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Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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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 of serotonin mediated pre-synaptic 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.