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Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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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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