Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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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).

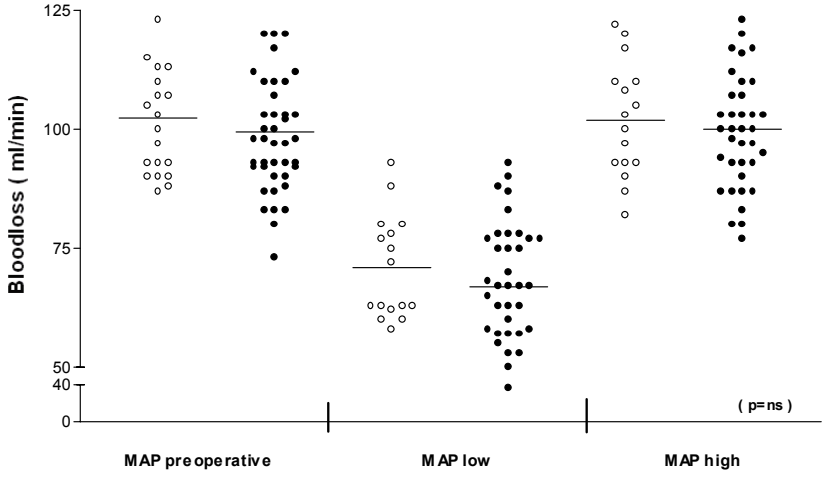

Figure 1 MAP preoperative: pre-operative mean arterial pressure
MAP low: peri-operative lowest mean arterial pressure
MAP high: peri-operative highest mean arterial pressure
° = patient without octreotide
• = patient with octreotide
(37 operations)

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)

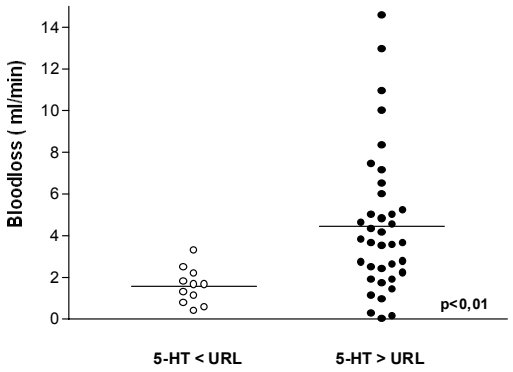

Figure 2 Blood loss per minute operating time (ml/min) for pre-operative platelet serotonin lower and higher than upper reference limit (URL = 5.4 nmol/10^9plt, $p<0.01$)

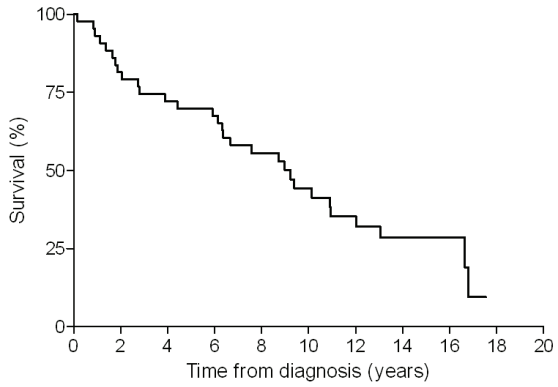

Figure 3 Kaplan-Meier survival curve (from first operation). Five-years actuarial survival is 69%

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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