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SURGICAL TREATMENT OF PATIENTS WITH THE CARCINOID SYNDROME

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Abstract

During the last 5-year period aggressive surgical debulking was performed in 19 of 21 consecutive patients with the midgut carcinoid syndrome. Two patients were excluded due to severe cardiac disease. Fourteen of the patients had hepatic metastases. Carcinoid symptoms can occur also in patients without proven liver disease with sole lymph node metastases or retroperitoneal tumours. In 4 patients all metastatic tumour tissue could be removed resulting in biochemical cure and no symptoms. In patients with multifocal hepatic metastases surgical debulking was followed by transarterial embolisations of the hepatic arteries. All patients had good symptomatic relief of the combined surgical and radiological treatment. Five patients had currently stable disease anatomically and biochemically, 2 slowly progressive disease and one patient has a more rapid progression. Three patients have just undergone debulking and are waiting for further treatment. During the observation period 4 patients have died. Of these deaths one was related to the surgical procedures. After the introduction of somatostatin analogues major surgery can be performed safely in these patients with little risk of carcinoid crises. The role of additional drug therapy in these rare patients must be evaluated critically in randomized multicenter trials using a common surgical primary treatment.

Key words: Carcinoid syndrome, tumour resection, tumour debulking, liver embolisation, somatostatin analogues.

The incidence of clinically relevant gut endocrine tumours is low: In a Swedish necropsy study, 199 cases were diagnosed among 16 194 patients over a 12-year period. When clinically diagnosed tumours were included the calculated annual incidence was as high as 8.4 per 100 000 inhabitants (1). This figure seems to be of little clinical relevance, since 9 of 10 patients died *with* the tumour, not *of* it, due to a large number of benign appendix tumours. Most carcinoid tumours are derivatives of the embryologic midgut: 45 % are located in the appendix and 28 % in the small intestine (2). The tumours are more common in the distal small intestine and are usually multiple. The incidence of metastases is related to the size of the primary small intestinal tumour (3, 4). At clinical discovery a large percentage (up to 70 %) of the small intestinal tumours are metastatic (5). Therefore considerable efforts have been made to enable earlier detection, i.e. provocation tests (6–8) and selective mesenteric vein samplings with determination of the main hormonal products, serotonin (5-HT) and tachykinins (9). Only a small percentage (4–9 %) of all patients with carcinoid tumours have symptoms compatible with the carcinoid syndrome (2, 5). The carcinoid syndrome usually occurs in the presence of hepatic metastases with excessive production of 5-HT and tachykinins (10). In certain cases localized retroperitoneal tumour masses or small hormonally active ovarian tumours may each drain their tumour products directly into systemic circulation thus bypassing the hepatic metabolism (5).

In the Mayo Clinic series it was demonstrated that the prognosis quo ad vitam was clearly related to distant spread of the disease (11). In patients with metastases to the liver the 5-year survival rate was only 21 %. Other prognostic factors have been discussed, i.e. the histologic growth pattern and DNA contents. Soga & Tazawa (12) suggested classification into 5 major growth patterns, where convincing prognostic differences have been shown between insular and undifferentiated growth patterns (13). DNA measurements indicate a high frequency of diploid pattern with little prognostic value (14).

Cytotoxic treatment of carcinoid tumours has included a wide variety of drugs, e.g. doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, streptozotocin and most lately interferons (15–18). These studies are difficult to evaluate, since carcinoid tumours display a large variation in spontaneous biological behaviour. Due to the

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relative infrequency of carcinoid tumours only few randomized controlled studies have so far been performed.

Over the last 5-year period we have treated our patients with the carcinoid syndrome with aggressive tumour reduction, i.e. primary surgical debulking and subsequent hepatic artery embolisations. In cases not further accessible to such therapy we have used palliation by a somatostatin analogue, which reduces the hormonal secretion by the tumour. In the future we look forward to randomized controlled studies evaluating adjuvant therapies in addition to a well-defined surgical program with careful anatomical staging of the disease as well as periodic monitoring of biochemical tumour markers.

Material and Methods

During the period November 1983 to June 1988 (56 months) 21 cases of the midgut carcinoid syndrome have been evaluated and treated at our unit. Seven patients were male and 14 female with a mean age of 63 years (range 49–77 years). Eleven of the 21 patients had had primary surgery (removal of the primary tumour in 5 patients and diagnostic laparotomy in 6) at their local hospital and were referred to us for additional treatment after varying delay periods (Figure). Fifteen of the patients had their primary gut lesion removed in association with the surgical debulking performed at our hospital (Table). Two of the patients (female 72 years and male 74 years) had severe carcinoid cardiac disease (tricuspid valve insufficiency grade IV and pulmonary stenosis) and were therefore not subject to any further surgical treatment. These patients were referred to us prior to the introduction of somatostatin analogues (SMS 201-995, Sandoz, Switzerland) and were therefore treated for palliation with a slow calcium channel blocker (Isoptin-verapamil, Knoll, FRG) and a 5-HT_2-receptor antagonist (ketanserin, Janssen, Belgium) (19). Both died within one year after the clinical appearance of cardiac insufficiency.

Of the 19 patients who were surgically treated 14 had hepatic metastases at referral (Table). Of the 5 patients without liver metastases patient No. 2 had previously had the primary lesion removed, but had persisting diarrhea and flushing due to retroperitoneal tumour masses. Patient No. 6 had flushing, diarrhea and asthmatic attacks. Patient No. 11 had a unique clinical picture with blocked lymphatic drainage from the mesentery due to huge paraaortal tumour masses causing lymphatic stasis of the small intestine and effusion of lymph into the peritoneal cavity. This patient also had a grade III tricuspid valve insufficiency and slight pulmonary stenosis in the absence of hepatic metastases. Patient No. 14 had emergency surgery due to an ileus. She had previous sole flushing symptoms, but no proven liver metastases. Patient No. 15 had a skin nodule that caused facial flush upon touch. Pathoanatomical diagnosis of a midgut carcinoid tumour metastasis led to extensive investigations (including mesenteric venous sampling with determination of 5-HT in whole blood and platelet-poor plasma) and surgical exploration revealing a small gut lesion and minor lymph node involvement, but no hepatic disease. A flush-inducing skin nodule was also the first symptom that brought patient No. 13 to investigation. The disease in this case, however, involved both regional lymph nodes and the liver.

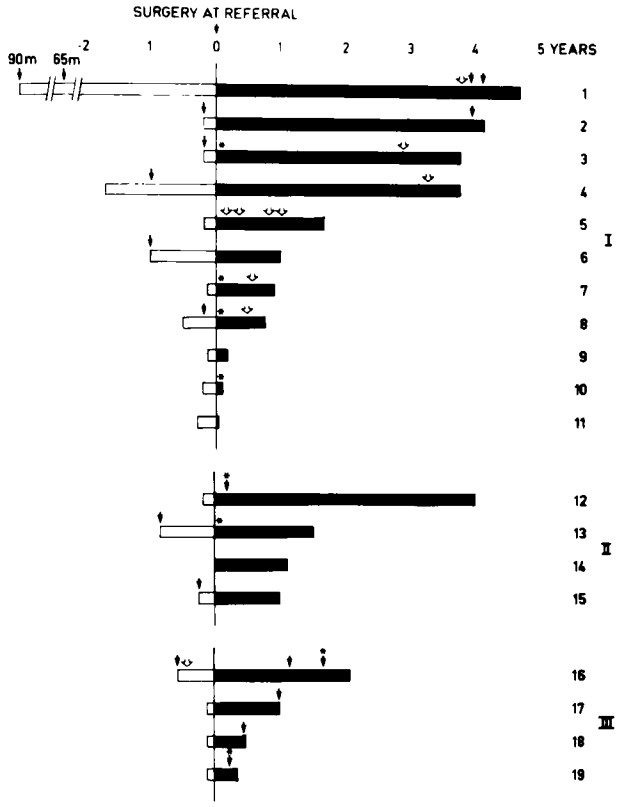

Figure. Survival rate in patients with the midgut carcinoid syndrome treated with surgical debulking at referral. The delay between diagnosis and referral varied between 1–90 months (□). Asterisks indicate hepatic surgery. (→) means major surgical interventions and (⇨) embolisation of the hepatic arteries. Patients in group I had tumour reduction, in group II all metastatic tumours were removed resulting in biochemical cure. Patients deceased during the study form group III. For details see text and Table.

Our policy during this period has been to perform a surgical exploration after biochemical evaluation of 5-hydroxy-indoleacetic acid (5-HIAA) in urine and 5-HT in peripheral blood at pentagastrin (PG) provocation (6) and after radiological work-up to localize the primary lesion and evaluate the extent of disease (barium series, angiography, computed tomography and, in certain cases, mesenteric venous samplings). During surgery further anatomical staging of the disease is performed. The surgical debulking procedures include removal of the primary gut lesion and removal or major reduction of mesenteric and paraaortic lymph nodes by a careful dissection of the mesenteric root.

Table

Anatomical and biochemical features of patients with the midgut carcinoid syndrome

Patient No.	Sex & age (years)	Extent of disease		Biochemical findings				Current clinical state	Current and planned treatment
		At referral	Latest follow-up	At referral		Latest follow-up			
				5-HIAA mmol/mol creat	Peak/basal 5-HT ng/ml	5-HIAA mmol/mol creat	Peak/basal 5-HT ng/ml		
1	M 56	N+L+P	N+L+P	25	610/200	38	650/270	Slow progr	Emb+SMS
2	M 74	N	L+P	11	330/220	10	290/210	Slow progr	Emb+SMS
3	M 65	G+N+L+P	L	–	450/220	12	210/170	Stable	–
4	M 55	N+L	L	22	–/310	9	270/170	Stable	–
5	F 54	G+N+L+P	L+P+H	110	–/990	91	–/470	Progr	Cardiac surg + emb+SMS
6	F 61	G+N	N	23	310/200	21	240/180	Stable	–
7	F 72	G+N+L	L	56	410/300	6	290/240	Stable	–
8	F 73	G+N+L	L	24	400/300	13	290/210	Stable	–
9	F 67	G+N+L	L	120	590/450	–	–	Under	Emb+SMS
10	F 66	G+N+L+P	L	130	–/1 030	–	–	treat-	Emb+SMS
11	F 65	G+N+P+H	N+P	23	270/210	–	–	ment	SMS
12	F 49	G+N+L	0	33	470/280	4	110/90	Biochem cure	
13	F 55	G+N+L+S	0	9	140/110	5	80/50	Biochem cure	
14	F 58	G+N	0	–	–	3	120/70	Biochem cure	
15	F 51	G+N+S	0	5	–	2	80/50	Biochem cure	
								Cause of death	
16	F 60	N+L+P	L+P	21	–/420	130	–/870	Progr + leukemia	
17	M 77	G+N+L+P	L+P	41	320/200	66	480/310	Progr + ileus	
18	F 73	G+N+L	L	340	1 210/970	230	–	Thromboembol post orthopedic surg	
19	M 57	G+N+L+P	L+P	92	790/520	–	–	Resp insuff postop	
	Reference values			(<6)	(no peak reaction/160)				

G=Gut lesion, N=Lymph node metastases, L=Liver metastases, P=Peritoneal lesions, H=Heart involvement (right-sided), S=Skin lesions.

In cases with severe fibrosis or massive lymph node involvement this procedure often required division of the ileocolic artery and a right-sided hemicolectomy. In certain cases other involved arterial branches were put on occlusion and divided after 20 min together with discoloured parts of the intestine. Peritoneal lesions were excised or treated locally by cauterization. Large superficial or well palpable liver lesions were removed surgically by wedge resections. Only 2 of the 14 patients with hepatic involvement had isolated liver lesions angiographically. Patient No. 13 had the lesions removed by wedge resection during primary surgery. Patient No. 12 underwent left-sided hemihepatectomy one month after primary surgery. Biochemical cure (normal PG test and urinary 5-HIAA levels) was achieved in both these patients. Another patient (No. 16) developed a massive hepatic tumour burden with right-sided dominance and therefore underwent a hemihepatectomy for palliation.

The majority of patients had multiple smaller lesions in both lobes of the liver, which were treated with subsequent transarterial embolisations of the hepatic arteries under antibiotic prophylaxis (20). Therefore, in all patients a cholecystectomy was performed to facilitate for future embolisation therapy of the liver. During the last 2 1/2 years surgery or embolisations have been performed after pretreatment of the patients with SMS 201-995 and ketanserin, followed by individual tests of the blockade by PG to avoid carcinoid crises. These anesthetic considerations have been reported in detail recently (21, 22).

Results

It is still too early to evaluate the survival rate in this surgical series. One evident result of the aggressive surgical treatment is that 4 patients with metastatic disease (2 patients with liver metastases) have reached a state with-

out macroscopic disease and completely normal biochemical findings (group II in the figure). In group I subtotal tumour reduction was performed. Five patients have stable disease both anatomically and biochemically and are presently symptom-free (Table). Two patients (Nos 1 and 2) have very slow progression of their disease. All these 11 patients in groups I and II have active lives and no disabling symptoms. The two patients with slow progression are presently on treatment with SMS 201–995 prior to future embolisations. One patient (No. 5) has been very active but has developed a grade II–III tricuspid valve insufficiency, where valvular replacement is planned. She is therefore on treatment with SMS 201-995. On this therapy she has very little symptoms of flush and diarrhea. Three patients (Nos 9ø11) have only recently been operated and cannot yet be evaluated.

The deceased patients are in group III: Two of these 4 patients died with tumour progression and intercurrent disease. Patient No. 16 had interferon as a final therapeutic effort after hemihepatectomy without any evident response. She also had a chronic myeloic leukemia. Patient No. 17 developed an ileus and died from intestinal ischemia. Patient No. 18 had a hip fracture during convalescence and died from thromboembolism after orthopedic surgery. Patient No. 19 was severely emaciated (20 kg weight loss) and had surgical debulking in 2 operations, one directed against the gut and mesenteric lesions and the other against pancreatic and splenic lesions. He died in respiratory insufficiency after 2 weeks.

Discussion

The most important treatment for small bowel carcinoid tumours has been and continues to be surgical. Despite slow growth of many carcinoid tumours, they must be regarded and treated as malignant neoplasms. If diagnosed prior to surgery, the investigation should be focused to stage the extent of disease both biochemically and anatomically. Metastatic tumours should be treated with *en bloc* resections regardless of the size of the primary lesion (5). Even small lesions may cause severe future problems with ileus (occluded gut lumen, kinking and retraction of the mesentery) and intestinal ischemia (due to vasoconstrictive actions of 5-HT and tachykinins secreted in excessive amounts) (23, 24). Palpation of the small bowel to detect synchronous tumours is important, as well as a careful surgical exploration of the abdomen, since the incidence of associated neoplasia is high (5).

The major problem is adequate treatment of the hepatic lesions. These are only occasionally accessible to radical surgical treatment (patients Nos 12 and 13). Davis et al. (25) have reported on the value of hepatic resection or lobectomy for palliation of the carcinoid syndrome. So far we have followed this policy in one patient (No. 16) with more advanced disease in one of the hepatic lobes and rapid progress. The palliation alternative, today available, is ischemic treatment of the liver, which can be achieved according to one of two somewhat different principles (temporary surgical liver dearterialization or transarterial embolisation of the hepatic arteries) (26, 27). We have used the latter principle as described by Lunderquist et al. (28). This treatment was instituted 1–2 months after our surgical treatment or at recurrence of carcinoid symptoms. Embolisation of each one of the main hepatic arteries was performed on 2 separate occasions (1–2 months apart). Repeated embolisations were performed at progress of symptoms, which was related to a synchronous elevation of biochemical tumour markers. In comparison with the temporary dearterialization technique (peri- and postoperative occlusion of the hepatic arteries by vessel loops), transarterial embolisation seems to cause less severe damage to the liver parenchyma as judged from the magnitude of the response of liver enzymes (27, 29). On the other hand, the period of symptomatic relief may be shorter after embolisation therapy (29). One advantage of transarterial embolisations is that the patient only seldom needs further surgical interventions after the primary debulking procedures. Repeated temporary dearterialization would require a new laparotomy.

The serious complication previously seen in association with ischemic treatment of the liver was gangrene of the gallbladder (20). Therefore cholecystectomy was performed in all our patients together with the surgical debulking. One major concern in the surgical treatment of patients with advanced carcinoid disease has been the hazard to develop a carcinoid crisis during surgery. With the introducton of the new somatostatin analogue and the subsequent clinical and biochemical evaluation of the patient with PG provocation prior to surgery this risk seems to be eliminated (22). In our experience it has been possible to perform the desired surgical debulking also in patients with far advanced disease (Nos 1, 5, 9, 10, 18 and 19) under such protection.

Like most studies on carcinoid tumours, the present surgical series was not randomized and can therefore in the future only be compared with historical controls. Our purpose has been to gain experience with a consequent aggressive surgical approach in a disease with most individual clinical expression. Our experience with interferon treatment is therefore limited. We have used this drug in one patient with the carcinoid syndrome, late in the disease, without any apparent effect. We have also used interferon in 7 patients with endocrine pancreatic tumours according to the schedule proposed by Öberg et al. (24). Our results are not in accordance with the reports from the Ludwig Institute in Uppsala. Only one of our patients with endocrine pancreatic tumours responded to interferon treatment with a temporary remission for 9 months. To evaluate drug treatment in patients with gut endocrine tumours properly, it is important to present the individual case histories as to duration and stage of disease, intercurrent diseases, other drug treatment and type of surgery

performed. Sole interpretation of biochemical data may be very misleading, especially after the introduction of new agents that modulate hormonal secretion from the tumours without certain cytotoxic effects, e.g. SMS 201-995. Transient variations in tumour volume, e.g. as reported by immune response modifiers, may not affect patient survival at all. Short-term evaluation of drug therapy in a patient like No. 1 (with present survival of 146 months due to slowly progressive disease in combination with the surgical treatment) is of little clinical relevance. There is an obvious need both medically and ethically for scientifically well-grounded information about the beneficial effects on morbidity and mortality of different treatment modalities. Differences in survival rate and quality of life between drug-treated and non-drug treated groups of patients in a randomized multicenter trial using a common surgical primary treatment will direct us to a better future therapy.

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