Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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ISBN: 90-5972-109-8

Uitgeverij: Eburon
www.eburon.nl

Cover design: Roy Haasewinkel
Painting: John van der Deure

RIJKSUNIVERSITEIT GRONINGEN

MIDGUT CARCINOIDS;

SURGICAL ASPECTS, BIOGENIC AMINES AND

VASCULAR EFFECTS

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 10 mei 2006
om 16.15 uur

door

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geboren op 16 mei 1962
te Den Helder

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General introduction

Carcinoids are rare slowly growing, neuroendocrine tumors. In 1907 Obendorfer was the first to use the term carcinoid (Karzinoide)[1]. He described an ileal tumor 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 supply, namely the celiac axis, superior mesenteric artery and inferior mesenteric artery. Carcinoids can develop in almost all organs arising from the primitive entoderm as well as the ovary and retroperitoneum.
In this thesis we will especially focus on the midgut carcinoids. The midgut carcinoids are usually referred to as the "classical" carcinoids. They arise from cells of Kulchitsky in the intestinal crypts and display, when producing serotonin, both an argentaffin and argyrophilic staining reaction.[3]
Midgut carcinoids can produce several biogenic amines such as serotonin, bradykinin, prostaglandin, catecholamines and substance P.[4] These products only exert their influence once they have passed the liver into the systemic circulation, as the liver is able to metabolize these amines. An ovarian carcinoid can therefore cause early symptoms because the ovary drains directly into the caval vein and not into the portal vein. In case of liver metastases, the liver itself becomes a production site of these amines which then enter the systemic circulation causing several symptoms we refer to as the carcinoid syndrome, i.e. hot flushes, diarrhea and circulatory imbalance. The carcinoid patient with the classical symptoms will often be diagnosed as having widespread hepatic metastases. This delay is partly explained by the relatively small mass effect of the primary tumor that causes only mild symptoms. At laparotomy a small primary tumor and massive metastatic disease is suggestive for carcinoid disease.
From the surgeon's point of view there are two major groups of carcinoid patients, those who are accidentally diagnosed during appendectomy for a suspected appendicitis and those who are referred by the gastroenterologist or medical oncologist, and are often metastasized. The first group offers no problems and abdominal spread or liver metastases are rare in these cases.[5-7] In case of metastasized patients however the medical oncologist, surgical oncologist and the patient have to weigh several treatment options and the timing of interventions. Although the treatment is usually palliative in case of metastases, patients can survive many years.

Aim of this thesis

The aim of this thesis is to get insight in surgical aspects of the treatment of carcinoid patients and the role of vasoactive substances produced by the tumor and their vascular effects.

Outline of this thesis

The first chapter reviews the literature on the incidence, prognosis, diagnosis and treatment of midgut carcinoids with emphasis on the surgical and peri-operative aspects.

In chapter 2 we evaluate the indications for surgery, the blood loss, hemodynamic parameters and complications during surgery in patients with a metastasized carcinoid in a referral center. A retrospective survey was performed regarding all surgical interventions between 1983-1998 in patients with an abdominal manifestation of a metastatic carcinoid in the University Medical Centre Groningen (UMCG).

Carcinoids are known to produce and release catecholamines.[8,9] These products are mainly responsible for the carcinoid syndrome and carcinoid crisis. In the past the high mortality during surgery resulted in a defensive attitude towards surgical procedures in patients with a metastasized carcinoid. The protective effect of the drug octreotide has changed this attitude towards surgery. To date it is still unknown what factors may trigger a carcinoid crisis. In chapter 3 we investigate the catecholamine release before during and after anesthesia and surgery in 16 octreotide receiving carcinoid patients undergoing a laparotomy compared to seven non-carcinoid patients receiving peri-operative octreotide for pancreatic surgery.

Chromogranin A is a product of neuroendocrine tumors among which the carcinoid tumor. Contrary to chromogranin A, the production of serotonin is pathognomonic for carcinoid disease. In chapter 4 a retrospective study is described in carcinoid patients for chromogranin A concentrations in serum comparing these data with the until now the most sensitive parameter in carcinoid patients, the serotonin content in platelets.

In general abdominal angina is rare. In patients with a midgut carcinoid however this symptom is more frequent because serotonin can induce vascular elastosis and kinking of the mesentery. Still, the relation of this symptom with carcinoid disease is largely unknown. In chapter 5 we describe the symptoms and treatment of six patients with abdominal angina caused by metastasized carcinoid disease.

Serotonin and other vasoactive amines produced by a carcinoid tumor are thought to be responsible for characteristic vascular changes in the mesentery known as vascular elastosis. It consists of elastosis and fibrosis of the media

and adventitia, causing narrowing of the vessel lumen. This is a well-defined pathological entity related to carcinoid disease which not seldom causes bowel ischemia. Moreover carcinoid patients suffer from vascular tone imbalance provoked by (surgical) stress. In chapter 6a we investigate the dynamic response in 16 patients with a metastasized carcinoid in vivo compared to 21 healthy age and sex matched controls, using the physiological response mechanism to temporary vascular occlusion of the arm. Furthermore the intima media thickness of the carotid artery was measured as a sign of (extramesenteric) vascular elastosis compared to controls.

Catecholamines released by a carcinoid tumor cause several symptoms, which are mainly vaso-active effects (i.e. flushing, abdominal angina, constriction of peripheral arteries). In chapter 6b a carcinoid patient is described with severe and prolonged vascular constriction of both legs caused by circulating catecholamines. Following amputation an ex vivo investigation of the dynamic responses of the popliteal artery was performed and data were compared with the results obtained in the same artery of a patient amputated following a trauma.

The options to use systemic treatment for tumor debulking in order to make patients accessible to surgery is described in chapter seven a and b.

In chapter 7a we report in response to an article by Cheng and co-workers in Cancer (1999) our results with the treatment of patients with an advanced islet cell tumor with streptozocine and doxorubicin.[10]

In chapter 7b, a case report is described of a patient who received systemic treatment for a liver metastasis in order to achieve radical surgery.

In chapter 8 the results of this thesis are summarized and future perspectives are given.

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Chapter 1

DIAGNOSTIC, SURGICAL AND MEDICAL ASPECTS OF THE MIDGUT CARCINOIDS

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Cancer Treatment Reviews 2002; 28:11-25

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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Chapter 2

PERIOPERATIVE ASPECTS IN PATIENTS WITH ABDOMINAL SURGERY FOR METASTATIC CARCINOID DISEASE

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Submitted

Abstract

Background: Specific medical treatment for metastatic carcinoid disease has prolonged survival, resulting in more disease-related gastrointestinal problems, necessitating surgical intervention. This study aims to evaluate the effect of surgery on morbidity in these patients.

Method: A retrospective survey in a carcinoid referral centre was performed in all surgical patients with abdominal manifestations of a carcinoid in order to get an impression of the indications for surgery, blood loss, peri-operative complications as well as their correlation with biochemical parameters.

Results: Sixty-seven operations in 46 patients were evaluated. The indication for surgery were: resection of primary tumour (n=6) or metastatic lesions (n=8), bowel obstruction (n=28), complications of prior surgery (n=9) and abdominal angina (n=5). Twenty-seven (58%) patients were operated twice, ten, three and two patients were operated on 3, 4 and 5 times respectively. Half of the patients had blood loss over 1000 ml. No carcinoid crisis occurred after premedication with octreotide (n=48) or ketanserin (n=19). The decrease of Mean Arterial Pressure (MAP) in patients under general combined with epidural anaesthesia was twice that of those without epidural anaesthesia. Forty one (61%) of the operations resulted in major and minor complications which proved to be fatal in three patients. Enterocutaneous fistulae were not amenable for further surgery and marked the end-stage of the disease. Levels of platelet serotonin but not urinary 5-hydroxyindolic-acetic acid (5-HIAA) excretion correlated with blood loss.

Conclusion: Surgery for metastatic midgut disease carries considerable morbidity. The combination of epidural and general anaesthesia resulted in a lower mean arterial pressure but premedication can successfully prevent a carcinoid crisis.

Introduction

A carcinoid tumour is usually a relatively slowly growing tumour originating from enterochromaffin cells. Surgery can provide curation, but can also have good palliative effects. Therefore some patients undergo a number of subsequent re-operations to alleviate problems caused by disease progression. Data about peri-operative morbidity and mortality are scarce. The carcinoid tumour can be diagnosed by measuring an increased level of serotonin in blood platelets and urinary secretion of 5-hydroxyindole-acetic acid (5-HIAA), the major metabolite of serotonin.[1,2] Particularly midgut carcinoids often produce large amounts of serotonin. Besides serotonin the tumour frequently produces other vaso-active agents for example bradykinin, substance P, dopamine, epinephrine and norepinephrine.[2-4] Well-known systemic effects of these substances in patients with a disseminated midgut carcinoid are flushing and diarrhoea. During surgery massive release of these amines can lead to a life-threatening carcinoid crisis. In the past these patients were treated peri-operatively with serotonin receptor antagonists (e.g. ketanserin).[5,6] In 1985 a case report described the use of a somatostatin analogue in the resuscitation of a patient in a severe peri-operative carcinoid crisis.[7] After this publication several case reports followed.[8,9]

Presently patients with a carcinoid are frequently treated prophylactically prior to surgery with the somatostatin analogue octreotide.[10] A prospectively randomised trial concerning the effects of octreotide during surgery is no longer considered ethical. Symptom control and survival in patients with a disseminated carcinoid have improved due to treatment with octreotide, interferon alpha, as well as new diagnostic strategies and intervention radiology.[11,12] Tumour growth can frequently be stabilised and sometimes even reduction of tumour size is achieved.[12-19] The prolonged survival confronts the surgeons with an increasing frequency of abdominal symptoms and compels them to repeated surgery.[20-25]

A retrospective survey in a carcinoid referral centre was performed in all surgical patients with abdominal manifestations of a carcinoid in order to get an impression of the indications for surgery, the blood loss, peri-operative complications as well as their correlation with biochemical parameters.

Methods

All patients with a metastasised carcinoid who underwent laparotomy between 1983 and 1998 in the University Hospital in Groningen were studied. Several patients underwent their first operation in another hospital but were referred after initial surgery. Included in our survey were all patients with a metastasised carcinoid who had at least one abdominal operation in our hospital. The data collected comprised patient characteristics, indication for surgery, localisation of the primary tumour, surgical procedure, blood loss, perioperative blood pressure, perioperative complications and biochemical parameters (blood platelet serotonin, urinary 5-HIAA). These data were obtained from the patient's medical records, reports of anaesthesia, surgery and pathology. Since 1990 patients routinely received octreotide 100 μg subcutaneously 3 times a day, starting 3 days before until 3 days after surgery. Before 1990 patients received ketanserin. All patients underwent echocardiography prior to surgery for detection of valvular disease. Patients with a history suggesting abdominal angina underwent selective angiography of the superior mesenteric artery. Anaesthesia was provided according to the anaesthetist's individual routine. There were no specific guidelines imposed regarding the use of epidural techniques or management of circulatory instability. The hemodynamic parameters were monitored by calculating the highest and lowest mean arterial pressure before, during and after the operation in order to reveal the occurrence of hemodynamic instability as one of the features of carcinoid crisis. Before 1990 gross perioperative hemodynamic instability was treated with ketanserin. All patients received an intravenous catheter the evening prior to surgery for overnight administration of glucose/saline (individualised volumes) to compensate for fasting. Induction of anaesthesia usually results in a temporary drop in blood pressure. Therefore, this period was disregarded while determining the lowest and highest perioperative mean arterial pressure (MAP). The hemodynamic data were stratified for prophylactic octreotide. Respiratory data (saturation, respiratory pressure) were collected for signs of bronchoconstriction. Data were analysed using Spearman's Rank test. P values ≤ 0.05 were considered significant.

Results

Forty-six patients, 18 males and 28 females, with abdominal localisation of metastatic carcinoid were studied. The mean age at surgery was 58 years (range 23-90). These patients underwent 92 operations, 67 of which were carried out in our hospital. Twenty-five patients had their first operation in our hospital, 27 a second, ten a third, three a fourth and two patients had a fifth operation. Thirty patients had hepatic metastases. Nineteen operations were carried out before 1990, before the use of octreotide. The localisations of the primary tumour are shown in table 1.

Site	nr
Terminal ileum	22
Appendix	8
Ileocecal	4
Ascending colon	2
Jejunum	2
Meckel's diverticulum	2
Lung	1
Stomach	1
Pancreas	1
Rectum	1
Unknown	2
Total	46

Table 1: localization of the primary tumour

Due to extensive tumour growth, it was not possible to establish the primary site in four patients. These patients were denominated "ileocecal". In two patients the surgeon was confronted with intraperitoneal metastases while no primary site could be found.

The indications for surgery are shown in table 2. Small bowel obstruction was the most frequent indication for surgery (42%), followed by surgical complications (14%).

	Number of operations					
Indication	1-st	2-nd	3-rd	4-th	5-th	Total
Bowel obstruction	10	11	6	-	1	28
Resection of primary tumour	8	-	-	-	-	8
Resection of liver metastases	2	4	-	-	-	6
Resection of locoregional recurrence	-	2	1	-	-	3
Surgical complications	-	4	3	2	-	9
Abdominal angina / small bowel ischemia	1	2	-	1	1	5
Miscellaneous	4	4	-	-	-	8
TOTAL	25	27	10	3	2	67

Table 2: Indications for the consecutive operations

Table 3 shows the complications observed. The recovery after the first and second operation (52 in total) was uneventful in about half the patients. The complication rate increased considerably from the third procedure onwards. Five patients suffered from post-operative bleeding, necessitating 3 re-operations. One of these patients died during surgery from uncontrollable

haemorrhage caused by fibrinogenolysis and afibrinogenemia. Earlier that day the patient underwent an elective ileocolic resection for a small bowel ileus. During the first half hour of that operation coagulation disorder became apparent. The diffuse bleeding could only be controlled by abdominal packing. After 8 hours uncontrollable hemodynamic instability patient required an emergency laparotomy during which haemorrhage proved fatal.

COMPLICATION		total	perc.	1-st	2-nd	3-rd	4-th	5-th
total number of operations		67	100%	25	27	10	3	2
GENERAL	total	16	24%					
post-operative haemorrhage		5		1	2	2		
central venous catheter sepsis		5		3	1	1		
collapse of unknown origin		3		1		1		1
abscess		3		1	1	1		
PULMONARY	total	12	18%					
pneumonia		4			2	2		
bronchospasm		2			1	1		
atelectasis		2		1	1			
pleural effusion		3		2		1		
pneumothorax		1				1		
CARDIAC	total	12	18%					
cardiac failure		7		1	4	2		
angina pectoris		3		1		1	1	
fatal myocardial infarction		2		1	1			
GASTRO-INTESTINAL	total	15	22%					
prolonged ileus		6		2	2	2		
enterocutaneous fistula		5			1	2	2	
anastomotic dehiscence		4		1	2	1		
HEPATIC	total	6	9%					
haemorrhage from metastasis		1			1			
cholangitis		2		1		1		
biliary fistula		3		1		1	1	
UROGENITAL	total	9	13%					
urine retention		3		1	1	1		
infection		2			1	1		
period of anuria		3			2	1		
renal failure		1			1			
MORTALITY	total	5	7%					
in hospital		4		1	3			
within 30 days		1					1	
total number of complicated procedures		41	61%	15	13	10	2	1

Table 3: complications in consecutive surgical procedures

Figure 1 shows the mean and range of the pre-, peri- and post-operative MAP, with or without the prophylactic use of octreotide, the anaesthetic induction period excluded. There was no significant difference between the two groups. There was also no difference regarding the induction anaesthetics; thiopental (n=26 operations), pentothal (n=9) and etomidate (n=21). Eighteen patients received peri-operative inotropic medication in order to maintain or raise blood pressure; these patients were equally divided over the groups receiving octreotide or not. Nineteen patients receiving supplementary epidural analgesia had an average drop of MAP baseline of 42% (+/- 9%) compared to 23% (+/-12%) of the group receiving general anaesthesia alone ($p<0.00001$). The addition of a local anaesthetic to the opioid for the epidural analgesia (9 operations) did not aggravate the drop in MAP seen in patients receiving opioids only in the epidural space (10 operations).

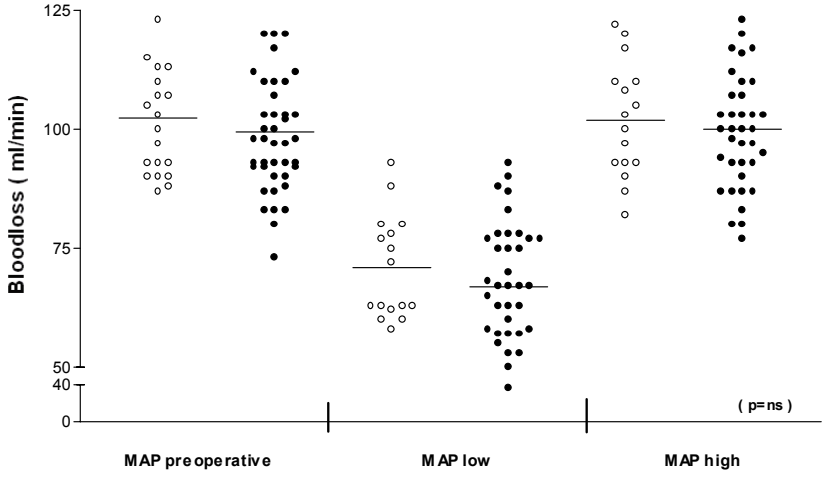

Figure 1 MAP preoperative: pre-operative mean arterial pressure
MAP low: peri-operative lowest mean arterial pressure
MAP high: peri-operative highest mean arterial pressure
° = patient without octreotide
• = patient with octreotide
(37 operations)

In 40 operations the levels of platelet serotonin, urinary 5-HIAA excretion and blood loss were available in the medical records. Approximately half the patients lost more than one litre of blood. Dividing the patients in those having received octreotide or not, revealed no difference with respect to blood loss. Mean blood loss was higher for operations in patients with platelet serotonin above the upper reference limit (URL) namely 4.6 ml/min versus 1.5 ml/min in those with normal platelet serotonin levels (figure 2, panel A, $p<0.01$). There was no relation between urinary 5-HIAA and blood loss (figure 2, panel B). The median survival since operation is 107 months, the 5 years actuarial survival is 69%, the 10 years survival 45% (figure 3)

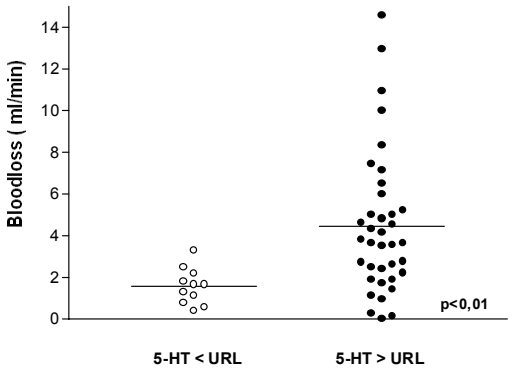

Figure 2 Blood loss per minute operating time (ml/min) for pre-operative platelet serotonin lower and higher than upper reference limit (URL = 5.4 nmol/10^9plt, $p<0.01$)

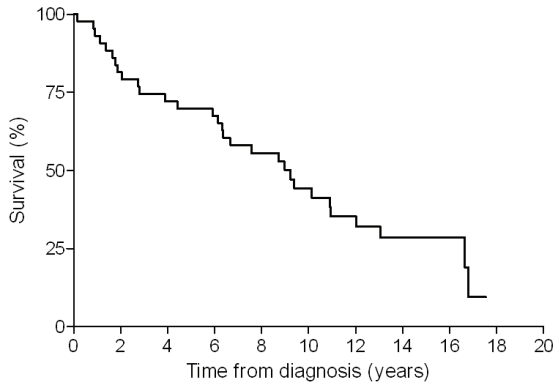

Figure 3 Kaplan-Meier survival curve (from first operation). Five-years actuarial survival is 69%

Discussion

This retrospective, single centre study shows that surgery in patients with a sub-diaphragmatically metastasised carcinoid can be accompanied by considerable morbidity.

The introduction of octreotide has altered the peri-operative management of patients with a carcinoid tumour. This retrospective study did not prove the effect of the administration of octreotide. A full-blown carcinoid crisis during operation is a rare phenomenon. In the pre-octreotide era patients received type 2 serotonin blockers (e.g. ketanserin), which have also shown to benefit in a carcinoid crisis.[26,5,27] In this study, bowel obstruction was the main indication for surgery. Only eight out of the 67 operations were performed for resection of the primary tumour. This low number is due to the fact that surgery often was already performed elsewhere. In general, surgery was performed to palliate complications of progressive disease. There are no guidelines regarding the indications for surgery in metastatic carcinoid disease. However, aggressive surgical approach aimed at reduction of hepatic metastatic tumour burden for palliation of symptoms is sometimes effective.[20,25,28-30] As a result of this, some patients are subjected to repeated surgery**.** Only limited data regarding the peri-operative complications in patients with metastatic carcinoid disease are available.[31,23,25,32] The number of complications of palliative surgery in patients with advanced disease is considerable. Fibrinogenolysis was responsible for a fatal uncontrollable haemorrhage in one patient. Nearly all complications occurred in the post-operative period. Most of them were manageable, but enterocutaneous fistulas in four patients proved persistent and attempts to close them failed. The number of post-operative cardiac complications was 6% and is therefore a reason for special attention.

Mean blood loss per minute operating time was threefold higher for operations in patients with elevated platelet serotonin levels. Platelets are an important storage place in case of elevated serotonin production. The increased blood loss might be due to a platelet-endothelium (dys)function in patients with elevated serotonin levels. It is surprising that a high level of urinary output of 5-HIAA excretion was not related to blood loss, considering its direct relation with serotonin overproduction. There are no data on blood loss during operation of carcinoid patients in a systematic way. Major blood loss during carcinoid surgery has been reported.[33,34] Comparison of blood loss during surgery in these patients and other patients with abdominal operations falls short because of the incomparability of the anatomical situation (i.e. fibrosis, shortened mesentery and adhesions).

Hemodynamic instability as a result of a carcinoid crisis during surgery is a serious complication.[10] There are no data on the incidence of hemodynamic

instability. Veall *et al* arbitrarily considered a deviation from the MAP of 20%-40% as "instability" and more than 40% as "severe instability". In a group of 21 carcinoid patients undergoing abdominal surgery under general anaesthesia, they found 18 with hemodynamic instability (no severe hypertension, 7 with hypertension, 6 with hypotension and 5 with severe hypotension). Our data are comparable, however, we found a lower incidence of hypertension (10%).[35] Furthermore, we found an additional effect of epidural analgesia on the MAP when compared to general anaesthesia alone. Although the hemodynamic instability arising from the use of epidural analgesia in our series proved manageable, caution is warranted.

There was no relation between the biochemical parameters for carcinoid and post-operative complications or fluctuations in blood pressure. With respect to blood pressure Veall *et al* were also unable to find a relation with pre-operative urinary 5-HIAA excretion in their smaller series.[35] A carcinoid can produce many vaso-active agents, besides the well known serotonin, kinines, histamine and substance P. There is growing evidence that many carcinoids harbour enzymes, which enable them to produce dopamine, epinephrine and norepinephrine in significant quantities.[2,4,36] Further investigation concerning the effect of (the balance of) these factors is warranted and may explain the variable effects of surgery on blood pressure.

General guidelines about the surgical treatment of patients with a disseminated carcinoid are hard to give. The decision to perform surgery in a patient with a metastatic midgut carcinoid should be based on the balance between the risks and the prospects of increasing the quality of life. It has been established that surgery can be an effective palliative treatment e.g. resection of small bowel in obstruction or ischemia.[25,32] Our study does not include patients who received radiofrequency ablation for liver metastases as this was not yet performed during the period studied. Currently this treatment modality may at least partly replace resection of liver metastases and induce a different spectrum of complications.[37-40] The tendency towards a more aggressive surgical approach and repeated surgery will undoubtedly be accompanied by more surgical morbidity. Consultation between internist, surgeon, cardiologist and radiologist is essential in order to tailor the treatment to the needs of the individual patient. Because of these considerations we recommend treatment in a specialised institute with experience in state of the art diagnostics and (surgical) treatment.

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Chapter 3

INCREASED PERIOPERATIVE CATECHOLAMINE EXCRETION IN PATIENTS WITH DISSEMINATED CARCINOID.

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Abstract

Carcinoid tumors can produce several other biogenic amines apart from serotonin. Catecholamines such as norepinephrine, epinephrine and dopamine may contribute to carcinoid crises especially during anesthesia and surgery.

Aim of this study was to analyze the catecholamine production peri-operatively in patients with a metastatic midgut carcinoid.

Methods Sixteen metastatic carcinoid patients and seven patients undergoing pancreatic surgery were studied. All patients received octreotide before, during and after surgery. Perioperative blood samples and urine were collected. Plasma and urinary serotonin, (nor)epinephrine, dopamine and metabolites were measured. During surgery hemodynamic parameters were monitored.

Results One patient was excluded because of early post-operative norepinephrine infusion for a carcinoid crisis. Eleven patients were especially monitored before during and after manipulation of the tumor. Five of these 11 carcinoid patients experienced a 25% drop in mean arterial pressure; the other six patients were stable. Besides serotonin no elevated plasma levels of other amines were found in carcinoid patients before, during and after surgery. However the mean urinary excretion of epinephrine, dopamine and serotonin were all markedly increased in carcinoid patients compared to the control group (respectively 20 times: $p<0.007$; 15 times: $p<0.001$; 80 times: $p<0.001$).

Conclusion In patients with metastatic carcinoid disease peri-operative urine levels of catecholamine and its metabolites are markedly elevated compared to controls, suggesting high levels of plasma catecholamines. However, in the presence of octreotide this did not threaten hemodynamic stability.

Introduction

Carcinoid tumors are endocrine neoplasms derived from the enterochromaffin cells. They are usually classified according to their site of origin into carcinoids of the foregut (respiratory tract, stomach, duodenum and pancreas), midgut (small bowel, cecum and appendix) and hindgut (colon and rectum).[1,2] Because of their presumed embryological origin from neuronal entoderm and their ability to take up and decarboxylate amine precursors, carcinoids are referred to as "gut APUDomas". The APUD (amine precursor uptake and decarboxylation) concept points out the ability of cells to synthesize and store biogenic amines and polypeptides. Tumors arising from the APUD system resemble histologically and functionally (endocrine properties) the cells from which they arose[3]. Catecholamines production by carcinoids has been studied rather limited. Goedert et al demonstrated substantial amounts of both dopamine and norepinephrine in addition to serotonin in a mesenteric metastasis of an ileal carcinoid tumor and the presence of the norepinephrine- synthesizing enzymes in the tumor.[4] Moreover, Feldman found in 35% and Kema et al in 38% of serotonin producing carcinoid patients increased plasma levels of dopamine, norepinephrine, epinephrine and their principle urinary metabolites.[5-8] There are however no data available concerning the extent of this production and the effects on the clinical situation during stressful situations such as surgery. A carcinoid crisis is a much feared peri-operative complication.

Aim of this study was to analyze the catecholamine production peri-operatively in patients with a metastatic midgut carcinoid.

Methods

Eligible were all patients with a histologically proven, disseminated midgut carcinoid, undergoing laparotomy because of carcinoid related problems from September 1998 till January 2000 in the University Medical Center in Groningen. The research protocol did not interfere with the scheduled treatment. The control group consisted of non-carcinoid patients who were scheduled for pancreatic surgery. The study was approved by the medical ethical committee of the University Medical Center Groningen. All patients gave informed consent.

All patients (controls included) received octreotide 100 μg 3 times a day subcutaneously starting three days before, till at least four days after surgery. The patients got an intravenous line the evening prior to surgery for overnight infusion with glucose/saline (individualized volumes) to compensate for fasting.

Anesthesia was performed according to routine procedures. There were no imperative guidelines regarding the use of epidural techniques or management

of circulatory instability. Besides a trial dose to assess the proper position of the catheter, patients did not receive epidural local anesthetics during surgery. The hemodynamic parameters were monitored using the arterial pressure before, during and after the operation in order to reveal the occurrence of hemodynamic instability, as one of the features of carcinoid crisis. Respiratory data (O_2 saturation, respiratory pressure) were monitored for signs of bronchoconstriction.

Patients received no dietary restriction other than those required before and after surgery. Twenty-four-hour urine was collected in polypropylene bottles during 5 days, starting one day before until 3 days after surgery. After volume measurement, samples were obtained to which $Na_2S_2O_5$ and EDTA were added. Samples were acidified with acetic acid and then frozen at –20°C. Starting of the urine collection was scheduled 24 hr prior to the time of surgery. Analyzed were: 5-hydroxyindolacetic-acid (5-HIAA), serotonin, total (free and conjugated) catecholamines (epinephrine, norepinephrine, dopamine) and free (unconjugated) catecholamine metabolites (metanephrine, normetanephrine, 3-methoxy tyramine vanillylmandelic acid (VMA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)).

Blood samples were collected every morning during 4 days, using EDTA Vacutainers tubes (6 and 10 ml) starting the day before surgery via a venous line introduced in the forearm at least 10 min before sampling or, during surgery, via an arterial line introduced in the forearm prior to surgery while the patient was anesthetized. Blood samples during surgery were collected with 30 min intervals starting from skin incision until 2 hr after detubation or arrival at the IC-ward. Furthermore, additional samples were collected after palpation (traction) of the mesentery and palpation of the liver (metastases). Plasma samples were put on ice without delay and processed within 2 hr after sampling. The tubes were centrifuged for 30 min at 120 g and 4 °C. Platelet counts were measured with a Coulter Counter Model S plus 4. Analyzed were serotonin, norepinephrine, epinephrine and dopamine. An extensive description of the analytical chromatographic methods used for measurement of the blood and urinary biogenic amine (metabolites) was published previously by Kema et al.[6]

Statistical analysis of the data of the two groups was performed using the Mann-Whitney U test (non parametric test for two independent samples) and correlations by a Spearman Rank test. Only p-values < 0.05 were considered significant.

Results

Sixteen consecutive carcinoid patients were entered in the study. Table 1 shows the patient and surgical characteristics. One patient was excluded from analysis because of peri-operative carcinoid crisis requiring norepinephrine to maintain adequate blood pressure. The control group consisted of seven patients. The median operating time of the control group was twice the operating time in the carcinoid group.

	carcinoid patients	control patients
Number	15	7
Median age in years (range)	55 (52-80)	62 (25-72)
Sex: male / female	7 / 8	4 / 3
Operation (number)	15	7
small bowel resection	13	
hemihepatectomy	1	
retroperitoneal mass resection	1	
pancreatic tail resection		1
lateral pancreaticojejunostomy (Puestow)		1
pylorus preserving pancreaticoduodenectomy		5
Operating time in min (range)	120(60-300)	250(180-390)

Table 1: Patients characteristics

None of the other patients experienced a carcinoid crisis peri-operatively; there were no complications during surgery.

Plasma epinephrine levels (figure 1A) before surgery were similar in both groups. During surgery there were no significant alterations in epinephrine levels at sample points. Noteworthy were the elevated levels of epinephrine during the stay at the recovery room. The days after surgery epinephrine levels were normal in both groups.

Plasma norepinephrine levels (figure 1B) before and during surgery were similar in both groups. Only at 30 min after recovery the epinephrine levels in the carcinoid patients were lower than in controls. During the two days after surgery, norepinephrine levels were similar in both groups but still elevated.

Plasma dopamine was below the detection limit in all patients.

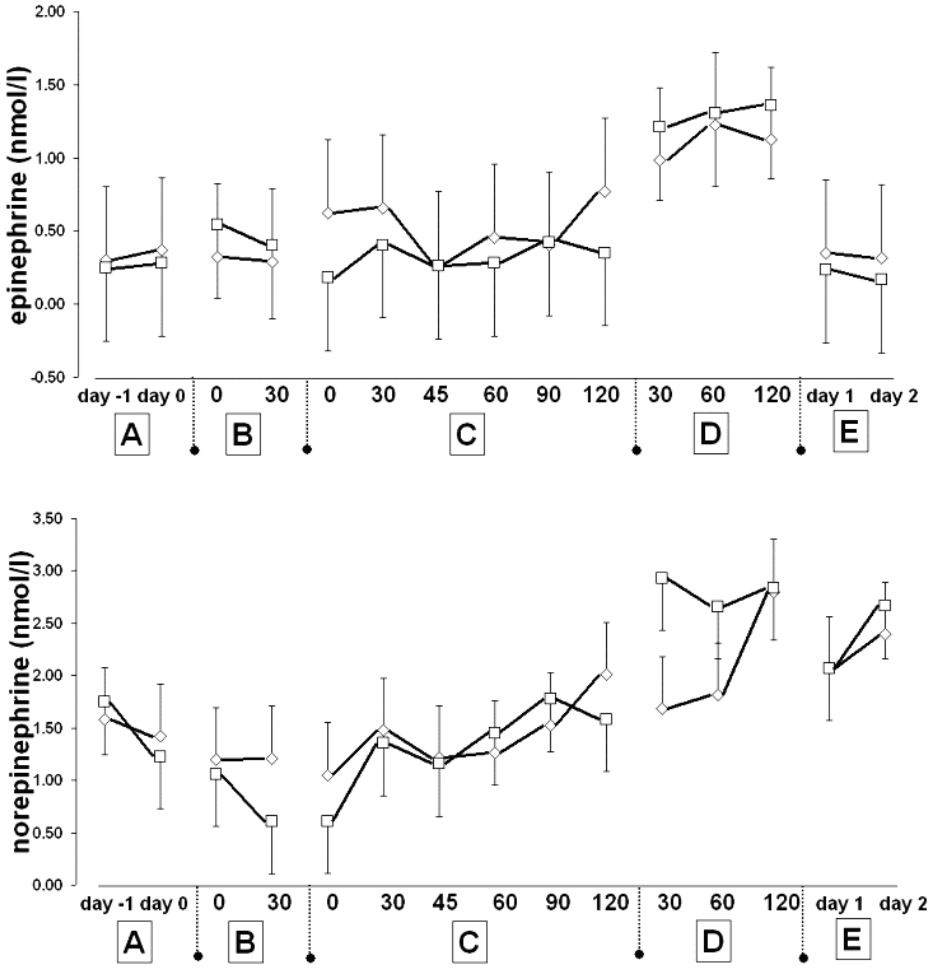

Figure 1a-b: Peri-operative catecholamine concentration in serum (mean ± SD); 1a: epinephrine, 1b: norepinephrine. A: before surgery, B: anesthesia, C: surgery, D: at recovery, E: days after surgery
◊ = carcinoid patients, □ = control patients

Sampling during tumor manipulation by the surgeon ("event") resulted in 5 of 11 patients in a median drop of mean arterial pressure (MAP) of 24% (SD: 13–30) combined with a 40% drop of plasma epinephrine at 15 min (p = 0.03, SD: 17%–82%, figure 2a). The plasma norepinephrine response at the moment of the "event" was varying, half of them increasing the other half decreasing (p = ns). In 6 of the 11 patients there was no significant change in MAP, and no significant alterations in plasma catecholamine concentration (figure 2b).

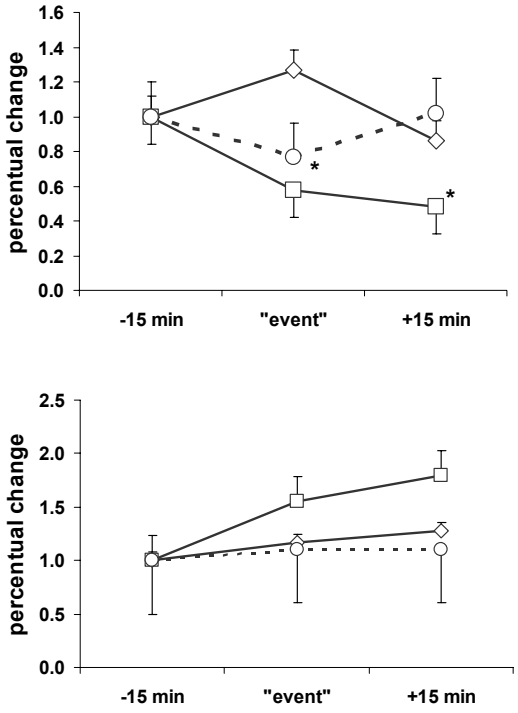

Figure 2a-b: Percentual changes in mean arterial pressure (MAP) and (nor)epinephrine concentrations before, during and after provocation ("event" e.g. tumor manipulation, mesenteric traction). 2a: patients responding with a fall in MAP following the event, 2b: patients responding without fall in MAP. X-axis: 15 min before and after the "event".
○ = MAP, Δ= norepinephrine, □ = epinephrine

Before during and after surgery there was no difference in plasma catecholamine concentration between carcinoid patients and controls. Figure 3 displays the urinary excretion of norepinephrine, epinephrine, dopamine, serotonin and 5-HIAA.

Urine excretion from carcinoid patients and controls showed markedly higher excretion of 5-HIAA ($p < 0.005$), norepinephrine ($p < 0.005$) and dopamine ($p < 0.01$) during all 5 days. In carcinoid patients epinephrine ($p < 0.05$), HVA ($p < 0.05$) and VMA ($p < 0.05$) were raised only during the first two days. Urine DOPAC ($p < 0.05$), normetanephrine ($p < 0.05$) and finally metanephrine ($p < 0.001$) were raised in carcinoid patients compared to controls on the 3 days after operation

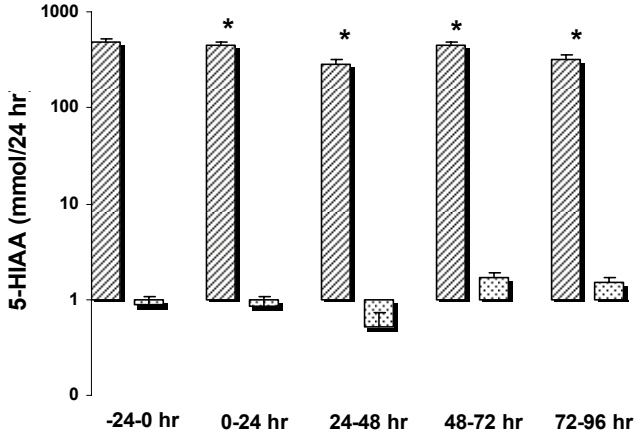

Fig 3a

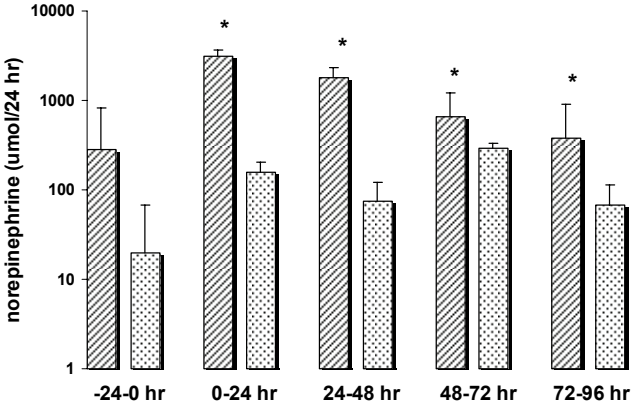

Fig 3b

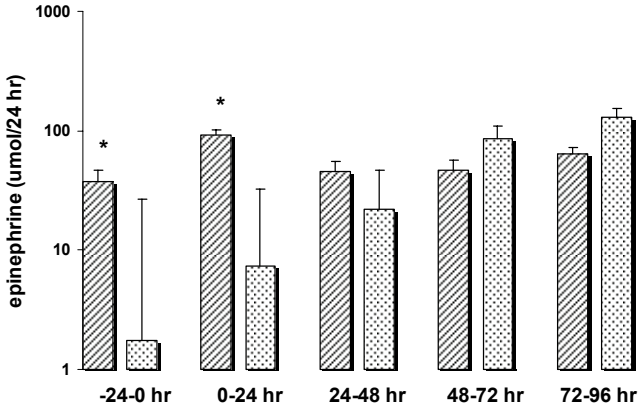

Fig 3c

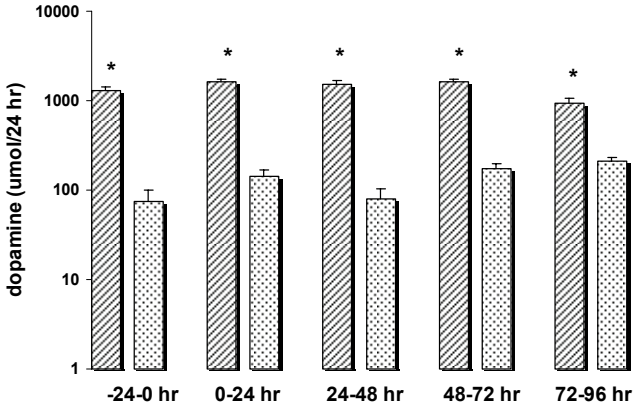

Fig 3d

Figure 3a-d: Peri-operative 24 hr urine excretion (* indicates $p<0.05$, mean ± SD) of 5-HIAA (mmol/24 hr) and norepinephrine, epinephrine and dopamine (µmol/24 hr)

(▨ = carcinoids, ⬚ = controls)

Discussion

To our knowledge this is the first article to describe to this extent the peri-operative amine output in plasma and urine. In carcinoid patients the peri-operatively collected urine showed highly elevated levels of catecholamine (metabolites) compared to controls. We were however not able to detect elevated levels of plasma catecholamines. In our series of carcinoid patients undergoing surgery no carcinoid crisis occurred except in one patient. This patient had to be excluded for biochemical analysis because of peri-operative infusion of inotropic medication. There are only few data with respect to the incidence of the carcinoid crisis. The estimated incidence is considered to be around 10% in patients not receiving octreotide.[9] The advent of octreotide strongly reduced the peri-operative carcinoid crisis.[10,11] In the present study there was no difference in baseline plasma catecholamines between carcinoid patients and controls. Analyzing the collected urine samples however, clearly demonstrated raised catecholamine (metabolite) excretion in the carcinoid group. One of the explanations of the absence of elevated plasma levels might be the site of venous sampling which was behind the two major metabolizing organs (liver and lung). Sampling in the portal vein and inferior caval vein might have been more effective. Another explanation might be an enhanced metabolizing capacity in carcinoid patients, due to persisting catecholamine production. There was a tenfold increase of 24 hr norepinephrine excretion in carcinoid patients on the day of operation compared to before operation. The percentage epinephrine excretion rose equally in both groups but in absolute terms much higher in the carcinoid group (2900 μmol/24 hr versus 150 μmol/24 hr).

The operating time was longer in the control group. Therefore bias with respect to the interpretation of the figures is unlikely, because the longer operating time in the control group might actually have led to a higher instead of a lower excretion of catecholamine (metabolites). The epinephrine excretion increased in both groups, but remarkable is the marked epinephrine increase 48-96 hr after operation in the control group. In both patient groups the same post-operative mobilizing regimen was applied. The increased epinephrine excretion is most likely caused by postoperative pain. The urinary dopamine excretion in the carcinoid patients was fairly stable. In the control patients it doubled on the day of operation and rose further the second and third day after operation.

One can easily understand the danger of imbalance during stress response with these large amounts of catecholamines stored in the tumor. Although octreotide is supposed to stabilize the plasma membrane of the carcinoid cells resulting in decreased excretion of hormones[12], our data suggest some effect in

stabilizing the end organ. One could hypothesize down regulation of catecholamine receptors or of the gene expression in downstream signaling pathways.

We conclude that high postoperative urinary excretion of catecholamine (metabolites) suggests increased levels of circulating catecholamines in carcinoid patients which appear not to pose a major threat to the homeostasis during operation induced stress in the presence of an umbrella of octreotide. However adequate reduction of stress especially pain after surgery should be taken care of.

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Chapter 4

DIAGNOSTIC VALUE OF SERUM CHROMOGRANIN A AND PLATELET AND URINARY INDOLES IN CARCINOID AND ISLET CELL TUMOR PATIENTS

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submitted

Abstract

Aim of this study was to compare the diagnostic value of the neuroendocrine marker serum chromogranin A (CgA) with platelet serotonin and serotonin and 5-HIAA in urine in metastatic carcinoid patients, patients with islet cell tumors and controls.

Serotonin in platelets, urine serotonin, urine 5-HIAA and CgA were measured in carcinoid patients and patients with pancreatic islet cell tumors. Serum samples of sex- and age-matched controls were obtained from healthy volunteers. Samples from 60 carcinoid patients and 12 patients with a pancreatic islet cell tumor were available for CgA analysis. Serum CgA concentrations did not differ between the two patient groups. Both groups had higher CgA compared to controls. Carcinoid patients had higher platelet serotonin, urine serotonin and urine 5-HIAA when compared to patients with an islet cell tumor. The diagnostic sensitivity of serum CgA proved to be at least equal to platelet serotonin for carcinoid diagnosis (88.3% [76.8-94.8] and 98.3% [89.9-99.9] respectively), but CgA appeared superior in diagnosing islet cell tumors: 91.7% [59.8-99.6] versus serotonin in platelets: 30.0% [8.1-64.6], $p<0.01$ urine serotonin 37.5%[10.2-74.1], $p<0.03$ and urine 5-HIAA 37.5% [10.2-74.1], $p<0.03$. The diagnostic sensitivity of CgA proved to be better than urine 5-HIAA and urine serotonin.

Introduction

Neuroendocrine tumor cells are characterized by a common phenotype consisting of the simultaneous expression of general protein markers of and hormonal products specific to each cell type.[1,2] Products are stored in secretory vesicles and may cause specific clinical symptoms such as carcinoid- (serotonin), Zollinger–Ellison- (gastrin) and hypoglycemic syndrome (insulin). Neuroendocrine tumors may arise in nearly every organ, but primary sites in the gastrointestinal- and bronchopulmonary tract are most frequent (57% and 25% respectively).[3] Carcinoid tumors are neuroendocrine tumors and are usually classified on the basis of their site of origin into fore-, mid- and hindgut tumors. They are often slowly growing malignancies with an annual incidence of approximately 2-4 per 100,000.[3] They are part of the group of neuroendocrine tumors, a collection of malignancies that originate from the diffuse neuroendocrine system which is spread throughout the body.[4-7] Their endocrine manifestation is diverse, dependent on tumor-product, related to the site of origin and the presence of metastases. Carcinoid tumors can produce a wide variety of peptide hormones and amines, such as serotonin, neurotensin, substance P, and catecholamines.[8,9]

For the biochemical diagnosis of carcinoid tumors several markers have been advocated. Their diagnostic performance is dependent on the distribution between for- mid- and hindgut in the groups studied. Serotonin overproduction, a hallmark of carcinoid tumors, can be established by measuring platelet serotonin and urinary 5HIAA and serotonin. Specific products such as ACTH and catecholamines can be used to explain tumor related endocrine symptoms.

Chromogranins are the major components of the secretory dense core granules of most neuroendocrine cells.[10,11] Within the secretory pathway, chromogranins are involved in granulogenesis, and in sorting and processing of secretory protein cargo prior to secretion. The chromogranin family includes chromogranins A (CgA) and B (CgB) and secretogranin II (SgII, formerly called chromogranin C). CgA, a 439 amino acid protein with a molecular weight of 49 kD, is water-soluble glycoprotein distributed in the secretory granules of endocrine and neuroendocrine cells. These glycoproteins are co-released with amines. Because of this co-release, elevated serum levels of CgA can be found in a variety of neuroendocrine tumors.[12] CgA levels can be particularly helpful in so-called "non-functioning" endocrine tumors. Once elevated levels have been detected, alterations in CgA levels can serve as a marker for tumor volume.[13] Detection of chromogranins depends on the use of antibodies, therefore different analytical properties of the commercial available kits can display different results.[14] Moreover, CgA compared to secretory hormones (e.g. serotonin in carcinoids) is more heterogeneous because of an extensive

proteolysis which leads to a large heterogeneity of circulating fragments of CgA which may result in lower sensitivity and specificity.[15,16]
The last decade several neuroendocrine markers with respect to detection and diagnosis have been reported. Serengi et al found CgA to be superior to 5-HIAA in the diagnosis of neuroendocrine tumors, sensitivity 68% *vs* 35% and specificity 86% *vs* 100% respectively.[17] In the follow up the concordance of tumor evolution and biomarkers for CgA was 81% and for serotonin 54%.[18] To date CgA is therefore supposed to be a superior marker in neuroendocrine tumors. No studies were performed including CgA and platelet serotonin as a tumor marker although several studies report platelet serotonin to be a superior marker in diagnosing carcinoids, especially those producing only small amounts of serotonin.[19,20] Aim of the present study was to compare the diagnostic performance of the neuroendocrine markers platelet serotonin, serotonin in urine and 5-HIAA in urine with serum CgA in metastatic carcinoid patients, patients with islet cell tumors and controls.

Patients and Methods

Subjects

All metastatic carcinoid patients and patients with pancreatic islet cell tumors diagnosed at the University Medical Center Groningen, in the period 1989-2001 were identified. Included were patients of whom archival samples were available for CgA analysis. The initial results of platelet serotonin, urine serotonin and urine 5-HIAA measurements were used for comparison. A maximum interval of 3 months was allowed between the samples collected for indoles and CgA analysis, provided that no therapeutic interventions were made within this period. Serum samples of sex- and age-matched controls derived from samples of apparently healthy volunteers who participated in 1999 in a previous study on reference values.[21] Samples were coded, meaning that the participants of the original study were not traceable.
All serum and urine samples were obtained during standard treatment and follow-up. For the present study, all relevant data were retrieved from a large computerized database into a separate anonymous database. In this separate database, patient identity was protected by study-specific, unique patient codes, which were known to two data managers, who also have responsibility for the larger database. In case of uncertainties with respect to the data, the larger databases could only be checked through the data managers, thereby ascertaining the protection of patient's identity. The volunteers gave their informed consent for storage of coded samples in the original study. Volunteers and patients were not informed about the research outcome according to rulings of the ethics committee.

Analytical methods

Sampling procedures of the blood samples are described in detail elsewhere.[20,22] Indoles were determined within 2 weeks after sample collection and storage at -20 ºC. Platelet-rich plasma and urine serotonin concentrations were determined by cation exchange chromatography clean-up combined with HPLC and fluorometric detection as previously described.[23] From 2000 onwards, serotonin concentrations in platelet-rich plasma were analyzed by automated in line solid phase extraction combined with HPLC with fluorometric detection.[22] Both methods of the measurement of platelet-rich plasma serotonin are highly correlated (r= .99). Platelet concentrations were measured in platelet-rich plasma with a Coulter STKS (Coulter Corporation). Urinary 5-HIAA concentrations were determined in ether extracts by HPLC with fluorometric detection, essentially as described by Rosano et al.[24] Creatinine levels were measured by a picric acid method on a Mega autoanalyzer (Merck, Darmstadt, Germany). Serum CgA of patients was analyzed immediately or after storage for a maximum period of 11 years at -20ºC. Serum samples of controls were analyzed for CgA in 2004, i.e. after 4.5 years of storage at -20 ºC. It has previously been reported that storage has no influence on serum CgA concentrations.[25] Serum CgA was determined using a radioimmunoassay (Bionovo BV, Purmerend, The Netherlands).

Data evaluation and statistics

Pearson's Chi-square tests were used to test differences between groups in gender-distributions and percentage subjects above reference limits. Differences between groups in ages, platelet serotonin contents, urine serotonin and 5-HIAA concentrations, and serum CgA concentrations were evaluated using the non-parametric Mann-Whitney U test. In all calculations a p-level <0.05 indicated a significant difference. Bonferroni adjustments were made to correct for type 1 errors in multiple comparisons. Spearman correlation tests were performed to investigate age-dependency, and correlations between indoles and serum CgA. Serum CgA reference values were calculated as 95% confidence intervals[26], using the data of the sex- and age-matched healthy volunteers. The upper-limit of the new CgA reference values and the previously established local reference values of platelet serotonin (2.8-5.4 nmol/10^9 platelets), urine serotonin (<66 µmol/mol creatinine) and urine 5-HIAA (0.8-3.8 mmol/mol creatinine) were used as cut-off level. Serum CgA and indole concentration differences between the patient subgroups (foregut, midgut, islet cell tumors) were investigated to gain insight in the specificity of these tumor markers.

Results

Subjects

Samples from 60 carcinoid patients and 12 patients with an islet cell tumor were available for CgA analysis. Their characteristics, together with those of the selected controls, are presented in the Table 1. Patients groups and the control group had similar ages and gender distributions. Serum CgA concentrations did not differ between the patient groups. Both patient groups had however higher serum CgA when compared with controls. Carcinoid patients had higher platelet serotonin, urine serotonin and urine 5-HIAA when compared with patients with an islet cell tumor. The percentage subjects with indole levels above the reference limits was also higher in the carcinoid patients group, as was expected. For details see Table 1.

Serum Chromogranin A reference values

CgA reference values were determined after log-transformation of the original data. CgA proved independent of age and gender. Retransformation of the mean ± 1.96 standard deviation of the transformed data gave rise to an age- and gender-independent reference interval of 21.5 - 75.1 mg/l.

Sensitivity and specificity

Figure 1 shows the serum CgA concentrations plotted against the indole contents and concentrations of both patient groups, together with the upper-limits of the reference levels of the corresponding biomarkers. Levels of CgA were significantly related to platelet serotonin ($r= 0.386$, $p< 0.0005$), urine serotonin ($r= 0.658$, $p< 0.0005$) and urine 5-HIAA ($r= 0.641$, $p< 0.0005$).

Carcinoid patients

Fifty-three of 60 patients (88.3% [76.8-94.8]) had elevated serum CgA (figure panel A,B,C and table 1). All of them had also elevated platelet serotonin (98.3% [89.9-99.9], panel A and table 1). Six of 60 (4 midgut, 2 unknown) had only elevated platelet serotonin. One of 60 (foregut) had normal values for both markers. Of the patients with elevated CgA, 10 had a normal urine serotonin excretion (1 foregut, 3 midgut, 6 unknown, panel B). Three of 60 patients (1 midgut, 2 unknown) had isolated positive urine serotonin. Four of 60 (1 foregut, 3 midgut) were negative for both markers. Two of the 53 CgA positive patients had no elevated 5-HIAA excretion (1 foregut, 1 unknown, panel C). Four of 60 patients (3 midgut, 1 unknown) had isolated positive 5-HIAA. Three of 60 (1 foregut, 1 midgut, 1 unknown) were negative for both markers.

Pancreatic islet cell tumor patients

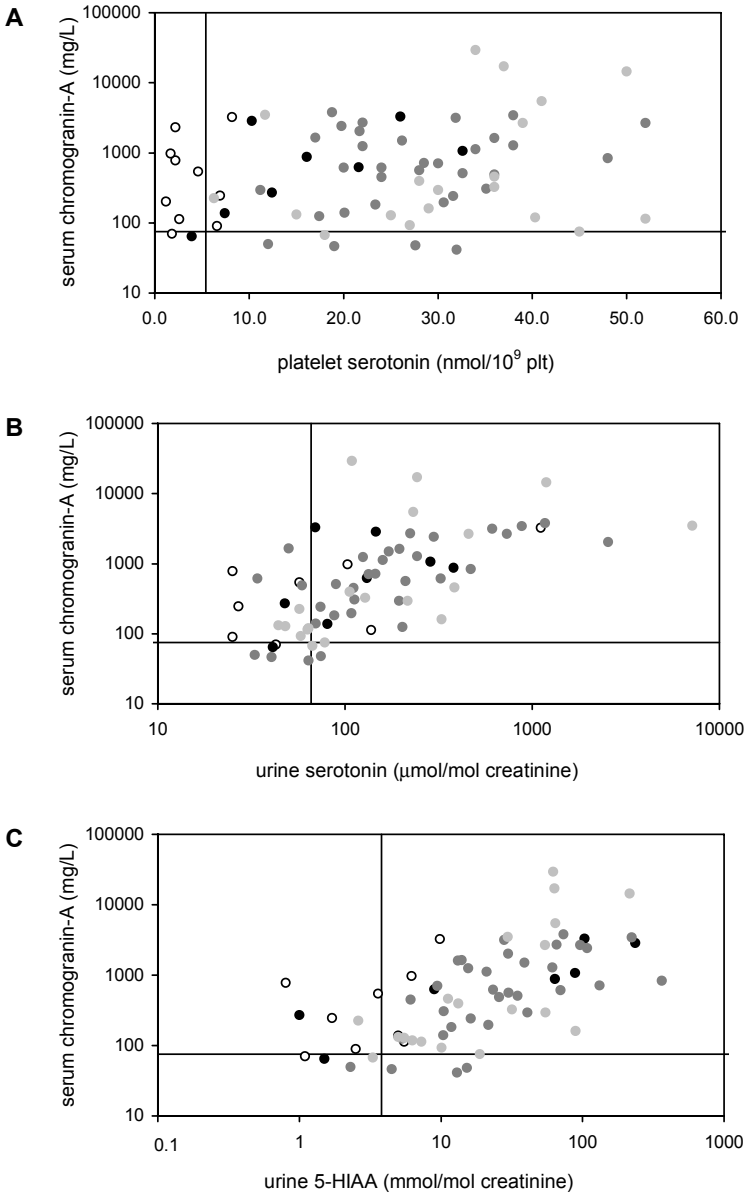
Nine of 10 patients (90% [59.8-99.6]) had an elevated serum CgA, of whom 3 (30% [8.1-64.6]) had only mildly elevated platelet serotonin levels (figure panel A and Table 1). Three of the CgA positive patients had an elevated urine serotonin and urine 5-HIAA excretion (panel B,C). The patients with a normal CgA had also no increased platelet serotonin, urine serotonin and urine 5-HIAA levels (panel A,B,C).

There were no differences in CgA concentrations in-between the carcinoid subtypes as well as the islet cell tumors. However, clear differences in indole concentrations were found between the different carcinoid subtypes. Notably platelet serotonin differed between carcinoid patients and islet cell tumor patients (98% above the upper reference limit (URL) versus 30% respectively, $p<0.01$)

Carcinoid patients with a midgut or unknown primary tumor localization had higher platelet serotonin contents compared with foregut carcinoid patients ($p<0.01$). No other differences in biomarkers existed between the various carcinoid patients. Carcinoid patients with midgut or unknown primary tumor location had higher urine 5-HIAA concentrations when compared with those with an islet cell tumor ($p<0.01$).

		Carcinoid	Islet cell tumor	Control
Number		60	12	27
Age (years)		62 ± 10	61 ± 12	59 ± 10
Male / female		25 / 35	5 / 7	13 / 14
Primary carcinoid localization	Foregut	8		
	Midgut	33		
	Unknown origin	19		
Liver metastasis	No	2		
	Yes	55	7	
	Unknown	3	5	
Lymfnode metastasis	No	2		
	Yes	28		
	Unknown	30	12	
Serum chromogranin A (mg/l)	median	537	394.5	36.9
	range	(47.2-15865.0) [2]	(75.5-12351.5) [2]	(24.3-64.4)
	> 75.1 (=URL), (95%CI)	88.3% (76.8-94.8)	91.7% (59.8-99.6)	
Platelet serotonin (nmol/10^9 platelets)	median	27.8	2.4	
	range	(6.8-51.1)	(1.3-7.9) [1]	
	> 5.4 (=URL), (95%CI]	98.3% (89.9-99.9)	30.0% (8.1-64.6)[1]	
Urine serotonin (µmol/mol creatinine)	median	129.5	49.9	
	range	(37.2-1906.0)	(25.0-943.2) [1]	
	> 66 (=URL), (95%CI)	76.7% (63.7-86.2)	37.5% (10.2-74.1)[1]	
Urine 5-HIAA	median	22.5	3.1	
	range	(1.9-229.2)	(0.9-9.2) [1]	
	> 3.8 (=URL), (95%CI)	91.7% (80.9-96.9)	37.5 %(10.2-74.1)[1]	

Table 1: Patient and control characteristics
1: versus carcinoid patients, p<0.03. 2: versus controls, p<0.0005.



Legend to figures

Serum Chromogranin A versus platelet serotonin (A), urine serotonin (B) and urine 5-HIAA (C) for 60 carcinoid patients and 10 patients with an islet cell tumor.

Lines indicate the upper-limits of the reference values of the corresponding parameters. The closed dots represent the data of the carcinoid patients (primary tumor localization: foregut (●); midgut (●); unknown origin (●)); open dots indicate the patients with pancreatic islet cell tumors.

Discussion

We compared the value of serum CgA with that of platelet serotonin, urine serotonin and urine 5-HIAA for the diagnosis of carcinoids and pancreatic islet cell tumors. To our knowledge this is the first report using platelet serotonin in comparison. To date, serum CgA in carcinoid disease has usually been compared with 5-HIAA. Platelet serotonin proved to be superior to CgA in carcinoid diagnosis, but in diagnosing islet cell tumors CgA was superior to all of the investigated indoles. Urine serotonin and urine 5-HIAA did not have an added value. There is evidence that once the diagnosis carcinoid tumor is established, CgA can be useful in monitoring tumor volume.[17,27] As described earlier by Serengi et al, CgA sensitivity in diagnosing carcinoid disease depends on the stage of disease (50% for stage I and II, 60% for stage III and 100% for stage IV tumors).[17] In our series we included only metastatic (stage IV) carcinoid patients. The number of patients with islet cell tumor was relatively low, however all but one islet cell tumor patient had elevated CgA levels. This is in concordance with literature.[17,28] Panzuto found the diagnostic value to be augmented by combining CgA findings with pancreatic polypeptide.[29]

In our series the platelet serotonin test showed the smallest overlap between carcinoids and islet cell tumors and therefore appeared to be the most discriminative test. Raising URL of platelet serotonin to 10 nmol/10^9 platelets in our series would augment this discrimination. A serum CgA above the URL and a platelet serotonin below 10 nmol/10^9 platelets would point in the direction of a neuroendocrine non-carcinoid tumor. However elevated CgA levels are not always related to neuroendocrine tumors. They can also be found in patients with an adenocarcinoma, atrophic gastritis, patients treated with gastric secretion inhibitors and in patients with renal failure or without any obvious cause.[30]

We conclude that in our patient groups the diagnostic sensitivity of platelet serotonin proved to be at least equal to serum CgA in carcinoid diagnosis, but serum CgA appeared superior in diagnosing islet cell tumors. The diagnostic sensitivity of urine 5-HIAA and urine serotonin proved to be lower than CgA in all cases.

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Chapter 5

ABDOMINAL ANGINA IN PATIENTS WITH A MIDGUT CARCINOID, A SIGN OF SEVERE PATHOLOGY

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World Journal of Surgery 2005;29:1139-1142

Abstract
In 36 consecutive patients with a foregut carcinoid with extensive local tumor growth and liver metastases with a carcinoid syndrome, six patients had complaints of postprandial abdominal pain and attacks of subileus based on segmental intestinal ischemia. A diagnosis of abdominal angina was supported by a positive response to nitroglycerin in two and ischemia of the ileum demonstrated by angiography in two other patients. Complaints improved in all patients by surgery. Histopathology of the resected small bowel specimens showed elastic vascular sclerosis in three and ischemic changes in three other patients, confirming the clinical diagnosis. Resection of ischemic bowel can provide relief in patients with segmental intestinal ischemia due to carcinoid-induced vascular sclerosis.

Introduction

Carcinoid of the midgut has an incidence between 0.46 and 1.13 per 100,000 persons per year.[1;2]

Abdominal pain is a frequent presenting symptom in these patients. Abdominal pain in carcinoid patients can also be due to bowel ischemia apart from bowel obstruction due to e.g. the primary tumor.

Reviewing 209 patients with a midgut carcinoid, Moertel in 1961 was one of the first to report bowel ischemia in four carcinoid patients.[3] Ten years later Anthony and Drury described elastic vascular sclerosis as a morphologic substrate for this disorder in carcinoid patients.[4] Due to its rare occurrence intestinal ischemia at diagnosis and during the course of the disease is not always considered as the main cause of abdominal pain in these patients. Mesenteric fibrosis, nodular involvement, progressive tumor growth and peritoneal adhesions causing intermittent subileus are other well known complicating factors. An exploratory laparotomy, following failure of conservative treatment of a subileus often does not disclose the bowel ischemia, which can be the origin of the problem. Abdominal angina can be diagnosed by a response to sublingual nitroglycerin.[5] A superior mesenteric artery (SMA) angiography prior to surgery can assist in making decisions before and during laparotomy. Over the last decades, new treatment modalities such as octreotide and interferon have been shown to suppress the release of vaso-active substances by carcinoid tumors. These improvements may have led to a longer survival, potentially resulting in more late vascular symptoms in these patients.[6;7] In a series of 36 consecutive patients with a carcinoid syndrome with extensive tumor growth and liver metastases, six patients complained of abdominal pain and episodes of subileus and underwent surgery based on definite criteria. The diagnostic work up and results are discussed.

Patient 1
A 67-year-old man with a metastatic carcinoid tumor had a history of left ventricular failure and a coronary bypass graft 10 years ago. He had experienced flushes for some months and an abdominal CT scan showed multiple hepatic metastases. A small bowel ileus required a laparotomy disclosing a 30 cm segment of purple-colored ileum, bearing a small, stenosing tumor and massive involvement of the liver. The mesentery of the small bowel was shortened by fibrosis and metastatic nodes causing kinking and twisting of the bowel. Segmental resection was considered hazardous because of vascular complications and a bypass of the stenosis was thought to be sufficient. The patient recovered uneventfully but was readmitted 2 weeks later for acute peritonitis. Laparotomy revealed necrosis of the bypassed small bowel segment requiring resection of 80 cm ileum followed by end-to-end anastomosis. Five days later a third laparotomy was needed to drain an anastomotic leak. Twenty days postoperatively the patients, while on total parenteral nutrition (TPN), died of left sided cardiac failure. The bowel necrosis was most likely caused by total inadequate bowel circulation, which was not recognized during the first laparotomy and subsequently leads to full blown necrosis.

Patient 2
A 61-year-old man presented with severe abdominal pain. Gallstones were diagnosed but a laparoscopic cholecystectomy did not alleviate his abdominal discomfort. Two months later an exploratory laparotomy showed a tumor in a Meckel's diverticulum with venous congestion and partial necrosis of the ileal wall, invading the mesentery and resection of 15 cm of the small bowel disclosed a carcinoid tumor with metastatic nodes in the mesentery. A few months later he was referred for continuous severe abdominal pain intolerable during the first few hours after each meal. Opioids did not sufficiently relieve the pain and the patient, having lost 21 kg in a few months time was put on TPN. Ultrasound of the abdomen and a small bowel series showed no abnormalities. The CT scan showed a mass anterior to the mesentery of the small bowel. An octreotide scan showed activity medially of the right kidney. A substraction angiography of the SMA showed the ileocolic artery to be absent, resulting from the previous operation (Figure 1). The distal ileal arteries were not visible. At laparotomy, the distal ileum was pale and covered with distended veins. Multiple enlarged lymph nodes were seen in the small bowel mesentery. After resection of 80 cm of the distal ileum, the patient recovered uneventfully and resumed enteral nutrition. Pathology showed ischemic enteritis with multiple distended veins. The routine

stains showed no vascular abnormalities in the specimen. Nine years later the patient can eat normally and is able to maintain his body weight.

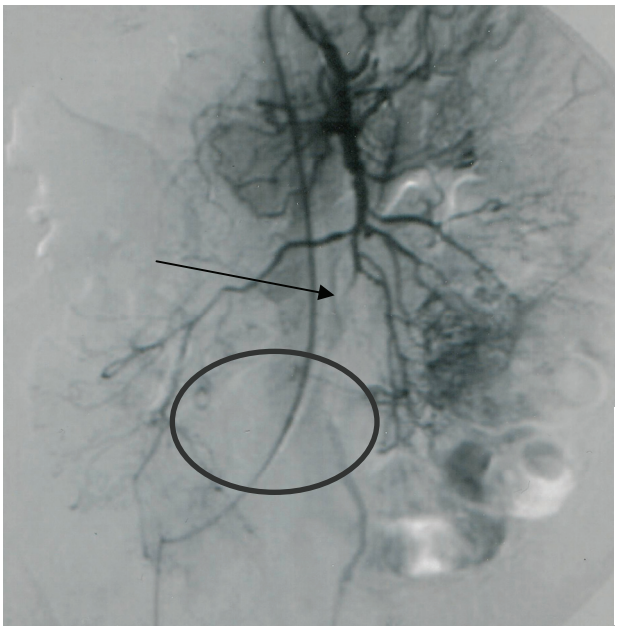

Figure 1:
Angiography of the SMA of patient 2. The ileocolic artery is absent (arrow) as a result of the first operation. The distal ileal arteries are not visible (oval).

Patient 3

A 48-year-old female underwent resection of the terminal ileum for a carcinoid tumor in another hospital, but a metastatic mass was left in situ. During the subsequent 2 years the patient underwent two laparotomies, one to relieve a mechanical ileus and one to bypass the duodenum compressed by metastatic nodes. Two years later abdominal complaints developed in a pattern suggesting abdominal angina; an angiography however was normal. At laparotomy an ileal loop adherent to the metastatic mass in the mesentery was resected, but showed no microscopic abnormalities. After some months the abdominal pain recurred and the patient could tolerate only liquids while using uploads. A carcinoid syndrome became apparent and the CT scan showed liver metastases.

Abdominal pain worsened by meals and subsided after sublingual administration of nitroglycerin. An angiography of the SMA showed compromised circulation in the distal ileal arteries, which deteriorated during tube feeding and improved during administration of nitroglycerin. Another laparotomy confirmed the absence of palpative ileal arteries in the distal 70 cm of the ileum. After resection of 60 cm the patient recovered uneventfully and normal enteral feeding was resumed. Microscopy, however, showed normal small bowel without evidence of ischemic

alterations. The absence of vascular abnormalities in the specimen and the beneficial effect of nitroglycerin suggested a compromised circulation by the combination of mechanical compression and vascular spasms. Three years later the patient is still doing well.

Patient 4
A 51-year-old man was referred with a carcinoid syndrome with flushes and diarrhea up to 10 times a day, which had progressed slowly over the last 5 years. He was treated with interferon-α. The history was consistent with partial obstruction of the small bowel. At laparotomy the mesentery contained numerous metastatic nodes and was shortened by fibrosis. The primary tumor was situated in a Meckel's diverticulum and removed by a segmental resection. The patient visited our outpatient clinic one year later with a small bowel ileus prior to which he could tolerate liquids only. At laparotomy adhesive segments of the terminal ileum with an aspect similar to radiation enteritis were resected. After resection of the affected small bowel segment we were concerned by the marginal circulation of the proximal side but further resection was not carried out in fear of causing a short bowel syndrome. Pathology showed ischemic enteritis reaching into the resection margins with increased elastin in the vascular adventitia. Postoperatively the patient developed a small bowel fistula refractory to conservative treatment. At subsequent laparotomy extensive adhesion prohibited access to the peritoneal cavity. The patient succumbed several weeks later.

Patient 5
A 69-year-old female was seen with a history of diarrhea and flushing caused by a carcinoid tumor with hepatic metastases. Over the past decade her weight had steadily decreased. At referral her body weight was 54 kg with a 1.76 m length. An octreotide scan showed lesions of metastases in the liver and both lungs. Subcutaneous octreotide was started and the diarrhea subsided. One year later she was admitted because of deteriorating condition and progressive weight loss, but she denied cramps or abdominal angina related to meals. A small bowel transit examination showed slow passage and inertia of the small bowel. Angiography of the SMA showed (probably congenital) absence of both the right and middle colic artery and equivocal circulation in both ileal arteries. A laparotomy was mandatory with the anatomy and circulation of the terminal ileum compromising the function of the intestinal tract. The terminal ileum showed venous congestion and was considerably narrowed and kinked due to shortening of the mesentery with several

metastatic foci. An ileocecal resection was performed and microscopy showed a small carcinoid tumor, metastatic nodes in the mesentery and tumor deposits on the surface of the mesentery without ischemic changes. The vessels showed sclerotic changes with thickening of the adventitia caused by elastic vascular sclerosis (Figure 2). After initial recovery the patient developed a small bowel ileus requiring a second laparotomy. The ileocolic anastomosis was trapped in an adhesive mass in the right upper abdominal quadrant, which necessitated a resection of the anastomosis. Histopathology showed serositis but no ischemia. An enterocutaneous fistula required TPN but cardiac condition deteriorated progressively and she died of cardiac failure. Post-mortem examination disclosed the presence of metastatic carcinoid tumor and valve abnormalities consistent with carcinoid heart disease.

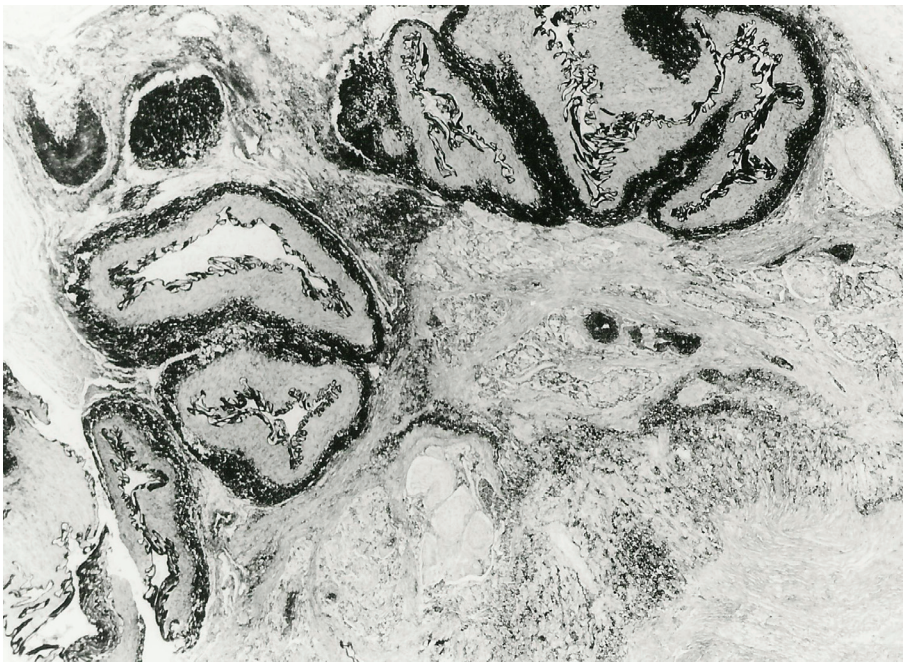

Figure 2
Microscopic aspect of the mesentery of the small bowel of patient 5. Extensive deposition of elastic fibers in the adventitia of the arterial wall with narrowing of the lumen (left upper corner). The elastin staining is responsible for the dark color of the elastic fibers in the arterial wall and in the surrounding soft tissue (enlargement 25:1).

	clinical presentation			investigation		pathology		outcome	remarks
patient	weight loss	ileus	angina	angiogram	nitroglycerin	ischemia	EVS	improved	
1	-	+	-	ND	ND	yes	-	-	died, cardiac failure
2	+	-	+	positive	ND	yes	-	yes	
3	+	-	+	positive	+	-	-	yes	
4	-	+	-	ND	ND	yes	yes	-	died, leaking anastomisis
5	+	-	-	not conclusive	ND	-	yes	-	died, cardiac failure
6	+	-	-	not conclusive	+	-	yes	yes	
total	**4**	**2**	**2**	**2**	**2**	**3**	**3**	**3**	

Table 1
Clinical presentation, procedures and pathology,
of the 6 patients in chronological sequence
ND = not done,
EVS = elastic vascular sclerosis,
+ = present

Patient 6
A 70-year-old female with a rectal adenocarcinoma underwent pre-operative radiotherapy followed by rectosigmoid resection and colorectal anastomosis in another institution. During re-laparotomy for post-operative hemorrhage the surgeon encountered and excised a small tumor of the terminal ileum, which proved to be a carcinoid. Post-operatively, food intake elicited intolerable abdominal pain lasting for about 20 minutes. The patient was admitted to our institution and placed on TPN. Angiography of the SMA revealed equivocal circulation of the terminal ileum. The abdominal pain promptly disappeared after sublingual administration of nitroglycerin. At re-laparotomy dense adhesions were found between the loops of the terminal ileum. The mesentery contained several enlarged lymph nodes. A 100 cm segment of terminal ileum was resected and continuity was restored by means of an ileocecostomy. Pathology showed multiple carcinoid tumors, metastatic nodes, peri-vascular fibrosis and elastosis of the vessel wall. The patient recovered and proved to be able to eat without any abdominal discomfort.

Discussion

These six cases demonstrate that postprandial abdominal pain in patients with a midgut carcinoid can be caused by segmental intestinal ischemia. The data about the clinical presentation, diagnostic procedures and pathology of the specimens are summarized in Table 1. Ultimately 3 patients died post-operatively from complications of enteric ischemia and end stage carcinoid syndrome. The initial symptoms are too aspecific to differentiate bowel ischemia from obstruction due to adhesions and/or mesenteric fibrosis. However, a history of pain occurring directly after meals or an intolerance for food with severe weight loss, as in patients 2, 3, 5 and 6, are suggestive for ischemic bowel disease. We earlier described the sublingual administration of nitroglycerin for the temporary relief of the pain to confirm bowel ischemia.[5] In some patients ileal transit is impeded by the intestinal stenosis. Plain X-rays, ultrasound, CT scanning and MRI do not help to differentiate between obstruction and ischemia. Only a selective angiography of the SMA with food challenge can distinguish between these two.[8] Angiography can confirm the diagnosis and informs about the appropriate segment to be resected. This will enable the patient to resume adequate feeding. Inadequate resection or a bypass procedure will leave the patient with (intolerable) pain (e.g. patient 2) and the hazard of subsequent necrosis of the compromised bowel segments, as happened to patient 1. There is still

much to be elucidated about the pathophysiology of intestinal ischemia in carcinoid disease. After the description of Anthony and Drury several authors have confirmed their observations.[4,9-16] Intestinal ischemia in carcinoid disease is only seen when the primary tumor is located in the midgut. They hypothesize that the fibrosis originating from serotonin release causes fibrosis with shortening and kinking of the mesentery and narrowing of the vessels by means of elastic vascular elastosis. The mechanical effect of metastatic nodes in the mesentery may be a third factor. Other authors postulate a direct effect of serotonin on the smooth muscle cells and the fibroblast of the vessel wall. The effect of nitroglycerin on abdominal angina is suggestive for reversible vasoconstriction. The authors agree that ischemia is only seen in patients with residual metastatic disease in the mesentery, consistent with a loco-regional biochemical effect.[9-16] Overexpression of acidic fibroblast growth factor (aFGF) in stroma of a carcinoid tumor might be another, additional local factor.[17] In 2004 Modlin et al surveyed the literature over the last 40 years covering the incidence, diagnosis, therapy and biological basis for carcinoid-associated fibrosis. Surgery remains the cornerstone of therapy. They conclude that the mechanism of fibrosis is still poorly understood and there are no means by which this complication can be predicted or monitored.[18] These six patients have taught us to consider the possibility of intestinal ischemia. In a patient with carcinoid syndrome, abdominal complaints inconsistent with ileus should be an indication for a nitroglycerin test and selective angiography to evaluate whether ischemia plays a role. Moreover, angiography can help the surgeon decide to operate or not. Prior to any surgery for residual carcinoid of the midgut, an angiography of the SMA should seriously be considered. Patients with carcinoid syndrome with abdominal angina due to a midgut carcinoid with loco-regional extension can only be helped by surgical resection even though the complication rate is high.

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Chapter 6a

DIMINISHED BAROREFLEX SENSITIVITY IN CARCINOID PATIENTS WITHOUT SIGNS OF EARLY ATHEROSCLEROSIS OR ENDOTHELIAL DYSFUNCTION.

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Submitted

Abstract

Serotonin or other vasoactive amines produced by a carcinoid tumor are thought to be responsible for the characteristic changes in the mesenteric vessels known as vascular elastosis. The aim of this study was to evaluate the structural and dynamic properties of the vessel wall of carcinoid patients outside the mesentery as compared to healthy controls.

In 17 carcinoid patients with elevated platelet serotonin level and 21 healthy age and sex matched volunteers the intima-media complex thickness (IMT) of the common carotid artery as a marker of early atherosclerosis, and flow-mediated dilation (FMD) of the brachial artery to assess endothelial function were determined. Baroreflex sensitivity (BRS) as function of autonomic modulation and regulation of vessel tone was measured using transfer function analysis of the Finapres® signal.

No differences were found in IMT or FMD between the two groups, suggesting no structural or functional alterations in the brachial and carotid artery in carcinoid patients. The BRS, however, was lower in the carcinoid group (1.5 ± 0.3 msec/mmHg) versus controls (2.1 ± 0.5 msec/mmHg, $p<0.0001$) indicating an overbearing sympathetic system.

In conclusion, the degree of BRS reduction may indicate an increased risk for cardiac events.

Introduction

A carcinoid tumor usually is a relatively slowly growing tumor originating from enterochromaffin cells. Especially the midgut carcinoids are able to produce various biogenic amines, among which serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA). Serotonin is thought to be responsible for the characteristic vascular changes in the mesentery known as vascular elastosis, which is pathognomonic for carcinoid disease. It consists of fibrosis of media and adventitia of mesenteric vessels causing narrowing of the lumen.[1,2-4] Abdominal angina is a known complication in advanced stage carcinoid disease.[5] The abdominal pain can be reduced with sublingual medication e.g. nitroglycerin, indicating a dynamic component in the mesenteric ischemia which might be due to endothelial dysfunction.[6] Elevated serotonin levels will eventually lead to carcinoid heart disease. This disorder is usually located within the right heart, consisting of fibrous depositions in the endocardium and the valves leading to valve insufficiency, cardiac failure and cardiac death.[7] Measurement of the intima media complex thickness (IMT) of carotid or femoral vessels has in recent years become a generally accepted method to assess structural abnormalities in larger arteries and to detect early atherosclerosis. Besides structural changes in the vessel wall several reports indicate functional changes due to circulating biogenic amines, presumably serotonin.[8-10] Since the original article of Celermajer and Deanfield in 1993, flow-mediated dilation of the brachial artery has become an important method to assess endothelial function.[11,12] Several articles have shown impaired flow-mediated dilation in smokers, patients with hypertension or diabetes or some of the other conditions associated with increased cardiovascular risk.[13] Vascular function includes not only endothelial function, but also autonomic modulation and regulation of vessel tone. These functional properties reflecting cardiac autonomic nervous balance can be assessed by measuring the baroreflex sensitivity (BRS). The primary purpose of the arterial baroreflex is to keep blood pressure close to a particular set point over a relatively short period of time via a negative feedback system, counteracting transient changes in blood pressure. A sudden fall in blood pressure will trigger an autonomic response in the baroreceptors situated mainly in the aortic arch and carotid artery in order to increase heart rate and cardiac contractility with the purpose to regain blood pressure. An impaired BRS is an independent risk factor for sudden death after myocardial infarction.[14,15] In hypertensive humans and animals, the baroreflex control of heart rate is diminished.[16] Besides the pathognomonic morphological changes in mesenteric vessel wall, there are no data on endothelial dynamic and

autonomic function or on structural disorders of the peripheral vessel wall in carcinoid disease even when such functional and structural vascular changes may have prognostic cardiovascular relevance. In this study these aspects were studied in carcinoid patients and healthy volunteers.

Patients and methods

From September 1999 to January 2000, all consecutive midgut carcinoid patients with platelet serotonin levels of 3 times the upper reference limit and higher during prior visits, visiting our outpatient clinic were invited to participate in this study. Patient's history was obtained regarding diabetes, cardiovascular disease and hypertension. From August 2003 to February 2004, controls matched for sex and within the age range with the patient group were recruited. In none of the controls manifest cardiovascular or renal disease, hypertension or diabetes was present. The study was approved by the Medical Ethical Committee. All patients and volunteers gave informed consent.

Carotid Intima-Media Thickness (IMT) measurements

IMT measurements were performed using a Pie Medical Scanner 200 device with a linear array transducer of 7.5 MHz. The IMT was measured at the posterior wall of the left common carotid artery approximately 1 cm proximal to the bulbus at 3 different positions. A B-mode image was obtained of the carotid artery after which a M-line was positioned perpendicular to the posterior wall, showing an intima-media complex. The radio frequency signals and the electrocardiogram were stored on hard disk for 3 periods of 4 sec and IMT was calculated for the total 4-sec periods. The recorded files were processed using the wall thickness calculation section of the Wall Track System 2.0 software (Pie Medical, Maastricht, The Netherlands). The mean of the 3 measurements was used to calculate IMT. Technicians blinded for patient characteristics performed all off-line analyses. The intra-observer variability in our laboratory is 0.051 mm, or 8.1% of the mean IMT, and is independent of wall thickness (R2=0.13, non-significant)

Flow-mediated dilation (FMD) procedure

The method is based on ultrasonography of the brachial artery to assess endothelium-dependent and -independent function. The measurement system consisted of an ultrasound scanner (Scanner 200, Pie Medical), and a personal computer with a high-speed data acquisition board, frequency sample 21.5 MHz. Dedicated software (Wall Track System 2.0, Pie Medical) was used to measure and analyze changes in brachial artery

vessel diameter. Using a 7.5 MHz transducer the brachial artery was visualized. A two-dimensional longitudinal B-mode image of the brachial artery was obtained. The radiofrequency (RF) signals from the M-mode output were relayed to the wall tracking system and stored digitally. Using the RF signal the anterior and posterior vessel wall are identified and marked. Vessel wall movements are tracked using off-line analysis. This enabled measurement of end-diastolic diameter for each beat. Measurements were conducted in supine position at a constant room temperature. A custom built holder was used to stabilize the probe during the measurements. Procedures were as follows: (1) two brachial artery baseline diameter measurements (2) arterial occlusion by inflation of a pneumatic tourniquet placed around the forearm distal to the segment of artery scanned (3) deflation of the tourniquet after 4 min, resulting in an increased blood flow to the distal part of the forearm inducing an endothelium-dependent vasodilatation (4) measurement of the brachial artery diameter after deflation continuously for 6 cycles of 22 sec (5) measurement of the brachial artery 2.5 and 5 min after giving nitroglycerin 0.4 mg sublingually, resulting in endothelium-independent vasodilatation. For each measurement consisting of 22 sec data acquisition the average end-diastolic diameter of these 22 sec was used. Intra- and inter-observer variability of this system is 2.5% and 5.0%, respectively. The off-line data analysts were blinded for the clinical parameters of the subjects. FMD was calculated as the percent maximal increase in arterial diameter during hyperemia compared to the average of 2 baseline diameters, and nitroglycerin induced dilation was calculated the same way for the maximal post-nitroglycerin diameter.

BRS measurements

BRS was investigated using Finapres® equipment (Ohmeda TM2300, Inglewood, Co, USA). Patients were asked not to drink coffee or smoke prior to the investigations. A Finapres cuff was applied to the midphalanx of the third finger for continuous beat-to-beat blood pressure measurement.

In short, the BRS was determined by the transfer function technique using the CARSPAN program (IEC ProGamma, Groningen, the Netherlands), as described previously.[17,18] This program allows discrete Fourier transformation of non-equidistant samples of blood pressure and RR interval series. After correction for artifacts and checks for stationarity, BRS is defined as the mean modulus between spectral values of systolic blood pressure variability and heart rate variability in the low frequency

(LF, 0.07-0.15 Hz) power spectrum band with at least 0.3 coherence, expressed in ms/mmHg.

Statistics
Statistical analysis of the data of the two groups was performed using the independent sample t-test. BRS values are given as natural logarithms. Only p-values <0.05 were considered significant.

Results

Eighteen consecutive midgut carcinoid patients meeting the inclusion criteria were invited to participate. One patient refused, 17 gave informed consent, 10 males and 7 females. Median age was 60 (range 51-73) years. The median platelet serotonin at time of the investigation was 24 nmol/10^9 platelets (range 17-39) and the median urinary 5-HIAA excretion 23 mmol/mmol creatinine (range 8-324). The median reported time of symptoms of disease prior to the investigation was 10 years (range 3-18). None of the patients had a history of diabetes, cardiovascular disease or hypertension prior to the onset of the carcinoid disease. The control group consisted of 21 healthy volunteers, median age 58 (range 43-73) years and were sex matched.

Common carotid Intima Media Complex
The mean IMT of the far wall of the left carotid artery in carcinoid patients was similar to that of control namely 0.70 mm ± 0.11 and 0.75 mm ± 0.17 respectively (p=ns).

Flow mediated and nitroglycerin-induced dilation of brachial artery
For this parameter there were also no differences between the carcinoid patients and the controls (Table 1). The mean diameter of the brachial artery was 4.9 mm ± 1.2 in carcinoid patients compared to controls 5.1 mm ± 0.8 (p=ns). After occlusion the mean diameter was 5.1 mm ± 1.1 and 5.3 mm ± 0.7 respectively. The mean percentage dilation after occlusion was 4.7% ± 7.5 and 6.9% ± 8.7 respectively (p=ns). Compared to the non-endothelial dependent dilation (i.e. after sublingual nitroglycerin), there was no difference between the groups either. In carcinoid patients the dilation after occlusion was 95.3% ± 5.9 of the dilation after nitroglycerin administration, in controls 92.2% ± 6.7 (p=ns).

Baroreflex Sensitivity

The mean BRS in carcinoid patients was 1.5 ± 0.3 msec/mmHg and in the controls 2.1 ± 0.5 msec/mmHg ($p<0.0001$, Table 1). In the carcinoid group no correlation was found between serotonin in platelets or urinary 5-HIAA excretion and the BRS. There were no differences in blood pressure between the two groups

Parameter	Carcinoid N=17	Controls N=21	p-value
CCA intima-media thickness (mm)	0.699 ± 0.113	0.751± 0.168	0.56
Baseline BA diameter (µm)	4920 ± 1234	5052 ± 797	0.78
Flow-mediated vasodilation (%)	4.7 ± 7.5	6.9 ± 8.7	0.78
NTG-mediated vasodilation (%)	4.7 ± 5.9	7.8 ± 6.7	0.09
Baroreflex sensitivity (msec/mmHg)	1.51 ± 0.34	2.11 ± 0.48	<0.001

Table 1: Vascular structure and functional parameters in carcinoid patients and controls. CCA: common carotid artery; BA: brachial artery; NTG: nitroglycerin; all values are means ± SD.

Discussion

To our knowledge this is the first study on both structural and functional characteristics of peripheral arteries in carcinoid patients. The BRS in the carcinoid patients is markedly diminished compared to sex and age matched controls.

However, no differences in carotid IMT or FMD were found. There is abundant literature pointing out a low value BRS as an unfavorable prognostic factor in post-myocardial infraction patients and as independent risk factor of cardiac failure.[14-16,19,20] For other patients like those with chronic kidney disease a low BRS also acts as a risk factor for cardiac events.[21] Our results suggest that carcinoid patients suffering from high levels of serotonin are at risk of arrhythmia and sudden cardiac death. We hypothesized that the well known vascular elastosis in mesenteric arterial and venous vessels in carcinoid patients could also be associated with both structural and functional abnormalities in the systemic vasculature. Remarkably however, no differences were found in either carotid IMT, or in FMD of the brachial artery as a marker of endothelial function between carcinoid patients and controls. Vascular elastosis is predominantly present in mesenteric arteries and veins.[1,2,4] Although it is generally considered to be the result of serotonin released from the tumor there is no explanation why just mesenteric arteries (which are

efferent to the tumor) and not extra-mesenteric arteries are involved. Several authors suggested local factors inducing local vascular fibrosis.[22,23] In 2004 Modlin et al surveyed the literature over the last 40 years covering the incidence, diagnosis, therapy and biological basis for carcinoid-associated fibrosis. They conclude that the mechanism of fibrosis is still poorly understood and there are no means by which this complication can be predicted or monitored.[24] The present study in carcinoid patients with high circulating serotonin levels tends to support the theory that vascular elastosis in patients with a midgut carcinoid is a local, rather than a systemic problem.

Increasingly data emerge that heart failure due to carcinoid heart disease is not merely a result of fibrotic plaques in the right side of the heart but also the left side, pericardial effusions and cardiac metastases.[25] Presumably loss of vasomotor control in carcinoid disease is caused by alterations in pre- and postsynaptic receptor configuration resulting in an impaired cardiac autonomic nervous function. Future investigation elucidating the cause of the BRS impairment in carcinoid patients should focus on autonomic dysregulation, rather than on structural morphologic changes in the vessel wall.[26,27]

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Chapter 6b

LOSS OF PRE-SYNAPTIC SEROTONIN VASOCONSTRICTOR CONTROL IN ISOLATED POPLITEAL ARTERY PREPARATIONS FROM A PATIENT WITH MIDGUT CARCINOID

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Abstract

Metastatic carcinoid disease can be associated with vasomotor instability causing flushes and hypotension or hypertension. In addition morphological changes in the vessel wall (i.e. vascular elastosis) with thickening of the intima-media complex resulting in reduced compliance can occur. Pharmacological studies on isolated arteries from carcinoid patients have not yet been performed. Therefore this study investigates functional alterations in serotonin response in isolated popliteal artery preparations of a carcinoid patient. The effect of pre-synaptic inhibition on serotonin induced contraction and the involvement of serotonin-2A (5-HT_{2A}) receptors in these responses as well as the role of contractile prostaglandins was analyzed.

Methods: In a metastatic carcinoid patient a below knee amputation was performed because of necrosis due to ischemia. The popliteal arteries were dissected and conserved for *in vitro* isolated vascular ring perfusion tests. In an organ bath tests were performed using increasing concentrations of serotonin (30 nmol L^{-1} - 30 μmol L^{-1}). Several serotonin induced contraction cycles were performed in the presence of pre- and post-synaptic blockers (ondansetron, ketanserin, indomethacin). The same tests were performed on popliteal vascular rings from a healthy control who underwent a posttraumatic upper leg amputation.

Results: A tenfold higher serotonin concentration was needed to start contraction in carcinoid rings compared to control rings. Contractions in carcinoid rings were predominately mediated by 5-HT_{2A} receptors, whereas in normal popliteal artery there were also other functional serotonin receptors besides the 5-HT_{2A} subtype. In the normal popliteal artery serotonin vasoconstrictor control is supported by a pre-synaptic rescue mechanism, becoming active in case of blockade of smooth muscle 5-HT_{2A} receptor by ketanserin. This mechanism might be activated by serotonin stimulation and is probably mediated via contractile cyclooxygenase-derived prostanoids. Such a rescue mechanism by pre-synaptic activation appeared to be absent in carcinoid artery rings.

Conclusion: In vitro midgut carcinoid vascular rings are characterized by loss of pre-synaptic serotonin vasomotor control and non-responsiveness to low serotonin concentrations.

Introduction

A midgut carcinoid is a neuroendocrine tumor that can produce several metabolic active substances, including serotonin, prostaglandins (PGEs) and catecholamines.[1,2] Vasomotor instability in patients with metastatic carcinoid disease is associated with hot flushes, hypotension or hypertension. Morphological changes can occur in the vessel wall (i.e. vascular elastosis) with thickening of the intima-media complex, resulting in reduced compliance of the vessel. This is observed, predominantly in mesenteric vessels, in the proximity of a carcinoid tumor mass. A well known distant effect of serotonin is carcinoid fibrotic heart disease.[3,4]

Carcinoid disease is often associated with high serum levels of serotonin and the symptoms mentioned are at least partly considered to be due to serotonin.[3,5] Elevated circulating serotonin levels in carcinoid patients might cause the display of impaired responses in the vessel wall. Pharmacologically consistent with long-term exposure to high serotonin levels, a downregulation of serotonin $(5\text{-HT})_{2A}$ receptors has been reported in platelets. Platelets form the serotonin reservoir of patients with carcinoid tumors.[6] Apart from direct effects of serotonin on vascular tone also an indirect effect via so-called contractile PGEs might be involved.[7] Highly increased plasma levels of contractile PGEs, particularly PGE_2, have been observed in carcinoid patients.[8-10]

So far, pharmacological studies on isolated arteries from carcinoid patients are not available. Normally serotonin causes at the vascular level constriction via activation of 5-HT_{2A} receptors present on the smooth muscle cells and/or activation of the 5-HT_3 receptor subtype present on post-ganglionic sympathetic neurons, representing an intrinsic transmitter-gated ion channel.[11] Dynamic responses to serotonin receptor stimulation within the vascular wall can be elegantly demonstrated using isolated vascular ring perfusions *in vitro*.[12,13] The role of vascular serotonin receptors in carcinoid disease could be elucidated by analyzing the pre-synaptic inhibition on serotonin-induced contraction as well as the involvement of 5-HT_{2A} receptors in these responses and the role of contractile PGEs.

Therefore we evaluated in the present study the functional alterations in serotonin responses in isolated popliteal artery preparations of a carcinoid patient and a normal popliteal artery.

Methods

Patients

A 60-year-old patient with spina bifida and a metastatic midgut carcinoid was admitted with ischemia and necrosis of both underdeveloped and short legs (see figure 1). On admission both femoral and popliteal arteries were patent, and there was no apparent major arterial obstruction. It was hypothesized that a vasoconstriction of the arteries by circulating amines had resulted in recent ischemia. After 3 days the demarcation revealed irreversible ischemia necessitating an amputations. Immediately thereafter the popliteal arteries were dissected and collected in saline on ice and sent to the laboratory for *in vitro* vascular studies.

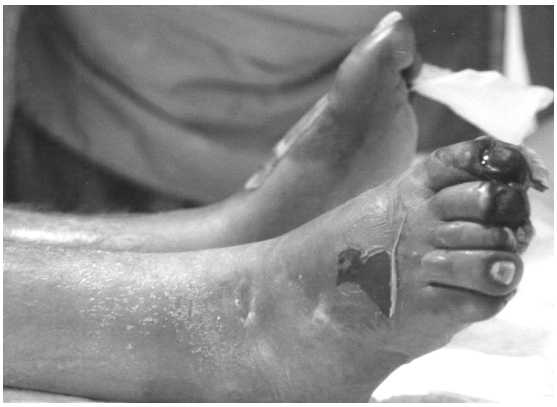

Figure 1: Both feet of the carcinoid patient at the time of admission with the peripheral necrosis.

A 57-year-old patient underwent an above knee amputation because of a non-union due to a recurrent osteomyelitis following an osteosynthesis of a comminutive femoral fracture one year earlier. The lower leg was unaffected. The popliteal artery was immediately dissected and collected in saline on ice, and transferred to the laboratory for in vitro vascular testing.

Preparation for in vitro studies with isolated popliteal artery rings

The arteries were cleaned of surrounding tissues and cut into several rings (2 mm). Rings were mounted in 15 ml organ baths, containing a buffer solution (Krebs) (mmol L^{-1}): NaCl (120.4), KCl (5.9), $CaCl_2$ (2.5), $MgCl_2$ (1.2), NaH_2PO_4 (1.2), glucose (11.5), $NaHCO_3$ (25.0). The medium was continuously aerated with 95% O_2 - 5% CO_2 and kept at 37 ^{o}C. The rings were connected to an isotonic displacement transducer by 5-0 braided, uncoated polyester sutures, where they received a preload of 1.4 g. The isotonic transducer, the recording system, and the software were custom made and calibrated at the University of Groningen, the Netherlands.

Artery rings were allowed to equilibrate for 60 min during which regular washing periods were performed. Rings were primed and checked for viability by repeated stimulation (three times) with 60 mmol L^{-1} KCl and intermediate washing and stabilization periods. The third response to KCl was referred to as the 100% referral maximum contraction amplitude for each ring and all other contractile responses were expressed as a percentage of this response to further reduce inter-ring variability.

Experimental protocol for contractile responses to serotonin

Parallel rings were simultaneously studied during three consecutive series of measurements for contractile responses to increasing concentrations serotonin (30 nmol L^{-1} - 30 μmol L^{-1} bath-concentrations) in each series, and in the selective absence and presence of various compounds known to interfere with receptor signal transduction processes. In the first series of measurements, parallel rings were studied for serotonin responses under control conditions and under conditions of pre-synaptic inhibition. In the second and third series of measurement, the additional involvement of serotonin receptors and cyclooxygenase-derived PGEs was studied.

To create these conditions, we used vehicle as a control, 10 μmol L^{-1} ketanserin to inhibit 5-HT_{2A} receptors[14], 10 μmol L^{-1} indomethacin to inhibit cyclooxygenase-derived PGEs[7], and 1 μmol L^{-1} ondansetron to obtain serotonin receptor mediated pre-synaptic inhibition.[15] To obtain general pre-synaptic inhibition general a combination of ondansetron with 1 μmol L^{-1} tetrodotoxin (an inhibitor of voltage sensitive Na^+ channels[16] and 300 μmol L^{-1} suramin (a blocker of pre-synaptic P_2-purinergic receptors) was used.[17] Rings were pre-incubated with the appropriate inhibitors for at least 30 min before stimulation with serotonin. Observations of serotonin contractility under certain conditions were obtained from 3-6 rings for each condition.

Thickening of the intima media complex causing a diminished compliance of the vessel wall, a well-known symptom in carcinoid patients, may interfere with contraction amplitudes. To correct for this and to reduce inter-ring variability, we expressed receptor-mediated vasoconstrictor responses to serotonin as percentage of maximal constriction with KCl.

Drugs used

The following chemicals and drugs were used: serotonin, indomethacin, ketanserin, suramin and tetrodotoxin (all from Sigma-Aldrich Chemie, Zwijndrecht, The Nederlands) ondansetron (Glaxo Smith Kline BV, Zeist, The Netherlands). Stock solutions were prepared of indomethacin (10 mmol L^{-1}, in ethanol), ketanserin (10 mmol L^{-1}, in H_2O), tetrodotoxin (1 mmol L^{-1}, in H_2O), suramin (300 mmol L^{-1}, H_2O), and ondansetron (1 mmol L^{-1}, H_2O), stored at -20°C and diluted in Krebs solution to reach final concentrations. Serotonin was prepared in H_2O (100 mmol L^{-1}), and further dilutions were performed directly in Krebs solution. Compounds for the Krebs buffer solution were all obtained from Merck (Darmstadt, Germany).

Calculations and statistical analysis

All responses of individual rings to serotonin were expressed as a percentage of the maximum contraction-response to 60 mmol L^{-1} KCl, and used for calculations and graphic representations. Maximal effect (E_{max}) and the effective concentration producing 50% of the maximal effect, expressed as negative logarithm (pEC_{50}), were obtained from the individual concentration-response curves. Observations of serotonin contractility under a specific condition were obtained from 3-6 rings. Comparison between percentual responses was made using Student's t-test. Data are expressed as mean ± standard error of the mean (SEM). P-values <0.05 were considered significant.

Results

Receptor-independent contraction induced by a high concentration of KCl (60 mM), resulting in maximal contraction in popliteal artery rings was 40% lower in rings from the carcinoid patient (593 ±73 μm versus 950 ± 68 displacement, $p<0.001$). Serotonin induced, concentration-dependent contractions in popliteal artery rings were obtained from the control patient and the carcinoid patient (Figure 2A, B). Maximal contraction (E_{max}) was similar; in carcinoid rings: 51.8 ± 8.7 % and in control rings 52.2 ± 7.5 % of the maximal contraction as induced by 60 mM KCl. Also pEC_{50} values were not different (carcinoid rings: 5.9 ± 0.1; control rings 5.8 ± 0.1), however the threshold of contraction was at a much higher serotonin concentration for carcinoid-derived rings 1 μM than 0.1 μM for control rings. In the presence of pre-synaptic inhibitors

similar results were obtained. Treatment with ondansetron alone, to block pre-synaptic serotonin receptors, was as ineffective as when given in combination with other inhibitors of post-ganglionic synaptic transmission, tetrodotoxin and suramin (data not shown). Indomethacin as inhibitor of cyclooxygenase-derived prostanoids synthesis, only slightly changed contraction in carcinoid rings (E_{max}: 26.2 ± 5.9 %; pEC_{50}: 5.7 ± 0.1, Figure 2A, p=n.s.) and control rings (E_{max}: 34.6 ± 10.7 %; pEC_{50}: 5.8 ± 0.1). In contrast, the 5-HT_{2A} receptor blocker ketanserin totally abolished contractions in carcinoid vascular rings with an E_{max}: -5.6 ± 0.1% and after presynaptic inhibition -8.3 ± 2.6%; $p<0.05$. In control rings ketanserin decreased contractions to 37.0 ± 0.4 % with pEC_{50}: 6.5 ± 0.1 ($p<0.05$) and in the presence of presynaptic inhibition even further (E_{max}: 13.4 ± 5.6%; pEC_{50}: 6.0 ± 0.1; $p<0.05$).

The combination of ketanserin and indomethacin in control rings slightly decreased contraction in the absence and presence of presynaptic inhibitors to E_{max}: 10.0 ± 3.2% and -0.5 ± 3.9%, respectively (Figure 2E), but totally blocked contractions in carcinoid rings.

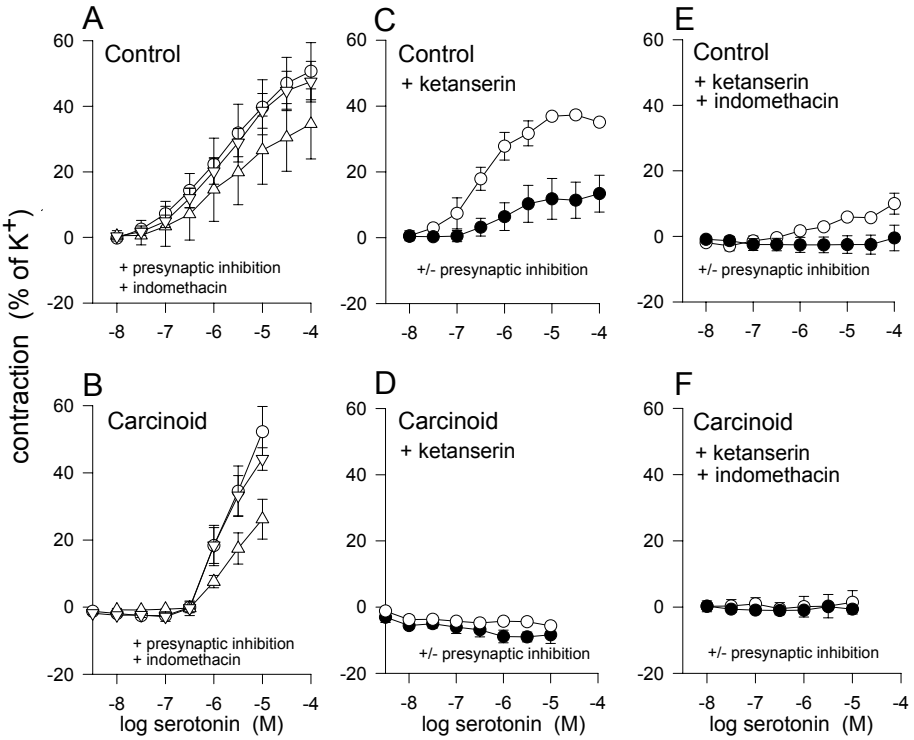

Figure 2:
Concentration-response curves of vascular rings prepared from the control patient (A, C, E) and carcinoid patient (B, D, F). Various conditions were applied: In panel A and B "control" (o), under pre-synaptic inhibition (∇), and under inhibition of prostaglandin synthesis by indomethacin (Δ). In panel C and D in the presence of the 5-HT_{2A} inhibitor ketanserin, "control" (o) and under pre-synaptic inhibition (•). In panel E and F in the presence of 5-HT_{2A} receptor blockade and inhibition of prostaglandin synthesis, "control" (o) and under pre-synaptic inhibition (•). Contraction was defined as % 60 mM KCl induced contraction and presented as mean ± SEM.

Discussion

This is the first study, on pharmacologically characterized vascular function of isolated arteries obtained from a patient with midgut carcinoid. Some striking differences became apparent in these arteries compared to arteries from a control patient. Carcinoid-derived popliteal artery rings were less responsive to the receptor-independent contractile agent KCl than control popliteal artery rings (0.6-fold). This decrease in contractility is probably due to structural changes in the vessel wall as observed in carcinoid patients.[4,18] Interestingly, a similar reduction of contractility due to structural changes in the vessel wall has been reported for popliteal artery rings obtained from patients with peripheral occlusive arteriosclerosis.[19]

When normalized for the maximal KCl contraction, receptor-induced contraction to serotonin appeared to be very similar for carcinoid rings and control. The presence of pre-synaptic inhibitors did not affect the responses to serotonin. This suggests that modulation of muscle contraction by activation of post-ganglionic neurons is not influenced by pre-synaptic factors. However, when the rings were incubated with the 5-HT_{2A} blocker ketanserin, contractions in carcinoid rings were totally blocked while control rings were still able to contract (figure 2A versus 2B). This contraction must be mediated via contractile PGEs and mainly involves pre-synaptic activation via pre-synaptic 5-HT_3 receptors in view of the results obtained with ondansetron and the PGE blocker indomethacin experiments (figure 2 C and E). This rescue mechanism is absent in carcinoid vascular rings suggesting loss of pre-synaptic control in these rings. A scheme depicting the hypothesized explanations of these findings is shown in figure 3. The mechanism by which this occurs remains to be solved. It could resemble the observations in tracheal ring preparations of the guinea-pig. In this previous study, a chain of events leads from receptor activation to production of contractile PGEs and subsequent smooth muscle contraction via prostanoid receptors.[20] PGE synthesis and secretion was induced by activation of Ca^{2+}-dependent cytosolic phospholipase-A2, generating arachidonic acid, the substrate for cyclooxygenase.[7] As mentioned, serotonin receptor activation results in Ca^{2+} influx, which might be well capable of starting similar events in the arteries tested. Functional downregulation of the pre-synaptic serotonin receptor subtype in carcinoid rings, due to long-term exposure to high serotonin concentrations in vivo, might be responsible for the

disappearance of the rescue mechanism in carcinoid patients. A general neuropathy as cause is less likely, since the effect observed is already detectable by solely blocking serotonin receptors by ondansetron. We studied the baroreflex sensitivity in carcinoid patients with elevated platelet serotonin and showed a reduced baroreflex sensitivity compared to sex and age matched controls.[21] Reason for this may be the loss of the fine-tuning of the sympathetic presynaptic control.
A ten-fold high serotonin was required to induce contractions in carcinoid vascular rings compared to control rings (Figure 2B). This is consistent with downregulation of 5-HT_{2A} receptors as observed in platelets of patients with carcinoid tumors.[6]

In conclusion, this is the first report to demonstrate that in the popliteal artery of a carcinoid patient the constriction of an isolated vascular ring was predominately mediated by 5-HT_{2A} receptors, whereas in normal popliteal artery there are also other functional serotonin receptors. Our results suggest, that in normal popliteal artery serotonin vasomotor control is supported by a pre-synaptic rescue mechanism, becoming apparent after blocking of the smooth muscle 5-HT_{2A} receptor. This mechanism might be activated by serotonin stimulation and can be blocked by indomethacin indicating a role for contractile cyclooxygenase-derived prostanoids. Such a rescue mechanism seems to be absent in carcinoid arteries.

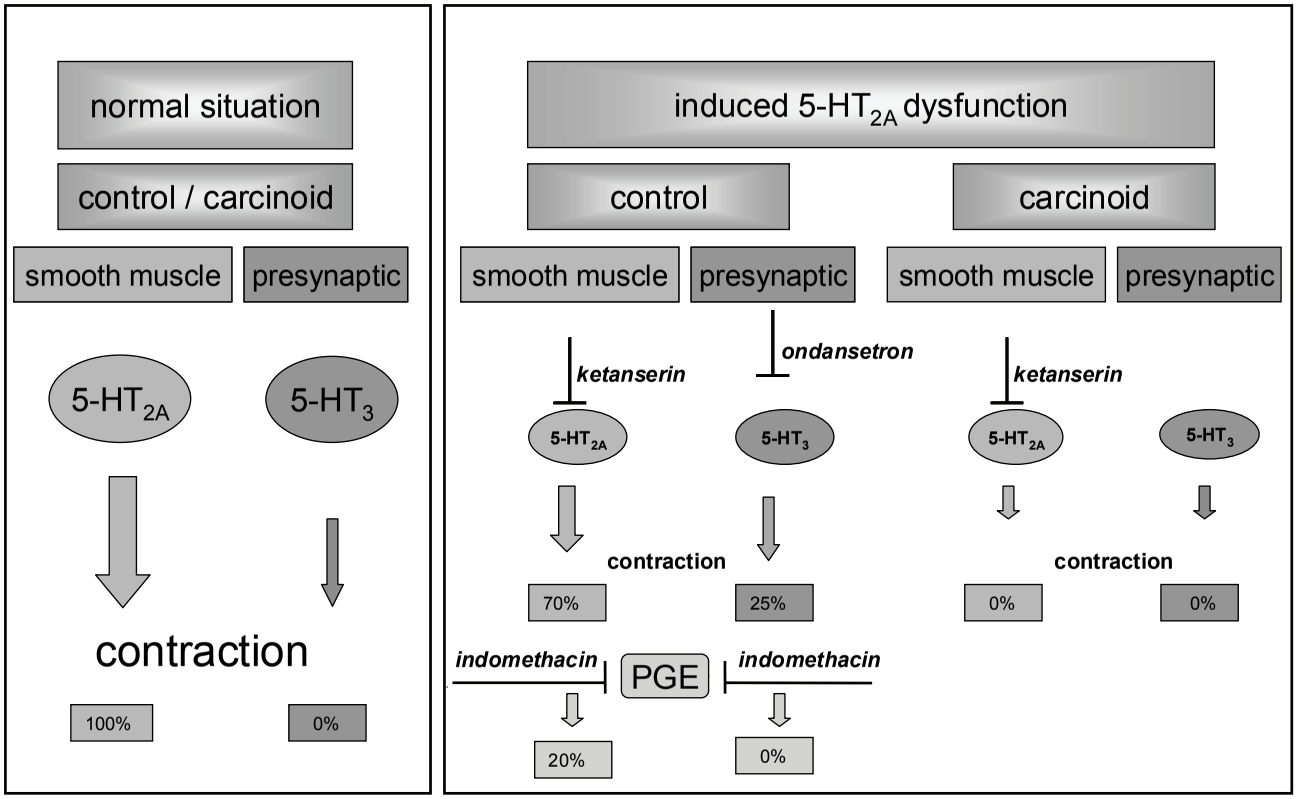

Figure 3: Schematic representation depicting the observed differences between carcinoid and control vessels. Two situations are presented, in the left panel the 'normal situation' and in the right panel when '5-HT_{2A} receptors are dysfunctional' by blocking with ketanserin. In the normal situation in carcinoid as well as in control rings, serotonin-induced contraction is mainly mediated by 5-HT_{2A} receptors on the smooth muscle cells and not by pre-synaptic stimulation via 5-HT_3 receptors. Blocking the 5-HT_{2A} receptor by ketanserin (right panel) abolishes the contraction in carcinoid rings whereas control rings can rescue 70% of the contraction, presumably via contractile PGEs as indomethacin can block this contraction to only 20%. After 5-HT_3 receptor inhibition by ondansetron 'rescued' contraction has dropped to 25%. In this experimental setting carcinoid derived vessels did not possess such rescue mechanism.

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Chapter 7a

FAILURE TO CONFIRM MAJOR OBJECTIVE ANTITUMOR ACTIVITY FOR STREPTOZOCIN AND DOXORUBICIN IN THE TREATMENT OF PATIENTS WITH ADVANCED ISLET CELL CARCINOMA

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Cancer 2000;88(9):2194-2195

We read with interest the article by Cheng et al addressing the antitumor effect of streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma.[1] They concluded that they were unable to confirm the findings from the Eastern Cooperative Oncology Group trial published in 1992.[2] In this trial of the 38 patients who received streptozocin and doxorubicin, 36 were evaluable and 69% showed any regression with 14% complete regression. For this study, criteria for response evaluation were a 50% decrease in hormone production; a 30% reduction in hepatomegaly; and measurable tumor reduction, with the product of the perpendicular diameters reduced 50%. Routine use of computed tomography (CT) scan was not indicated. From this study it is in retrospect difficult to calculate how many patients had a response based only on hormone reduction or reduced liver size. Cheng et al. used CT scan, magnetic resonance imaging, or X-rays of bidimensional measurable lesions as the only criteria for response as defined by Miller et al.[3] With the same streptozocin and doxorubicin regimen given to all of their 16 patients with islet cell tumours, Cheng et al. observed 1 objective response, 9 patients with stable disease, and 6 patients with progressive disease. The median overall survival was not yet reached, with 60% alive after follow-up ranging from 10 to 67+ months. We would like to add 6 islet cell tumor patients to this series. From 1995–1999, we treated these patients according to exactly the same chemotherapy scheme. The patients were evaluated as described by Cheng et al.

None of the patients were hormone producers. One patient experienced a partial response, 3 had stable disease, and 2 had progressive disease. Overall survival after initiation of chemotherapy ranged from 4 to 17+ months. Apart from cardiotoxicity, which was most likely due to doxorubicin treatment (with cardiac failure responsive to antidiuretic treatment), no severe toxicity of the regimen was observed. Combining the data from Cheng et al and our results in 2 objective tumor responses out of 22 (9%; 95% confidence interval, 1–29%). Although we find with these criteria a lower response rate than Moertel et al, it is also true that in these two series a good effect on survival cannot be denied. In islet cell tumor studies, to report precisely on the objective regression of tumor size may be of major relevance. If there is a regimen that results in a realistic option to create a reduction in tumor size, this would potentially allow surgical tumor resection and thus increase the potential for curative tumor resection. If the main goal of this regimen is quality of life rather than remission, the objective response rate of only 9% with the

streptozocin/doxorubicin regimen justifies more interest in interferon treatment of patients with islet cell tumours. After an initial study with leukocyte interferon[4], interferon in a doses of 5–6 MU 3–5 times per week resulted in biochemical responses in 50% of the patients and tumor responses in 12%.[5] Surprisingly, this option is not even mentioned in the National Cancer Institute's PDQ information for health care professionals on islet cell carcinoma.[6] Treatment with somatostatin analogs is mentioned in the PDQ, reporting improvement of symptoms but little to no effect on tumor size. Attempts to combine the several options have been initiated. Because of the rarity of the disease, it is difficult to conduct large studies to confirm earlier interesting results or to design studies to improve these results. It will be of major importance to consider future multicenter studies in order to improve the outcomes of patients in this category.

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Chapter 7b

SURGICAL RESECTION OF PRIMARILY IRRESECTABLE CARCINOID LIVER METASTASIS WITH INDUCTION INTERFERON THERAPY WITH A REVIEW OF THE LITERATURE

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Introduction

Carcinoid tumors are rare. Midgut carcinoids usually grow slowly and are often not detected before the tumor has metastasized to the liver. The carcinoid syndrome will become obvious only in the presence of hepatic metastases or metastatic disease in areas draining directly into the systemic circulation, bypassing the liver. At laparotomy the primary tumor is often smaller than the metastatic lymph nodes and hepatic metastases. The therapy of choice is surgery. The primary goal of surgery is radical resection, even in the presence of liver metastases. When the liver metastases are irresectable, debulking of the primary tumor and metastasis in the mesentery is another option because residual tumor can cause severe complaints such as bowel obstruction and ischemia. Hepatic resection may become easier subsequent to tumor reduction with new drugs. Recombinant Interferon and somatostatin analogs have been used since the late eighties.[1] Interferon has proven to be beneficial in symptom relief, showing in 40-60% of the patients a biochemical response, stabilization of disease in 40-80% and tumor reduction in 10-15% of the patients.[2,3-6] Somatostatin analogs yield little effect on tumor size.[7] Chemotherapy has also only limited antitumor effect.[8-14]
This article reports the effect of interferon alpha on tumor size of an initially irresectable hepatic metastasis. Furthermore the value of serotonin and its metabolites as a marker is discussed.

Case report

In 1986 a 39 years old man suffered from flushes, abundant perspiration and paroxysmal atrial fibrillation. The patient was referred to our hospital suspected of having a paraganglioma. Flushing and a high platelet serotonin (24.6 nmol/10^9 platelets = 4.6 x upper reference level) suggested a carcinoid syndrome. The urine 5-HIAA excretion however, was only marginally elevated. A MIBG scan showed a hot spot in the right lower quadrant of the abdomen and one in the liver, consistent with a neuro-endocrine tumor. The abdominal CT scan showed a large mass in the left hepatic lobe bulging into the right lobe and a 3 cm lesion in the ileal mesentery. In May 1986 a laparotomy was performed. The abdomen was explored via a midline incision. Inspection revealed a solitary hepatic tumor with a 10 cm diameter in segment 4 of the liver bulging over Cantlie's line. The hepatic surgeons considered this metastasis to be unresectable. A tru-cut needle biopsy was performed. A Meckels diverticulum containing the suspected carcinoid was found at 70 cm from the

ileocecal valve. Opposite the diverticulum a metastatic focus with a diameter of 5 cm was found in the ileal mesentery. A 20 cm segment of the ileum was resected with the corresponding wedge of the mesentery. The patient recovered uneventfully and left the hospital one week after surgery.

Histopathological examination revealed a Meckel's diverticulum containing a carcinoid tumor with invasion of the serosal fat. The number of mitotic figures observed, was low. The tumor in the mesentery was a metastasis without residual lymphoid tissue. The hepatic biopsy showed a carcinoid with the same histology. The flushing increased after the operation and interferon alpha medication was initiated in September 1987(2.5 MU subcutaneously once daily). After 3 weeks the frequency and the intensity of the flushes had decreased considerably with a reduction of platelet serotonin and urinary excretion of 5-HIAA (figure 1 panel 1 and 2). In December 1987 because of visual disturbance the dose of interferon alpha was reduced to 50%. In March 1988 the interferon medication was increased to the original dose of 2.5 MU because flushes worsened. Platelet serotonin varied accordingly. Subsequently the frequency of the flushes decreased to the extent that they stayed away for weeks. The CT scan showed a reduction of the hepatic metastasis so it was decided to attempt to resect this metastasis.

The second laparotomy was carried out via a bilateral subcostal incision. A 4 cm metastasis was identified in segment 4 of the liver. Frozen section of the nodes sampled from the celiac trunc and the hepatoduodenal ligament revealed no tumor. Elaborate exploration of the peritoneal cavity yielded no evidence of tumor elsewhere. A left hemi-hepatectomy was tedious because of anomalies of the portal vein. The postoperative course was uneventful. Interferon alpha medication was stopped. The histological aspect of the hepatic metastasis and the initial hepatic biopsy were identical. The resection margin measured 2 mm. Biochemical analysis of the liver metastasis revealed a high quantity of serotonin (36.350 nmol/g wet tissue). The serotonin in platelets and urine normalized(figure1, panel 1). Flushes did not reappear after the resection. In August 1990 the patient resumed work again. MIBG scan, carried out in January 1994, showed no evidence of endocrine carcinoid activity. Fifteen years later in 2004 there is still no sign of clinical or biochemical recurrence.

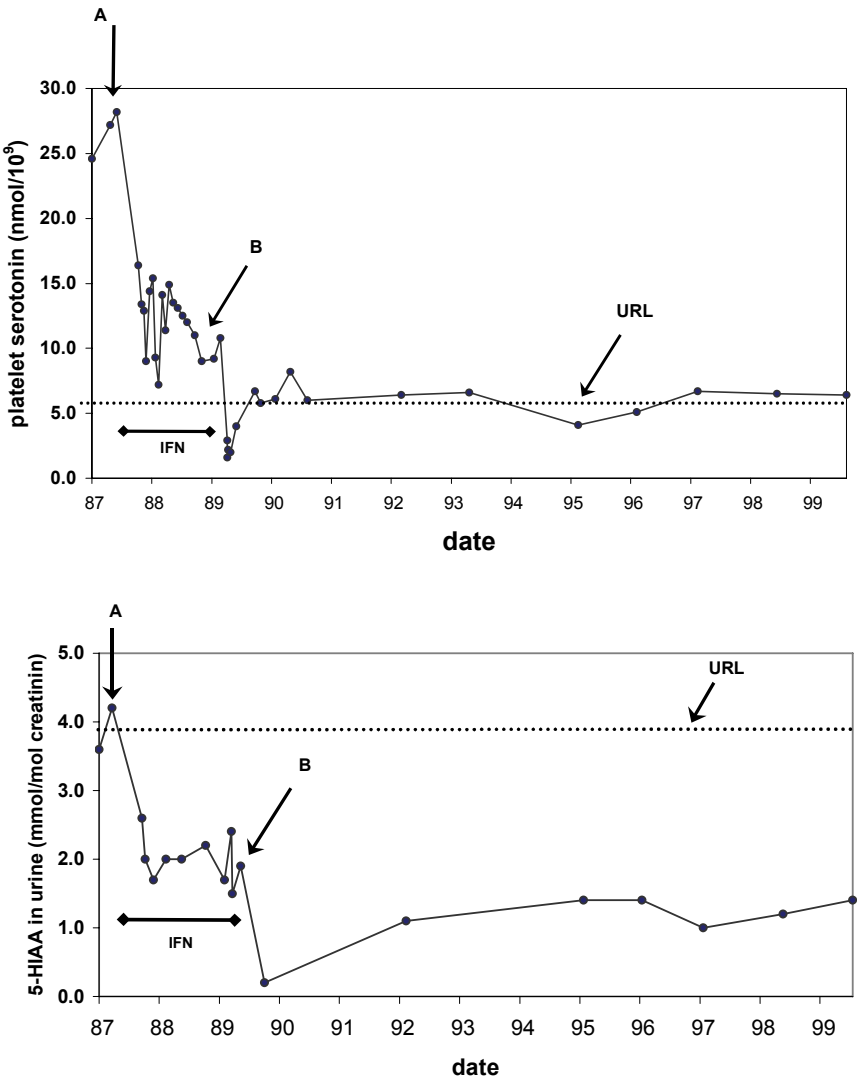

Figure 1:

panel 1: Platelet serotonin content in nmol/10^9 platelets during course of disease
panel 2: 24 hours 5-HIAA excretion mmol/mol creatinine during course of disease
A = resection of primary tumor and mesenteric metastases,
IFN = Interferon,
B = hemi-hepatectomy,
URL = upper reference limit

Discussion

This case shows a long-term remission as result of a response to administration of interferon alpha and subsequent resection of a hepatic metastasis. To our knowledge, this is the first report of the use of interferon alpha aimed to reduce the tumor size prior to resection of a hepatic metastasis. Reduction of the tumor size by interferon alpha[15-18] enabled adequate resection of the hepatic metastasis in our patient. Although the outcome in this patient is not exemplary for the treatment of carcinoids in general, this case supports clinicians favoring aggressive surgical intervention, even in the presence of marginally resectable hepatic metastases.[19,20] When curative resection is impossible, debulking the tumor can still lead to symptom relief and longer survival.[21-23]

Many other treatment modalities have been tried, all aiming at reduction of the tumor load in the liver with subsequent symptom relief, but long-term follow up reports following (neo-adjuvant) treatment of patients with a hepatic metastasis are scarce. Some articles report about dearterialization of the metastases by ligation of hepatic arteries.[24,25] Subsequent publications about chemo-embolization reported a symptom relief in most patients and reduction of biochemical parameters in 60-90% of them. Tumor response varied from stable disease to 80 % reduction with a duration between 12-24 months.[26-30] Some treatments such as radio frequency ablation using a laparoscopically introduced catheter are experimental.[31,32,33] Only a few authors mention good palliative results of (laparoscopic) cryosurgery but no long-term follow up data are available and no cures have been reported.[34-36] Orthotopic liver transplantation has been proposed in patients without extra-hepatic manifestations after initial surgery for the primary tumor.[13,37-39] There is only one report mentioning long-term survival with a 69% five-years survival in 15 metastasized carcinoid patients undergoing liver transplantation. The longest follow-up was 119 months.[13]

In the literature the predominant marker of carcinoid disease is urinary excretion of 5-HIAA. In our patient with a metastasized carcinoid of a Meckel's divertikel, the 5-HIAA excretion was only marginally elevated and therefore of no use. However, platelet serotonin appeared to be an excellent marker reflecting tumor load and treatment response. As mentioned, the tumor of our patient contained a serotonin load of 36.350 nmol/g wet tissue. To put this figure into perspective: as little as 2 g of the tumor contained the equivalent of the normal total body content of serotonin.

Surgery with of without prior systemic medical treatment, is to date the only possibility for cure of a metastatic carcinoid. Diagnosis and treatment of patients with a carcinoid tumor is challenging. As it is a rare disease, it is recommended to treat patients suffering from this disease in a center with an experienced multidisciplinary group. Reducing (hormone producing) tumor tissue must be the primary goal. As long as there is no other curative treatment, surgery remains the cornerstone of cure and locoregional control.

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Chapter 8

Summary
Aim of this thesis is to get insight in surgical aspects of the treatment of carcinoid patients, the role of products produced by the tumor and their vascular effects.

The review in chapter one covers diagnostic, surgical and medical aspects of carcinoid disease with emphasis on the surgical and peri-operative aspects.
Midgut carcinoids are rare neuro-endocrine tumors, which in most cases will only become manifest when they have metastasized to the liver. Treatment of metastatic disease can aim at radical surgical resection but is usually palliative. The tumor grows relatively slowly. Besides the biochemical effects resulting in the carcinoid syndrome, patients can suffer from mechanical mass effects of the tumor. Systemic treatment with octreotide or interferon-alpha can alleviate the biochemical effects of the tumor, but has a limited effect on tumor growth. The perioperative use of octreotide allows surgical treatment to be performed more safely.
Treatment aimed at cytoreduction of hepatic metastases and diminished secretion of bioactive amines can achieve good palliation. In this chapter we describe how cytoreduction can be achieved by means of partial liver resection, hepatic arterial ligation, (chemo)embolization, cryosurgery, radio-frequency ablation, internal radiation and even liver transplantation.

The increased efficacy of medical treatment of metastatic carcinoid disease has led to prolonged survival, resulting in more gastro-intestinal problems, necessitating surgical intervention. In chapter 2 the study is described which evaluated the indications for surgery, the blood loss, hemodynamic parameters and complications during surgery in patients with a metastatic. This retrospective survey covers all surgical interventions between 1983 and 1998 in patients with an abdominal manifestation of a metastatic carcinoid. Sixty-seven operations in 46 patients were evaluated. Indications for operation were: resection of the primary tumor or metastatic lesions in 14 (21%), bowel obstruction in 28 (42%), surgical complications in 9 (13%) and abdominal angina in 5 (7%) patients. Twenty-seven (58%) patients were even operated twice, 10, 3 and two

patients were operated 3, 4 and 5 times respectively. Half of the operations was accompanied with a blood loss of more than 1 liter. No patient suffered from a carcinoid crisis during surgery. Forty-eight procedures were performed under a shield of octreotide and 19 operations under ketanserin. Patients operated with epidural anesthesia in addition to general anesthesia experienced a twofold decrease in mean arterial pressure compared to those operated without epidural anesthesia. Half the operations were accompanied by (peri-operative) complications, being fatal in three patients. Post-operative enterocutaneous fistulae proved resistant to surgery and marked the end stage of the disease. Levels of platelet serotonin but not 5-hydroxyindolacetic acid (5-HIAA) were correlated with blood loss during operations.

Carcinoid tumors are known to produce several other biogenic amines apart from serotonin. Catecholamines such as norepinephrine, epinephrine and dopamine may contribute to carcinoid crises especially during anesthesia and surgery. As described in chapter 3 we evaluated the extent and time course of catecholamine productions in patients with a metastatic midgut carcinoid, compared to controls. Sixteen metastasized carcinoid patients and seven patients undergoing pancreatic surgery were studied. All patients and "controls" received octreotide before, during and after surgery. Perioperative blood samples and urine were collected. Plasma and urinary serotonin, (nor)epinephrine, dopamine and metabolites were measured. During manipulations of the tumor in 11 patients, five carcinoid patients experienced a median of 25% fall in mean arterial pressure. The six other patients were stable. Besides serotonin none of the catecholamines plasma levels were elevated. However the mean urinary excretion of epinephrine, dopamine and serotonin were markedly increased compared to the control group (for a factor 20, $p < 0.007$, 15, $p < 0.001$ and 80, $p < 0.001$ respectively). In conclusion, even after manipulation of the tumor, raised levels of catecholamines in the plasma could not be detected during surgery. Surgery however raises levels of urinary catecholamine metabolites, therefore intermittently raised plasma levels of catecholamines are likely to have occurred peri-operatively.

Chromogranin A (CgA) is a relatively sensitive marker for neuroendocrine tumors, however not for specific subtypes like carcinoids. In chapter 4 we evaluate the diagnostic use of CgA, platelet serotonin and urinary 5-HIAA excretion. Sixty carcinoid patients and 12 patients with

an islet cell tumor were studied. Levels of serum CgA was similar in the two patient groups but were markedly higher compared to controls. Carcinoid patients had higher platelet serotonin, urine serotonin and urine 5-HIAA when compared to patients with an islet cell tumor. The diagnostic sensitivity of platelet serotonin was similar to serum CgA in carcinoid diagnosis (98.3% [89.9-99.9] and 88.3% [76.8-94.8] respectively), but CgA appeared superior in diagnosing islet cell tumors; CgA: 91.7% [59.8-99.6] versus serotonin in platelets: 30.0% [8.1-64.6] urine serotonin 37.5%[10.2-74.1] and urine 5-HIAA 37.5% [10.2-74.1]). The diagnostic sensitivity of urine 5-HIAA and urine serotonin proved to be lower than CgA in all cases.

An abdominal carcinoid tumor can be accompanied by vascular elastosis, shortening and kinking of the mesentery of the small bowel and/or mass effects nearby vessels causing bowel ischemia or intermittent small bowel obstruction. In chapter 5a series of 36 consecutive patients with a carcinoid syndrome due to an extensive primary tumor growth or liver metastases, six patients with abdominal pain and intermittent small bowel obstruction are described. Diagnosis was improved by a positive response to nitroglycerin in two and ischemia of the ileum demonstrated by angiography in two other patients. Histopathology showed elastic vascular sclerosis in three and ischemic changes in three other patients confirming the clinical diagnosis. Three patients improved after resection. In three patients the abdominal angina marked the end stage of the disease. Resection of ischemic bowel can provide relief in some patients.

Vascular elastosis of the mesentery consists of elastosis and fibrosis of the media and adventitia, which can cause intestinal ischemia by narrowing of the vessel lumen. Aim of the study described in chapter 6a was to investigate dynamic and/or structural changes in the vessels of carcinoid patients compared to healthy controls. In 16 carcinoid patients with elevated platelet serotonin level and 21 healthy age and sex matched volunteers we measured the intima-media complex of the common carotid artery as a marker of early atherosclerosis, and flow-mediated dilation of the brachial artery to assess endothelial function. Baroreflex sensitivity was measured using computerized transfer function analysis of Finapres signal, a non invasive method using a finger-cuff for measuring arterial pressure in combination with heart rate variability measurements. No differences were found in the intima media complex or flow-

mediated vasodilatation between the groups. This suggests that there are no structural or functional alterations in the brachial and carotid artery in these patients. The baroreflex sensitivity however, was significantly lower in the carcinoid group with 1.5 ± 0.3 msec/mmHg versus 2.1 ± 0.5 ($p < 0.0001$) in the controls. The degree of baroreflex sensitivity reduction may indicate an increased risk for cardiac or vascular events

Vascular dynamics in metastatic carcinoid patients can be severely disturbed. Hypotension or hypertension is a well-known symptom as part of a carcinoid crisis.
To date, no pharmacological studies have been performed on isolated arteries of carcinoid patients. In chapter 6b we study functional changes of the vessel wall of a carcinoid patient caused by high levels of serotonin compared with that of a control patient. Vascular ring contractions were tested using serotonin in the presence of pre- and postsynaptic serotonin blockers. Prostaglandins were studied as well. In a patient suffering from severe ischemia resulting in necrosis of both feet, a below knee amputation was performed. Vascular rings were dissected from the arteries and placed in an organ bath with different serotonin levels. Several contractions were performed in the presence of pre- and postsynaptic serotonin blockers (ondansetron, ketanserin and indomethacin). Identical study protocol was applied to vascular rings obtained from a patient undergoing a posttraumatic above knee amputation. Contractions in carcinoid rings appeared to be primarily mediated through the 5-HT_{2A} receptor, whereas in control rings besides the 5-HT_{2A} receptor, also other serotonin receptors were involved. After blocking the 5-HT_{2A} receptor, control rings were able to contract, presumably via 5-HT_{3A} receptors. This rescue mechanism via pre-synaptic activation was absent in carcinoid rings. The difference between carcinoid vascular rings and control rings can be characterized by loss off serotonin mediated presynaptic vasomotor control.

Cytoreduction in selected cases can make a metastasized tumor resectable and allow a curative resection.
In chapter 7a we concur with an article of Cheng and co-worker. Failure to confirm major objective anti-tumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. In Cancer 1999;86:944-8. Cheng et al respond to the article of Moertel et al (N Engl J Med 1992;326:519-23) in which they reported a

good response to a combination of streptozocin-doxorubicin (regression in 69% and a median time to progression of 20 months). This original paper was particularly of interest because it showed the possibility of cytoreduction which enabled the curative resection of advanced disease in some selected cases. Cheng et al were not able to confirm the data of Moertel et al. In our institution only one out of six patients with an advanced islet cell carcinoma treated with streptozocin and doxorubicin experienced a partial response. Three patients had stable disease and two suffered progression during treatment. Based on our data and of Cheng et al we conclude that patients with advanced islet cell carcinoma have a only a small chance to obtain a response on streptozocin and doxorubicin therapy. Therefore treatment with this combination in order to make the tumor resectable will rarely be successful.

In chapter seven-b a patient is presented who received a multidisciplinary treatment because of a metastatic carcinoid. Most of the metastatic carcinoid patients cannot be cured by means of surgery. However in a small group of patents with minimal tumor burden, multi-modality treatment might enable a curative resection. We present a 39-year-old carcinoid patient with a unilobar liver metastasis not suited for hemihepatectomie for technical reasons. During the first procedure the primary tumor was resected, situated in a Meckel's diverticulum. Because of the invalidating carcinoid syndrome, the patient was treated with interferon-alpha. The biochemical response was prompt. Three years later a CT scan showed reduction of the hepatic metastasis without evidence of further spread. Subsequently a hemihepatectomie was performed after elaborative exploration of the abdomen revealing no evidence of disease outside the liver. The biochemical markers returned to normal and after 15 years follow up there is still no evidence of recurrence.
Treatment of carcinoid patients should be multidisciplinary. As described in this case, interdisciplinary collaboration, in selected cases, can enable curative treatment. If curation is not an option, this approach can lead to better palliation and possibly a longer survival.
Because of a better survival, metastatic carcinoid patients will more often encounter complications needing a surgical intervention. Metastatic midgut carcinoids are known to have a higher production of catecholamines. In this thesis we describe that the high circulating levels of catecholamines can have vasomotor consequences like for instance a dimin-

ished baroreflex sensitivity and a lower sensitivity of the vessel wall to serotonin. Disturbance of vasomotor activity may contribute to hemodynamic instability as part of a carcinoid crisis. With the advent of medication like ketanserin and octreotide, the threat of a carcinoid crisis during an intervention, is no longer a (relative) contra-indication for surgery. In vitro ketanserin appears to exert its effect by inhibition of the smooth muscle contraction in the vessel wall of arteries. The complexity of problems that may occur in metastatic carcinoid patients, emphasizes the recommendation to treat these patients in, or in collaboration with, a referral center.

Future perspectives

Profiling the catecholamine production of a carcinoid tumor.

During surgery and on intensive care units, inotropic medication is routinely given in case of circulatory imbalance or failure. Inotropic medication may have adverse effects in case of a metastatic carcinoid patient, because it may further imbalance an otherwise already overbearing catecholamine system, resulting in a carcinoid crisis. Every carcinoid tumor may have a specific catecholamine profile that causes an imbalance or overshoot in circulating catecholamines. Especially patients with a history of a carcinoid crisis despite octreotide treatment will probably benefit from catecholamine profiling before surgery. Knowing the patients specific profile will enable tools for anesthesiology and intensive care medicine to choose the correct peri-operative inotropic medication for the carcinoid patient at risk of a life threatening (peri-operatieve) carcinoid crisis.

Understanding the cause of the carcinoid syndrome

During central vascular surgery facial flushes may occur after traction of the mesentery resembling carcinoid flushes in their distribution pattern. The mesenteric traction syndrome consists of hypotension, tachycardia and cutaneous hyperemia. The responsible factor in the mesenteric traction syndrome appeared to be Prostacyclin (PGI_2) as described by Gottlieb in 1988. These symptoms can be counter-measured by the cyclooxygenase inhibitor indomethacin. Our results with ex-vivo vascular ring perfusion, the use of indomethacin revealed marked differences in contraction by serotonin between carcinoid and control vascular rings (chapter 6b). Several studies report on elevated prostaglandins in carcinoid disease. It would therefore be interesting to investigate circulating PGI_2 and prostaglandins (metabolites) in vivo and vitro to clarify whether they are related to vascular imbalance, carcinoid syndrome or even a carcinoid crisis. Keeping in mind the mesenteric traction syndrome, it would also be interesting to investigate whether PGI_2 plays also a role in causing hot flushes.

Pre- and post-synaptic serotonin receptor (subtypes)

Although there is a considerable amount of data regarding the several subtypes of serotonin receptors distributed throughout the body, there is little knowledge about the receptor expression and the pre- and post-synaptic receptor activity in carcinoid patients. The persistent high levels

of circulating serotonin will probably downregulate receptors on several end organs. In the study with the ex-vivo vascular rings perfusion (chapter 6b) model, there appeared to be an alteration in the release of prostaglandins due to the loss of the pre-synaptic 5-HT_{3A} receptor function compared to control rings. In the control rings, contraction was partially mediated by prostaglandins. Indomethacin attenuated this response. Vascular imbalance (a prominent symptom of a carcinoid crisis) may be caused by loss of control by pre-and postsynaptic serotonin receptors as reflected in a disturbed baroreflex sensitivity. Further studies on pre- and postsynaptic configuration of serotonin receptors may be helpful in understanding the vasomotor imbalance in carcinoid patients.

Octreotide

To date we do not have a clear picture on the mechanisms involved in the peri-operative prophylactic effects of octreotide. In our study on peri-operative catecholamine production it became clear that octreotide did not prevent release of catecholamines. It was hypothesized that octreotide may exerts its effect via stabilizing the end organ. As vascular imbalance is the major problem in a carcinoid crisis during surgery, it would be of interest to see if octreotide alters contractions in vascular ring perfusions as a first step in elucidating the pathways of octreotide prophylaxis.

Surgery in metastatic carcinoid

The last decades, especially since the advent of octreotide, surgery plays a more prominent role in the palliation of carcinoid disease. Most of the surgical interventions in the past were for small bowel obstruction. Nowadays the balance is gradually moving to cytoreductive procedures and more extensive mesenteric dissections to prevent bowel obstruction and/or vascular complications such as mesenteric vascular encasement. Less invasive techniques are gaining popularity. Radiofrequency ablation for liver metastases with or without laparoscopic support is a relatively new treatment modality. There are however no comparative data available on survival benefit. Tumor reductive surgery by means of a hemihepatectomie remains rare and the indications for an allogenic liver transplantation are still controversial, as the chances of cure by liver transplantation are still minimal. New palliative treatment modalities with more specific, targeted drugs resulting in a more chronic state may further improve the outcome of patients with metastatic carcinoid

disease. In this respect the results of phase II studies using bevacizumab, the VEGF-antibody and other anti-angiogenic compounds, are of interest. Hopefully these drugs can also induce responses that will make patients more amenable to surgical resection

Samenvatting

Doel van dit proefschrift is inzicht verkrijgen in de chirurgische aspecten van de behandeling van patiënten met een carcinoïd, de rol van de door de tumor geproduceerde biogene amines en hun vasculaire effecten.

Het overzichtsartikel in hoofdstuk 1 omvat de diagnostische, chirurgische en medische aspecten van het carcinoïd met nadruk op de chirurgische en peri-operatieve aspecten. Midgut carcinoïden zijn zeldzame neuro-endocriene tumoren die zich meestal pas klinisch manifesteren nadat ze gemetastaseerd zijn naar de lever. De behandeling van carcinoïdmetastasen kan gericht zijn op curatie maar is meestal gericht op palliatie. De tumor groeit vaak relatief langzaam. Naast de effecten van de aminen, zoals serotonine, die door de tumor worden geproduceerd, resulterend in het carcinoïdsyndroom, kunnen patiënten hinder ondervinden van de massawerking van de tumor. Systemische behandeling met octreotide of interferon-alpha kan de klachten veroorzaakt door de biogene aminen verlichten maar heeft meestal weinig effect op de tumorgroei. Door octreotide gebruik rond operaties werden de chirurgische interventies veiliger. Behandeling gericht op het verkleinen van de levermetastasen en de daaraan gerelateerde vermindering van de productie van bioactieve amines kan vaak goede palliatie bewerkstelligen. In dit hoofdstuk wordt beschreven hoe cytoreductie bereikt kan worden door een partiële leverresectie, ligatie van de arterie hepatica, chemoembolisatie, cryochirurgie, "radio frequency ablation", bestraling met radioactief octreotide of zelfs levertransplantatie.

De toegenomen effectiviteit van de medische behandeling van carcinoïdmetastasen heeft geleid tot een langere overleving waardoor de kans op een complicatie waarvoor een chirurgische interventie noodzakelijk is, toeneemt. In hoofdstuk 2 wordt het onderzoek beschreven waarin de indicaties voor de chirurgische interventie, bloedverlies, diverse hemodynamische parameters en complicaties tijdens operaties van gemetastaseerde carcinoïdpatiënten worden geanalyseerd. Dit retrospectieve onderzoek betrof patiënten met een naar het abdomen gemetastaseerd carcinoïd die geopereerd werden in de periode 1983 – 1998. Er werden 67 operaties in 46 patiënten bestudeerd. Indicaties voor operatie waren: resectie van de primaire tumor in 14 (21%), dunne darm obstructie in 28 (42%), chirurgische complicaties in 9 (13%) en angine abdominale in 5 (7%) patiënten. Zevenentwintig (58%) patiënten werden twee-

maal geopereerd, 10 patiënten driemaal, 3 patiënten viermaal en 2 patiënten werden vijfmaal. Bij de helft van de operaties trad tijdens de ingreep meer dan 1 liter bloedverlies op. Bij geen van de patiënten ontstond tijdens de ingreep een carcinoïdcrisis. Achtenveertig operaties werden uitgevoerd onder perioperatieve octreotide en 19 onder ketanserin profylaxe. Patiënten met een periduraal katheter (n=19) ondervonden tijdens de operatie een daling van de 'mean arterial pressure' die tweemaal zo groot was als bij patiënten zonder peridurale anesthesie ($p<0,00001$)). De helft van de operaties ging gepaard met peri-operatieve complicaties die bij drie patiënten fataal bleken. Vooral postoperatieve entero-cutane fistels bleken therapieresistent en markeerden het eindstadium van de ziekte. De concentratie van serotonine in bloedplaatjes correleerde met operatief bloedverlies maar de 5-hydroxyindolazijnzuur (5-HIAA) excretie in de urine niet. De chirurgische behandeling van een gemetastaseerd carcinoïd gaat gepaard met een aanzienlijke morbiditeit.

Carcinoïden staan bekend om de productie van diverse bioactieve amines naast het bekende serotonine. Catecholamines zoals adrenaline, noradrenaline en dopamine dragen mogelijk ook bij aan de ontwikkeling van een carcinoïdcrisis tijdens operatie. Daarom werd onderzoek verricht, in hoofdstuk 3 beschreven, naar het tijdsverloop van de catechol-amine productie in patiënten met een gemetastaseerd carcinoïd. Zestien gemetastaseerde (midgut) carcinoïdpatiënten en zeven patiënten die een pancreasoperatie ondergingen, werden onderzocht. Alle carcinoid patiënten en "controles" kregen profylactisch octreotide voor, tijdens en na de operatie. Perioperatief werd bloed en urine verzameld. Tijdens geregistreerde manipulaties van de tumor in elf patiënten, werd in vijf patiënten een verlaging van de gemiddelde arteriële bloeddruk gezien van 25%. De zes andere patiënten bleven hemodynamisch stabiel. Er werden geen verhoogde plasma catecholamines gevonden bij de carcinoïdpatiënten. De 24 uurs excretie in urine van adrenaline, dopamine en serotonine bij carcinoïd patiënten was evenwel fors verhoogd, respectievelijk 20 maal ($p<0,007$), 15 maal ($p<0,001$) en 80 maal ($p<0,001$) vergeleken met controle patiënten.
De operatie veroorzaakt een sterke toename van de urine excretie van catecholamine (metabolieten) hetgeen inhoudt dat er perioperatief intermitterend verhoogde plasmawaarden moeten hebben bestaan.

Chromogranine A (CgA) is een sensitieve serummarker voor endocriene tumoren die echter minder specifiek is voor subtypen zoals bijvoorbeeld de carcinoïdtumoren. In hoofdstuk 4 wordt het nut van serum CgA, serotonine in bloedplaatjes en urine 5-HIAA excretie voor de diagnostiek. Zestig carcinoïdpatiënten en 12 patiënten met een eilandjesceltumor van de pancreas werden geanalyseerd. De hoogte van de serum CgA concentraties was vergelijkbaar tussen beide patiëntengroepen en de CgA waarden waren, zoals te verwachten, aanzienlijk hoger dan in de controlegroep (carcinoïd 15x hoger, eilandjesceltumoren 10x hoger dan de controlegroep). Carcinoïdpatiënten hadden hogere plaatjes serotonine, urine serotonine en urine 5-HIAA concentraties dan patiënten met een eilandjesceltumor. In beide tumortypes was de sensitiviteit van urine 5-HIAA en urine serotonine lager dan die van CgA. Met name voor de diagnose van een eilandjesceltumor is CgA dus van grotere waarde dan de overige parameters.

Het carcinoïd kan gepaard gaan met vasculaire elastose, intrekking/schrompeling en afknikken van het mesenterium van de dunne darm en/of massa effecten van de tumor op de nabijgelegen vaatstreng resulterend in ischemie en intermitterende obstructie. In hoofdstuk 5 worden 36 patiënten beschreven met een carcinoïd syndroom met uitgebreide locale tumorgroei en/of levermetastasen. Van deze patiënten hadden 6 last van buikpijn aanvallen en incomplete ileus die verbeterden na een operatie. De vasculaire origine van de klachten werd duidelijk na afname van de klachten na sublinguaal nitroglycerine in twee en angiografisch bewezen ischemie in twee andere patiënten. Histopathologisch onderzoek toonde vasculaire elastose in drie en ischemische darmveranderingen in drie andere patiënten. Resectie van het ischemische darmdeel gaf vermindering van de klachten.

Vasculaire elastose van het mesenterium bij carcinoïdpatiënten bestaat uit elastose en fibrose van de media en adventitia met vernauwing van het lumen die kan resulteren in darmischemie. Het is minder duidelijk of er ook vaatschade elders in het lichaam optreedt. Het doel van het onderzoek beschreven in hoofdstuk 6a was het bepalen van de dynamische en structurele vaatveranderingen van de extra-mesenterische vaten van carcinoïdpatiënten vergeleken met gezonde proefpersonen. Zestien carcinoïdpatiënten met een verhoogd plaatjes serotonine en 21 gezonde voor leeftijd en geslacht gepaarde vrijwilligers werden getest. Er werden

metingen verricht van het intima-media complex van de arteria carotis communis om vroege atherosclerose op te sporen en flow gemedieerde dilatatie van de arteria brachialis bepaald om de endotheelfunctie te meten. Tevens werd de baroreceptor reflex gevoeligheid gemeten met behulp van de Finapres®. Dit is een niet invasieve methode die gebruik maakt van een vingermanchet voor het meten van de bloeddruk in combinatie met hartfrequentie en intervalmetingen tussen hartslagen. Er werden geen verschillen aangetoond in het intima media complex en de doorstromingsafhankelijke vaatverwijding tussen de twee groepen. Dit suggereert dat er geen veranderingen in de structuur en dynamiek van de arterie brachialis en carotis communis in de patiëntengroep aanwezig zijn. De baroreceptor reflex gevoeligheid echter was aanzienlijk lager in de carcinoïdgroep (1,5 ± 0,3 msec/mmHg) dan de controlegroep (2,1 ± 0,5, $p < 0,0001$). De mate van deze verlaging is mogelijk een maat voor het toegenomen risico op cardiovasculaire complicaties.

De vaatdynamiek in gemetastaseerde carcinoïdpatiënten kan ernstig verstoord zijn. Een bekend symptoom is de hemodynamische instabiliteit als onderdeel van een carcinoïdcrisis die gekenmerkt wordt door zowel hypotensie als hypertensie. Tot op heden zijn er geen farmacologische studies verricht op geïsoleerde stukjes slagader van carcinoïdpatiënten. In hoofdstuk 6b wordt gekeken naar de functionele veranderingen in de vaatwand van een carcinoïdpatiënt, die langdurig blootgesteld is aan hoge concentraties serotonine in bloed. Hiertoe werd het effect van serotonine op vaatringetjes getest al dan niet blokkade van pre- en postsynaptische serotonine receptoren. Tevens werd de rol van prostaglandines bestudeerd. Bij een patiënt met een gemetastaseerd carcinoïd werd een onderbeenamputatie verricht vanwege ernstige ischemie van het onderbeen met necrose van beide voeten. Vaatringetjes van de uitgeprepareerde arterie poplitea werden geïncubeerd met oplopende concentraties serotonine. Registratie van vaatcontracties werd uitgevoerd in de aanwezigheid van pre- en postsynaptische serotonine blokkeerders (ondansetron, ketanserin en indomethacine). Dezelfde proeven werden verricht met vaatringetjes van een controlepatiënt. Deze patiënt onderging een posttraumatische bovenbeenamputatie. De contracties in de carcinoïd vaatringetjes bleken voornamelijk gemedieerd door de serotonine $(5\text{-HT})_{2A}$ receptor terwijl in de controleringetjes naast de 5-HT_{2A} receptor ook andere receptoren betrokken waren bij de contracties. In de controleringetjes bleek na blokkade van de 5-HT_{2A} receptor de contractie

toch te kunnen plaatsvinden. Dit gebeurt vermoedelijk via de 5-HT_{3A} receptor door activatie van contractiele prostaglandines. Dit "compensatie mechanisme" via een pre-synaptische activatie leek afwezig in de carcinoïd vaatringetjes. Geconcludeerd wordt daarom dat het verschil tussen carcinoïd vaatringetjes en controleringetjes gekenschetst kan worden door het verlies van de pre-synaptische vasomotore serotonine controle.

Het bereiken van voldoende tumorreductie kan in sommige patiënten de kans op een resectie van een tumor vergroten zodat een in opzet curatieve ingreep mogelijk wordt. In hoofdstuk 7A beschrijven wij vergelijkbare bevindingen als in het artikel van Cheng et al "Failure to confirm major objective anti-tumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma" in Cancer 1999;86:944-8. Cheng et al reageert hierin op een artikel van Moertel et al. (N Engl J Med 1992;326:519-23). Moertel rapporteerde een goede tumorrespons kans op een combinatie van streptozocine-doxorubicine met tumor regressie in 69% van de patiënten en een mediane tijd tot progressie van 20 maanden. De resultaten verkregen in dit artikel boden potentieel de mogelijkheid door cytoreductie de kans op een curatieve resectie te vergroten. Cheng et al waren echter niet in staat de resultaten van Moertel met deze behandeling te reproduceren. In ons eigen instituut had slecht één van de zes patiënten behandeld met streptozocine en doxorubicine een partiële tumorrespons. Drie patiënten hadden stabiele ziekte en twee waren progressief onder deze behandeling. Op basis van onze gegevens en die van Cheng et al concluderen wij eveneens dat patiënten met een eilandjescelcarcinoom die worden behandeld met de combinatie streptocozine-doxorubine slechts een kleine kans hebben op een dusdanige tumorrespons dat uiteindelijk een curatieve resectie mogelijk wordt.

In hoofdstuk 7b wordt een patiënt gepresenteerd die multidisciplinair behandeld werd voor een gemetastaseerd carcinoïd. Het merendeel van de patiënten met een gemetastaseerd carcinoïd kan niet curatief geopereerd worden. Een klein aantal geselecteerde patiënten kan echter door een combinatiebehandeling toch gecureerd worden. Wij beschrijven een 39-jarige patiënt met een carcinoïdmetastase in een leverkwab die om chirurgisch technische redenen niet resectabel was. Tijdens de eerste ingreep werd de primaire tumor verwijderd die was gelokaliseerd in een

Meckel's divertikel. Vanwege het invaliderende carcinoïdsyndroom werd patiënt behandeld met subcutane injecties interferon-alpha. Er volgde een biochemische respons. Drie jaar later toonde de CT scan een reductie van de omvang van de levermetastase zonder aanwijzingen voor intra-abdominale lokalisaties. Er werd vervolgens een hemihepatectomie verricht nadat chirurgische exploratie van het abdomen geen verdere tumordeposities toonde. De biochemische parameters normaliseerden hierna. Nu, na 15 jaar follow up, zijn er nog steeds geen aanwijzingen voor een tumor recidief.
De behandeling van een carcinoïdpatiënt is een multidisciplinaire behandeling. Zoals beschreven in deze casus, kan de samenwerking tussen de diverse disciplines in geselecteerde patiënten leiden tot een curatieve behandeling. Indien curatie niet mogelijk is, zal in het algemeen deze multidisciplinaire behandeling leiden tot betere palliatie en mogelijk overlevingswinst.

Door betere overleving van gemetastaseerde carcinoïdpatiënten zal vaker, later in het beloop, chirurgische interventie nodig zijn.
Midgut carcinoïden met levermetastasen kennen een verhoogde productie van catecholamines. In dit proefschrift wordt beschreven dat deze blijvend hoge concentraties circulerende catecholamines vasomotore gevolgen kunnen hebben zoals een verminderde gevoeligheid van de vaatwand voor serotonine en een verlaagde baroreflex sensitiviteit. Het is waarschijnlijk dat deze verstoring van vasomotore dynamiek bijdraagt aan de hemodynamische instabiliteit als onderdeel van een carcinoïdcrisis. Door de bescherming van de patiënt met de medicijnen ketanserin en vooral octreotide is de dreiging van een zo gevreesde carcinoïdcrisis geen contra-indicatie meer voor operatie. In vitro lijkt ketanserin haar effect te hebben via inhibitie van de contractiele respons van glad spierweefsel in de vaatwand van arteriën. De complexe problematiek die zich voor kan doen bij patiënten met een gemetastaseerd carcinoïd, maakt behandeling van deze patiënten in, of in overleg met, een centrum met veel ervaring gewenst.

Dankwoord

Prof. dr . E.G.E. de Vries, beste Liesbeth,
In mijn 'psion' stond op 11 juni 1998: "Prof. De Vries 12.30 uur Kidney Alley". Dat was de eerste keer dat wij bij elkaar kwamen. Na een korte gedachtewisseling schreef je 10 punten op, tekende er een kader omheen en zei: "dit moet je boekje worden". Er volgde een vliegende start. Het lijstje van 10 wilde redelijk vlotten totdat in juli 2000, vlak voor een vrij-geplande werkperiode van 4 maanden, een ingrijpende gebeurtenis het onderzoek van mijn kant vrijwel stil legde. Met enige regelmaat informeerde je of ik nog verder wilde gaan met het onderzoek en waar je me mee kon helpen. Je was geduldig waarbij je wel duidelijk aangaf dat het promotieonderzoek niet, zoals je het verwoordde, "een etterende wond" moest worden. Dat is taal die een chirurg begrijpt. De wond is intussen gesloten. Het lijstje van 10 van het begin is grotendeels zo gebleven. Jouw commentaren waren zakelijk en to the point en altijd duidelijk. Ik ben je zeer dankbaar en zie het als een voorrecht om jou als promotor te hebben.

Dr. P.H.B. Willemse, beste Pax,
Jouw rust en relativerend vermogen heb ik bijzonder gewaardeerd. Het terugsturen van commentaren ging in hoog tempo. Je record is binnen 10 uur! Het heeft er mede voor gezorgd dat ik 'op tijd' klaar was. Jouw commentaren waren tekstueel altijd scherp en doordacht. Menigmaal wist je met een minieme wijziging een zin twee maal zoveel zeggingskracht te geven. Een wisselend aantal balpenstipjes in de kantlijn of onderaan de bladzijde als stille getuigen van je denkproces. Vaak dacht ik bij het lezen van jouw commentaar: "Precies dát bedoelde ik te zeggen." Toen ik laatst je kamer niet meer kon vinden, wist ik dat ik mijn tijd in het AZG (inmiddels UMCG) moest afronden.

Dr. I.P. Kema, beste Ido,
Onze gesprekken over het onderzoek en gerelateerde onderwerpen zijn mij dierbaar. Met je vriendelijkheid en behulpzaamheid wist je steeds de juiste toon te zetten. Jouw kenmerkende eigenschappen kon ik ook herkennen in jouw laboratorium. Toen ik bij de start van het onderzoek op een ochtend één van de laboranten 3 liter urine overhandigde werd er niets tegen mij gezegd. De volgende dag kwam ik met een dubbele hoeveelheid. Ik ontmoette een glimlach en er werd mij voorzichtig meegedeeld dat het toch meer gebruikelijk was om een monster in te leveren met opgave van het volume in plaats van al die potten. Die kalme welwillendheid lijkt zo gewoon maar blijkt elders zo vaak niet aanwezig. Ik kan niet anders denken dan dat jij daar een rol in speelt. Alle medewerkers van het laboratorium, in het bijzonder de analisten Enge Venekamp-Hoolsema en Herman Velvis; heel hartelijk dank voor jullie hulp.

Dr. R.C.J. Verschueren, beste René,
Het is een gemis dat je er niet bent bij deze afronding en de promotie. Ik heb veel van je geleerd. Wanneer ik als ouderejaars assistent een "moeilijke buik" moest behandelen en ik, ondanks dat jij geen dienst had, je advies onmisbaar vond was jij telefonisch altijd bereid om mij te coachen. Je steun bij het ochtendrapport de volgende morgen wanneer dit onderonsje bekend werd, was altijd onvoorwaardelijk en werd vergezeld van een knipoog en een ingehouden glimlach. Je kennis en kunde heb je altijd met enthousiasme overgedragen op je pupillen. Dank voor je inzet om het chirurgische deel van dit boekje

te laten slagen. In het Deventer Ziekenhuis zijn veel oud-assistenten uit Groningen. We hebben het nog vaak over je……

De beoordelingscommissie bestaande uit Prof. dr. I.H.M. Borel Rinkes, Prof. dr. H. Hollema en Prof. dr. T. Wiggers ben ik dank verschuldigd voor het beoordelen van het proefschrift.

Dr. Rebecca Fokkema en Drs. Anouk van der Horst wil ik bedanken voor hun hulp bij het verzamelen van de data. Bij een aantal grafieken had ik jullie hulp hard nodig. Van Rebecca heb ik geleerd hoe je excelgrafieken zodanig kunt oppoetsen dat het net lijkt of *Word* en *Excel* écht compatibel zijn.

Dr A.J Smit en dr. J.A. Gietema, beste Andries en Jourik,
Dank voor de opzet en commentariëren van het vaatlabonderzoek. Zonder jullie hulp was dit onderdeel niet tot stand gekomen.

Anne van Gessel bedankt voor je inzet voor het onderzoek op het vaatlab en het voor een chirurg begrijpelijk presenteren van de data.

Dr. H. Buikema en dr. S.A. Nelemans, beste Hendrik en Ad,
Het heeft even geduurd, niet alleen van mijn kant. Het geheel overziende blijkt het onderzoek op jullie afdeling waarschijnlijk de verklarende de link te zijn tussen "kliniek" en onderzoek op het vaatlab. Hopelijk heeft het een vervolg.

Gretha Beuker en Bianca Smit wil ik bijzonder bedanken voor hun steun. Altijd aanspreekbaar, altijd hulpvaardig en opgewekt. Fijn om jullie op het secretariaat te kunnen bellen met vragen wanneer anderen het te druk hebben.

Beste vakgroepvrienden in Deventer,
Veel dank voor jullie steun bij het afronden van het onderzoek. De maand vrijaf in 2002 was net het zetje dat ik nodig had om een belangrijk/omvangrijk deel te analyseren. De rest was voornamelijk afronden.

Roger van der Wal en Han Dietz, bedankt voor jullie hulp met de softwareprogramma's. Goed gereedschap is het halve werk.

Mijn ouders wil ik bedanken voor hun steun en de mogelijkheden om mij te ontplooien. Jullie belangstelling en vertrouwen zijn stimulerend.

Lieve, lieve Margreet, mijn onlosmakelijke maatje en richting in mijn leven. We zijn er zeker van dat God ons bij elkaar heeft gevoegd. Je hebt een zware tijd achter de rug. Gelukkig kunnen we voorzichtig opademen. Jouw promotieonderzoek dwingt bij mij veel respect af. Waar een trein met verschillende wagons vaak als metafoor wordt gebruikt voor een onderzoekslijn, heb jij zèlf een trein in beweging gezet. Ik ben slechts door iemand op een wagonnetje van de voortrazende carcinoïdtrein gezet. Hoewel we op verschillende treinen zitten, gaat het lukken om op dezelfde dag op het station aan te komen. Je zult daar nog wel 6 uurtjes op me moeten wachten.

Curriculum Vitae:

Harry de Vries werd geboren op 16 mei 1962 te Den Helder. Na enig rondzwerven in de noordelijke provinciën volgde de middelbare school (HAVO en VWO) in Doorn. Uitgeloot voor geneeskunde koos hij voor Lucht en Ruimtevaart techniek in Delft. In 1981 werd hij nageplaatst voor de studie geneeskunde aan de Rijkuniversiteit Utrecht. De Propaedeuse behaalde hij in 1982 en het doctoraal in 1988. Als onderdeel van de wetenschappelijke stage in het kader van het doctoraal werkte hij op het Laboratorium van de psychiatrie in het AZG. Daarbij was hij betrokken bij het onderzoek van (inmiddels) prof. dr. J.A. Den Boer naar de werking van serotonine heropname remmers bij patiënten met angststoornissen en dwangneurosen. Gedurende de doctoraalfase was hij nauw betrokken bij alles wat te maken had met de studenten vertegenwoordiging in diverse gremia van de faculteit. Dit resulteerde in een twee jaar durend lidmaatschap van het faculteitsbestuur (decaan en leermeester: prof. dr. Mebius Kramer. De basis voor de liefde voor de chirurgie werd gelegd in Tilburg. Onder leiding van prof. dr. Chris van der Werken deed hij tijdens de co-schappen dierexperimenteel onderzoek naar de werking van gentamicine-collageen matjes in de behandeling van abcessen. In december 1991 volgde het artsexamen. Tijdens militaire dienst werkte hij als reserve Eerste-Luitenant in het Centraal Militair Hospitaal in Utrecht alwaar hij als militair arts werd gedetacheerd op de spoedeisende hulp van het AZG (hoofd: prof. dr. Th.J.M.V. van Vroonhoven). In januari '93 ontmoette hij zijn grote liefde Margreet Schot met wie hij trouwde in mei 1993. In februari 1993 zwaaide hij vervroegd af zodat hij kon aanvangen met de opleiding tot chirurg in Leeuwarden (opleider: dr. Piet de Vogel). In maart 1996 startte de opleiding in het AZG (opleider: prof. dr. R. van Schilfgaarde). De opleiding tot chirurg werd voltooid in februari 1999 waarna aansluitend de opleiding tot chirurg-oncoloog werd gevolgd in het AZG (opleider: prof. dr. H. Schrafford Koops, later waarnemend opleider dr. R.C.J. Verschueren). Tijdens deze fase werd het onderzoek naar carcinoïden gestart onder leiding van prof. dr. Liesbeth de Vries. In augustus 2000 werd de opleiding tot chirurg oncoloog 'voltooid'. Inmiddels was de sollicitatie bij de vakgroep heelkunde afgerond in het Deventer Ziekenhuis alwaar hij startte met zijn werkzaamheden op 1 januari 2001 met als aandachtsgebieden de speciële chirurgische oncologie, de hoofd-hals chirurgie en de longchirurgie.