors used a combination of embolization and antineoplastic drugs, chemo-embolisation.[95,111-113] Complications are limited though not unimportant. The post embolization syndrome is characterised by pain in the liver region lasting for 3-6 days. It is the most severe during the first 36 hours, often requiring intravenous analgesia. Nausea and vomiting occur in almost all patients but can be effectively controlled by anti-emetics. Patients often become febrile, which may last as long as 4 to 7 days, however, infection must be excluded. To avoid gallbladder necrosis, a cholecystectomy is advocated when a laparotomy is performed prior to the embolization. Hepatic abscesses usually can be drained percutaneously.[114-116]

Cryosurgery

Since 1995 several articles have addressed the use of cryosurgery in carcinoid liver metastases.[117-120] A total of 21 patients were reported. About 80-90 % of the patients had a biochemical response (5-HIAA, serotonin). There were only minor side effects. One of the problems of this procedure is the formation of an ice ball around the probe once cryotherapy has started, making it impossible to reposition the probe for optimal targeting. Furthermore, the frozen liver can crack, causing massive haemorrhage after thawing.[119] It is concluded that cryotherapy can alleviate symptoms and may improve survival.[117-120]

However, no randomised study comparing cryotherapy with other palliative options has been performed. The role of cryosurgery in palliative care has not yet been assessed.

Thermal ablation

Siperstein and co-workers reported in 1997 a procedure of thermal ablation using radiofrequency energy to hepatic metastases. After preclinical validation of the procedure using a porcine model, they performed laparoscopic thermal ablation in seven patients with hepatic metastases, two of whom had disseminated disease. No per-operative complications were reported and patients were discharged the day after the procedure. One patient had no symptom relief, the other patient experienced symptom relief in frequency of flushing and was able to diminish the octreotide dose.[121] Recently Wessels reported three patients who had refractory lesions in the liver following chemo-embolization. They were treated with radio frequency ablation. The tumour size and symptoms diminished in all three patients. Two patients diminished their daily octreotide dosage, one patient was able to discontinue octreotide.[122] Further evaluation of this minimally invasive cytoreductive therapy seems to be worthwhile

Liver transplantation

Orthotopic liver transplantation (OLT) has been proposed in patients without residual extra-hepatic manifestations after initial surgery.[123-125] Less than 50 liver transplantations have been described with often short follow-up. Le Treut is the only author able to report a 5-years survival of 73% (47% NED) in 15 carcinoid patients in a group of 31 patients undergoing OLT for metastatic neuro-endocrine tumours. Overall post-operative mortality in these 31 patients was 19%. Fifty percent of the carcinoid patients suffered from one or more major complication i.e. peritoneal bleeding, acute/chronic rejection and acute pancreatitis. In considering an OLT one should take in account these figures, the morbidity of the post-operative OLT treatment regimen and the non-oncological OLT survival curves and compare these with the survival and quality of life in patients undergoing cytoreductive surgery and/or medical treatment.

Heart valve replacement

Connolly *et al* described 26 patients who underwent tricuspid valve replacement because of progressive right sided heart failure. He compared this group with 40 medically treated patients. The perioperative mortality was 35%, mainly due to postoperative bleeding and right ventricular failure. Of the 17 surgical survivors, eight were alive at a mean of 28 months of follow-up. The

postoperative functional class of these eight surviving patients was substantially improved. The late deaths were due to progressive carcinoid disease.[126] Robiolio et al reported 19 valve replacements in their institute and a review of literature (excl. article of Connolly). This review revealed a 30-day mortality of 56% for patients >65 years of age and 0% for those ≤ 60 years of age ($p<0.0001$). Careful preoperative risk stratification by age and comorbidity may provide a means for optimal selection of surgical candidates.[127]

Peri-operative complications

Only limited data regarding the peri-operative complications in patients with disseminated carcinoid disease are available. Soreide *et al* (1992) found a complication rate of 14 % for the primary operation, 9 % for a second operation and no complications for 3rd - 5th operations. There were no peroperative deaths. Within 90 days after surgery, 6/65 (9%) patients died after primary surgery and 5/22(23%) patients after the first re-operation.[16] Makridis found 8% temporary postoperative gastrointestinal paralysis, 5% short bowel syndrome (only in acute patients) and 5% abdominal infections.[19] Wangberg reported 2 duodenal perforations caused by mesenteric lymph node dissection and 3 enterocutaneous fistula in 64 patients.[95] No cardiac complications were mentioned in these articles.

Anesthesia

Careful assessment of the patient's state is mandatory before surgery. Signs of the carcinoid syndrome (flushing, diarrhoea, and carcinoid heart disease) are important predispositions. Fluid and electrolyte abnormalities due to severe diarrhoea must be corrected. Several drugs can block the release or action of mediators produced by carcinoids. Drugs used earlier amongst others are methysergide[128,129], the serotonin receptor antagonist ketanserin[130,131] and the kallikrein inhibitor aprotinin to treat hypotension. In 1981 Long *et al* reported that ethanol-provoked flushing could be inhibited by somatostatin.[132] The first report of the use of a somatostatin analogue during operation is from Thulin *et al* in 1978. He used somatostatin against hypotension resulting from carcinoid tumour manipulation.[133] Kvols *et al* reported the use of a somatostatin analogue during an operation for a severe hypotension due to a carcinoid crisis, which rapidly responded to intravenous administration of the drug, in 1985.[134] More case reports have followed since.[135,136] From the late eighties the octreotide is in general use as premedication before and during surgery and anaesthesia. Due to its perceived beneficial effects, a randomised study regarding the perioperative use of octreotide is nowadays considered unethical.

A carcinoid crisis is a major challenge to the anaesthetist. The wide range of clinical presentations of the carcinoid syndrome can be explained by the interaction of the various mediators released by the tumour. It is less clear which stimuli cause these mediators to be released and why tumours vary so widely in the type of mediators they secrete. Histamine release for instance is predominantly seen in foregut carcinoids, causing severe bronchospasm. Kallikreins (protease enzymes) generate kinins from kininogens. Bradykinin can cause profound hypotension by vasomotor relaxation. It can also cause bronchospasm especially in the presence of cardiac disease. However, bradykinin seems to play no major role in the onset of flushing or hypotension.[36] Kallikrein release, resulting in high levels of circulating bradykinins, is triggered by sympathetic stimulation.[137] Tachykinins e.g. substance P, neuropeptide K, vaso-active intestinal polypeptide, may be associated with the carcinoid syndrome and the long-term effects on carcinoid heart disease.[138,139]
This heterogeneity in mediators and their interrelated responses constitutes the challenge to anesthesia in the carcinoid patient. In contrast there are many case reports but only few series describing anesthetic viewpoints.[140,141] One should always keep in mind the complicating heart status in a patient suffering from carcinoid heart disease. The use of epidural anesthesia remains controversial. To date there are no specific studies covering the use of epidural anesthesia in this setting. However, many clinical handbooks and reviews warn against its liberal use in patients suffering from the carcinoid syndrome.[141-143] In general the peri-operative management should refrain from triggering the release of mediators, especially by the use catecholamines. Extradural anesthesia techniques with local anaesthetics can cause hypotension as a result of peripheral vasodilatation, which on its turn can trigger catecholamine release, therefore caution is essential.

Conclusion

Midgut carcinoids are rare neuroendocrine tumours. The disease often manifests itself by the presence of amines secreting hepatic metastasis. Improvement of palliative treatment in advanced stages of disease aimed at cytoreduction and symptom control should be a major goal in clinical investigations. The emphasis should lie on both medical treatment and cytoreductive interventions or a combination of both. Over the last decade, progress has been made in both fields. Especially the advent of octreotide for symptom control was a major step forward. Prolonged survival can result in a relative increase of abdominal problems such as ileus and bowel ischemia needing surgical interventions. The protracted course of the disease permits an offensive (surgical) treatment attitude.

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