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EMBOLISATION THERAPY IN THE MIDGUT CARCINOID SYNDROME: JUST TUMOUR ISCHAEMIA?

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Forty-eight patients with midgut carcinoid tumours and disseminated disease were treated at our unit 1986-1991. All patients underwent primary surgery with optimal tumour reduction. Twenty-seven patients with bilobar liver metastases had subsequent embolisations of the hepatic arteries to further reduce the functional tumour mass and were thereafter treated with a low dose of octreotide. The response to this treatment was evaluated by CT at 3 months postembolisation. The patients could then be divided into 13 responders (no visible hepatic tumours or more than 50% reduction, group I) and 14 non-responders (less than 50 reduction or progression, group II). When these patients were studied biochemically and in terms of prognosis, the reduction of 5-HIAA levels postembolisation was much more pronounced in group I ($80 \pm 3\%$) then in group II ($28 \pm 12\%$). The biochemical and radiological responses were long-lasting in group I, none of the patients needed further ischaemic treatment. Of specific interest were 3 patients with bilobar disease, who after selective unilobar embolisation normalised their 5-HIAA levels and had bilateral tumour regression. These findings indicate involvement of systemic effects in addition to tumour ischaemia alone. The initial biochemical response with marked decrease of 5-HIAA levels in combination with tumour regression may thus serve as an indicator of good prognosis.

Disseminated midgut carcinoid tumours represent a difficult therapeutic problem with intestinal complications due to residual tumour and disabling symptoms due to excessive hormone secretion (serotonin and tachykinins) from hepatic metastases. Major surgical procedures have involved the hazards of uncontrolled hormone release (carcinoid crisis). In historic controls the 5-year survival was only 21–30% in patients with hepatic metastases (1–3). Modern interventional and medical treatment, e.g. hepatic arterial embolisation, somatostatin analogues (octreotide), interferons, or combinations thereof, has considerably improved the prognosis and quality of life for these patients (4–8).

Over a 6-year period we have treated patients with the midgut carcinoid syndrome according to a strict program (cf. 8): 1) *Tumour reduction.* Optimal tumour reduction was achieved surgically by removal of the primary tumour and regional lymph node metastases. Retroperitoneal tumours were excised and cholecystectomy performed to reduce complications at subsequent embolisation (gangrene) and octreotide treatment (gallstone formation); 2) *Liver resection or arterial embolisation.* Patients with unilobar liver disease underwent hepatic resection in a second operation, while bilobar disease was treated with successive embolisations of the hepatic arteries (1–2 months apart). All interventional procedures were performed under protection with octreotide; 3). *Octreotide treatment.* For optimal symptom palliation all patients with residual disease were allowed to titrate their own dose of octreotide. In general this resulted in a low maintenance dose

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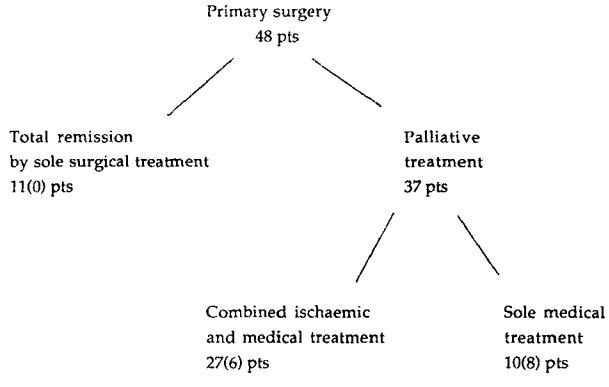
(100–200 μg daily) 4). *Follow-up program.* The follow-up included measurement of urinary 5-HIAA levels every 3 months and abdominal CT every 6 months. Repeat embolisations were considered at radiological evidence of tumour progression in combination with more than two-fold increased 5-HIAA levels (cf. 8).

The purpose of this investigation was to study tumour response by CT in 27 patients, who were treated by hepatic arterial embolisation in combination with octreotide, and to evaluate objective responders and non-responders biochemically and in terms of prognosis.

Material and Methods

Patient material. Over a 6-year period (1986–1991) 48 consecutive patients with midgut carcinoid syndrome were treated at our unit (Fig. 1). In 11 patients total remission was achieved by surgical treatment alone. Liver surgery was performed in 6 of these patients (4 hemihepatectomies and 2 wedge resections). The other 5 patients had extensive lymph node dissections and excision of retroperitoneal tumours, but no hepatic disease. In this group, followed for 42 ± 7 months (mean ± SEM), no patients have died. Thirty-seven patients were treated for palliation (Fig. 1). Ten were treated only medically by octreotide subsequent to primary surgery. Two of these patients had concomitant malignancies (ovarian carcinoma and leukemia), three were scheduled for embolisation but died from cardiovascular disease prior to treatment (myocardial infarction and thromboembolism). Three patients were excluded from embolisation therapy, one due to cachexia and psychosis, and two due to cachexia and liver cirrhosis. Two patients obtained good quality of life after primary surgery and octreotide treatment and are not willing to undergo further interventional treatment at present time. During a mean observation time of 19 ± 3 months, 8 patients in this group have died. The program with hepatic arterial embolisation and medical treatment by octreotide was given to 27 patients. Six of these patients have died during the observation period, 4 from their tumour disease (Table).



* Number of deceased patients within parenthesis

Fig. 1. Patients with disseminated midgut carcinoid tumours treated at Sahlgrenska sjukhuset 1986–1991.

Embolisation procedure. The anaesthetic and radiological considerations and potential complications at embolisation have earlier been reported in detail (cf. 8). Before embolisation, a transfemoral diagnostic angiography of the coeliac and superior mesenteric arteries were performed to demonstrate pattern of arterial blood supply to the liver and patency of the portal vein. A catheter was then advanced into the right or left hepatic artery and embolisation performed. For the first 11 procedures, the angiography catheter (7 F) was used, the superselective catheterisation being accomplished with use of a 0.035″ floppy tip guide wire and subsequent advancement of the angiography catheter over the wire. In remaining 51 procedures a 3 F coaxial catheter system (Tracker™, Target Therapeutics, San José, Ca, USA) was advanced through the diagnostic catheter in the coeliac or superior mesenteric artery (cf. 9). The embolisation was performed with gelfoam powder (Spongostan A/S Ferrosan, Danmark). The agent was mixed with contrast medium and injected until blood flow was interrupted as evaluated by fluoroscopy. Great care was taken to avoid spill-over to the gastroduodenal and pancreatic arteries.

Classification of radiological responses by CT. Images from examinations before embolisation were compared with images obtained at examinations 3 months after. The pre-embolisation studies were not always performed at our hospital and besides, all patients had disseminated metastases. It was therefore often difficult to compare individual lesions before and after treatment by measurement. An estimation of tumour response was thus made, taking all lesions into consideration and 2 groups were defined: No visible remaining tumour lesions or more than 50% reduction (group I), and less than 50% decrease or progression (group II) (Fig. 2).

5-HIAA evaluation. The 24-h urinary excretion of 5-HIAA was evaluated: 1). After primary surgery without octreotide treatment (2–4 weeks postoperatively). 2) Just before the first embolisation when all patients had been treated chronically (=more than 4 weeks) with octreotide (100 μg × 2). 3) After the last embolisation with a maintained dose of octreotide (2–4 weeks postembolisation). 4) At regular check-ups every 3 months. This time schedule allows an estimation of the reduction in 5-HIAA excretion caused by octreotide alone and by the subsequent ischaemic treatment.

Results

In this study we have focused our analysis on the group of 27 patients with combined medical and ischaemic treatment. Twenty-one of these patients are alive and 6 are

Table

Clinical and biochemical data (mean ± SEM) of patients with biochemical response in combination with tumour regression (group I) or sole biochemical response (group II)

Pat No.	Sex	Age at first embolisation years	At onset of treatment μmol/24h	On octreotide μmol/24 h	Group I (n = 13) 5-HIAA (μmol/24 h) Reduction by embolisation %	Present μmol/24 h	Radiol response	Obs. time after first embolisation months	Daily dose of octreotide μg
Group I (n = 13)									
I	M	54	210	110	76[1)]	47	CR	52	100
II	F	62	—	600	71[1)]	53	CR	49	—
III	F	72	140	82	60[1)]	39	CR	45	100
IV	M	56	180	180	64[2)]	42	PR	34	200
V	M	74	390	370	80[2)]	420	CR	34	200
VI	F	60	300	110	89[2)]	80	CR	34	100
VII	M	70	2100	980	81[2)]	280	PR	10	200
VIII	M	63	—	480	88[2)]	120†	PR	13	200
IX	M	65	860	410	91[2)]	64	PR	27	200
X	M	43	1034	620	87[2)]	85	PR	19	100
XI	F	69	156	67	90[2)]	27	CR	18	200
XII	F	64	680	420	84[2)]	80	PR	5	200
XIII	M	70	1600	610	—	—†	CR	3	200
Mean		63 ± 2	696 ± 197	388 ± 76	80 ± 3	111 ± 34		26 ± 5	
Group II (n = 14)									
Mean		62 ± 4	595 ± 126	345 ± 64	28 ± 12	278 ± 50	NR	37 ± 4	200

[1)]Unilateral embolisation
[2)]Bilateral embolisation
† = pat. deceased
CR = complete response
PR = partial response
NR = no response

dead, 4 from their tumour disease. After the initial treatment with octreotide (100 μg × 2) for 2–4 weeks prior to embolisation the 5-HIAA levels were markedly reduced (Table).

At CT 3 months after embolisation no remaining tumour, or more than 50% decrease was demonstrated in 13 patients (group I), complete disappearance occurred in 7 of these. No tumour regression, or less than 50% regression, was demonstrated in 14 patients (group II). When these groups, which were similar in age, sex, tumour extension and levels of 5-HIAA at the onset of treatment (Table), were evaluated biochemically the following observations were made:

—Both groups had an equivalent initial reduction of 5-HIAA levels by octreotide alone (44% and 42% respectively).

—After completion of embolisation therapy (bilateral procedures in 10 out of 13 patients in group I and in 12 out of 14 in group II) the reduction of 5-HIAA levels, monitored 2–4 weeks after embolisation was much more prominent (80 ± 3%) in group I than in group II (28 ± 12%) with one exception (pat. No. V). This patient slowly developed retroperitoneal tumour recurrence with hormone secretion by-passing the hepatic metabolism.

—The biochemical and radiological responses were long-lasting (Fig. 3) in group I, where none of the patients required re-embolisation during the observation period (26 ± 5 months). Of special interest in this group were 3 patients (Nos I–III) with bilobar metastases, who after unilateral embolisation had biochemical normalisation of 5-HIAA levels and bilateral tumour regression. In group II 3 patients underwent re-embolisation 9, 12, and 48 months respectively after the primary treatment due to progressive disease with increased tumour markers.

Discussion

Ischaemic treatment of hepatic metastases of carcinoid tumours is based on obliteration of their main blood supply from the hepatic arteries (10). Selective embolisation of these arteries will cause a temporary, but rather complete ischaemia, since the arterial tree distal to the point of injection is filled with embolisation material (11, 12). Previous biochemical studies have shown that the

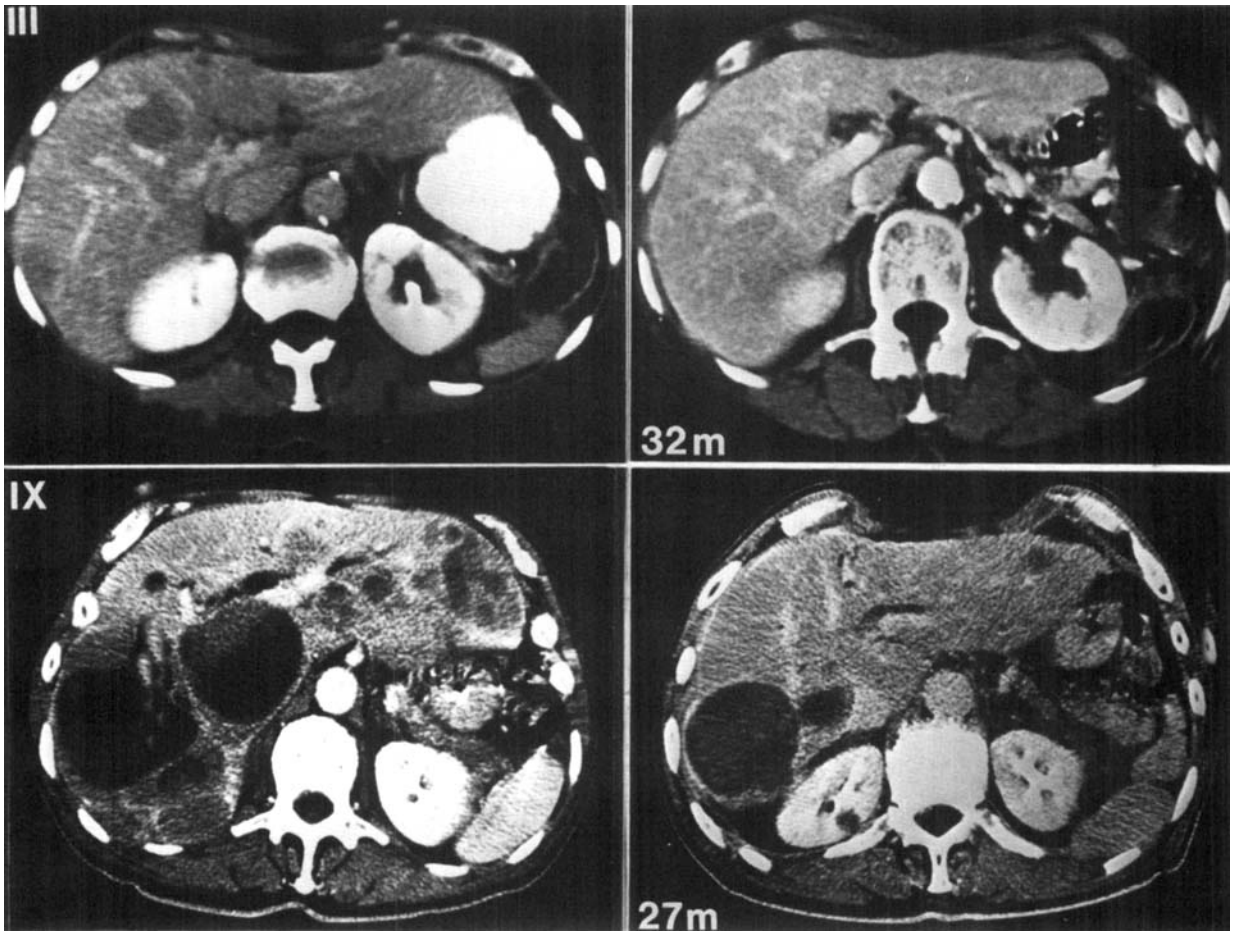
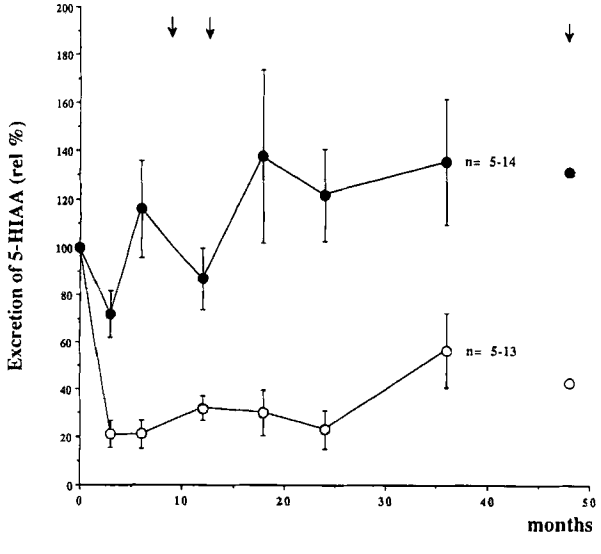


Fig. 2. CT-scans before (left panel) and after bilobar embolisations (right panel) in two patients (Nos III + IX, cf. Table) with the midgut carcinoid syndrome studied at 32 and 27 months respectively. A complete radiological response was observed in patient No. III and a partial response was observed in patient No. IX. Note the volume reduction of the liver in the latter patient.



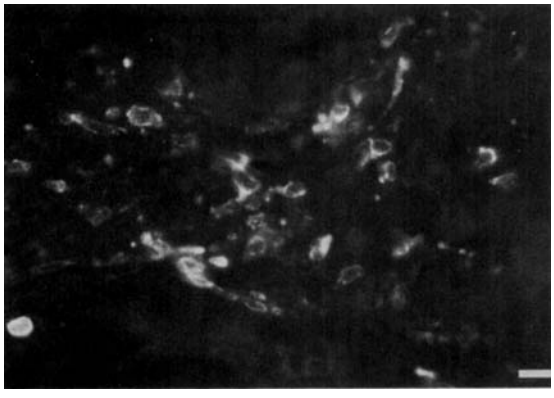
release of serotonin and the transaminase reaction are somewhat delayed (24–48 h postembolisation). The tumour cell necrosis is also reflected by fever and leukocytosis (8, 12–16). In previous studies, embolisation therapy has in general been instituted at a late stage of carcinoid disease and therefore added little to survival (15, 17). In this series, however, embolisation therapy was initiated

Fig. 3. Urinary 5-HIAA studied over time in 27 consecutive patients with the midgut carcinoid syndrome subsequent to primary embolisation therapy (mean ± SEM). Group I (unfilled circles, n = 13) showed tumour regression on CT and group II (filled circles, n = 14) showed no tumour regression. Three patients in group II were excluded at 9, 12 and 48 months respectively (arrows) due to tumour progression in the liver (treated with re-embolisation). No patients in group I showed progressive hepatic disease.

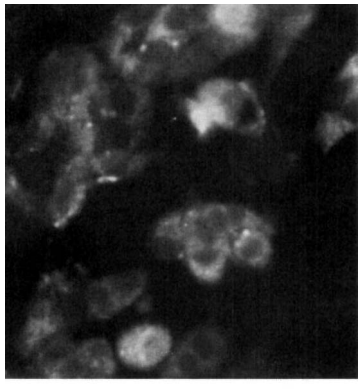
shortly after the diagnosis of bilobar hepatic metastases was made.

The marked difference in radiological and biochemical response between groups I and II is intriguing. It may, of course, relate to the completeness and duration of the ischaemic treatment. These parameters are difficult to evaluate exactly by routine examinations and we have no such data at present. The pronounced radiological and biochemical tumour responses in group I were observed for prolonged periods and are not easily explained by acute tumour ischaemia alone. Rapid development of collateral circulation has been observed after more proximal ischaemia, e.g. as obtained by hepatic artery ligation (18). Furthermore, 3 patients (Nos I–III) with tumour dominance in one liver lobe had their first embolisation directed against this lobe without evidence of spill-over. Since all these patients showed marked bilobar tumour regression, a second embolisation was not needed for palliation. These patients have now been observed for 52, 49 and 45 months without any signs of tumour progression in the liver. One patient (II) is completely free of symptoms and has not used octreotide as additional medical therapy. Taken together these findings may indicate activation of a systemic antitumour mechanism by the embolisation procedure in certain individuals. Activation of such a mechanism would help to explain the excellent long-term results in group I, in which no patient has needed re-embolisation so far. The initial biochemical response to embolisation therapy with pronounced decrease of a tumour marker in combination with objective tumour regression may in the future serve as an indicator of good prognosis.

Rosenberg et al. (19, 20) recently reported on the presence of tumour-infiltrating lymphocytes (TIL cells) in metastases of advanced melanomas. If TIL cells were isolated from tumour biopsies by culture in the presence of exogenous interleukin-2 (IL-2), TIL cells were loaded with IL-2, but kept their tumour recognition mechanism intact. When these loaded TIL-cells were given back to the patient, marked tumour regression was observed in individual patients. Endogenous interleukin production was recently demonstrated by osteoblasts in Paget's disease (21). Biopsies of hepatic metastases and tumour cell cultures from three patients with the carcinoid syndrome were studied immunocytochemically for the presence of TIL cells and IL-2. All three tumours were infiltrated by TIL-cells. Immunoreactive IL-2 was observed in cytoplasmic granules of tumour cells in long-term culture, indicating endogenous synthesis of IL-2 by tumour cells (Fig. 4). Hypothetically, embolisation and secondary tumour ischaemia may liberate TIL cells from the liver and endogenous cytokines from tumour cells, leading to an enhanced immunological response against the tumour. Alternatively, after necrotisation of tumour cells the immune system is exposed to new antigens attracting different subsets of lymphocytes. Prospective studies regarding the degree and duration of tumour ischaemia, presence of TIL cells in individual tumours, and activation of immunological mechanisms will hopefully increase our knowledge about the tumour response following embolisation therapy in patients with the midgut carcinoid syndrome.



(a)



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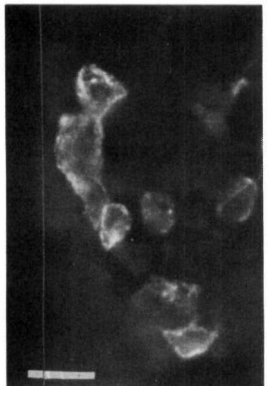

(c)

Fig. 4. a) Immunocytochemical demonstration of tumour infiltrating lymphocytes (CD-8 subset) in liver metastasis of a midgut carcinoid tumour (monoclonal antibody, clone B9.11, Immunotech, France). b) and c). After cell culture for 3 months interleukin-2 immunoreactive material was still demonstrated within cytoplasmic granules of tumour cells indicating endogenous synthesis of interleukin-2 (monoclonal antibody DMS-1, Genzyme, US). Bars indicate 25 microns (c).

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