The Carcinoid Syndrome: Palliation by Hepatic Artery Embolization

C. Humberto Carrasco[1]
Chusilp Charnsangavej[1]
Jaffer Ajani[2]
Naguib A. Samaan[3]
William Richli[1]
Sidney Wallace[1]

A group of 25 patients with malignant carcinoid syndrome underwent hepatic artery embolizations to palliate the symptoms of this syndrome. Twenty-three patients could be evaluated: 20 (87%) of them responded to embolization with a median response duration of 11+ months, one (4%) did not respond, and two (9%) died of complications from the embolization. The symptomatic responses correlated with two variables: (1) a decrease in the extent of the hepatic metastases in 17 of the 18 patients who had follow-up hepatic imaging, and (2) a decrease in the urine 5-hydroxyindoleacetic acid values to a mean of 41% of pretreatment levels in the 18 patients for whom this test was available. Hepatic artery embolization provides the most effective treatment for the carcinoid syndrome and the hepatic metastases. Periodic embolizations will maintain clinical remissions for prolonged periods of time.

Carcinoids are relatively rare neuroendocrine neoplasms that usually originate in the appendix, small bowel, rectum, and bronchi, and less frequently in the stomach, duodenum, biliary tract, pancreas, and ovary [1]. These tumors were originally considered to be benign, but it is now known that extraappendiceal carcinoids—particularly those arising in the small bowel—are frequently malignant [2]. Malignant carcinoids may secrete pharmacologically active substances such as serotonin, kallikrein, substance P, and prostaglandins, which have been implicated in the production of the carcinoid syndrome. The symptoms are cutaneous flushing, diarrhea, and wheezing, and may, less frequently, include fibrosis of the pulmonic and tricuspid valves, arthropathy, psychiatric symptoms, and pellagra. At least some of the secretion products are metabolized by the liver during the first pass, so that gastrointestinal carcinoids almost never produce the syndrome in the absence of hepatic metastases [3].

The carcinoid syndrome may be extremely incapacitating, and various forms of palliative therapy have been employed. Many pharmacologic agents including adrenergic blockers, kinin and serotonin antagonists, and corticosteroids have been used with limited success in attempts to neutralize the effects of the active substances secreted [4]. Because the presence of hepatic metastases usually determines the occurrence of the carcinoid syndrome and probably also the length of survival in most patients, it is logical that antineoplastic therapy should be directed primarily against liver secondaries to improve the symptoms and attempt to prolong survival. Surgical resection of the hepatic metastases appears to be the best palliative treatment for patients with localized disease [5–7]. In patients with unresectable hepatic metastases, interferons [8–10] and chemotherapeutic agents [11–20] have yielded relatively low response rates. Chemotherapy has also been administered intraarterially and, at times, in conjunction with ligation of the hepatic artery [21–23]. The best responses have been achieved with hepatic artery embolization [24–33] and surgical devascularization of the liver [34–39], alone or in combination with arterial or systemic infusion of chemotherapeutic agents [21, 23, 40–44]. Unfortunately, these responses are of relatively short duration. In order

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[1] Department of Diagnostic Radiology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bernter Ave., Houston, TX 77030. Address reprint requests to C. H. Carrasco.

[2] Department of Medical Oncology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, TX 77030.

[3] Department of Internal Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, TX 77030.

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to prolong the remission of the carcinoid syndrome achieved by embolization of the hepatic artery, we have performed periodic embolizations in 25 patients with this disease.

Materials and Methods

Materials

The medical records of 25 patients with the carcinoid syndrome who were treated with hepatic artery embolization from January 1981 to October 1985 were reviewed retrospectively. Seven of these patients had been included in a previous report [32]. In all 25 patients, there was histologic documentation of primary or metastatic carcinoids and elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA). This report does not include patients who had hepatic metastases from carcinoid tumors but did not have the carcinoid syndrome or patients who had the syndrome but did not have an elevated urinary excretion of 5-HIAA. There were 15 men and 10 women; the median age was 58 years (range: 23–69). The sites of the primary neoplasms were the small bowel (16 patients), bronchus (4 patients), colon (1 patient), and pancreas (1 patient). The primary site was unknown in three patients. In 24 patients, the median duration of symptoms before hepatic artery embolization was 1 year (range: 1 month to 20 years); in one patient, it was not documented. Extraabdominal metastases were present in three patients with bronchial carcinoids and in four patients with gastrointestinal carcinoids. Ten patients had right-sided cardiac valvulopathy. Eight patients had received chemotherapy before embolotherapy. Three patients received chemotherapy in combination with or after the start of embolotherapy.

Technique

Embolization was performed after selective catheterization and angiography of the hepatic artery or one of its branches [45]. The embolic materials used consisted primarily of Ivalon (Unipoint Laboratories, High Point, NC) particles measuring 150 to 590 μm. Gelfoam (Upjohn, Kalamazoo, MI) pieces and coils were used to occlude collateral vessels (inferior phrenic, gastroduodenal, and inferior pancreaticoduodenal arteries) after peripheral embolization with Ivalon. Patency of the main trunks of the hepatic artery was maintained to allow repeated peripheral embolizations. The first embolization was limited to one lobe in 21 patients and encompassed both lobes in the remaining four patients. Subsequent embolizations were performed to both hepatic lobes in all 19 patients in whom the procedure was repeated. Embolization through collateral vessels was performed in four patients because of partial or complete occlusion in the main branches of the hepatic artery caused by previous embolizations.

Seventy-nine embolizations were performed in the 25 patients, ranging from 1 to 8 (median = 3) embolizations per patient. Six patients underwent a single embolization, and the remainder were embolized at intervals of 1 to 3 months for the first two to three times; subsequently, the intervals varied depending on the clinical response.

A response was defined as symptomatic improvement of the carcinoid syndrome. In addition, follow-up hepatic angiography in 19 patients, CT in 9 patients, and urine 5-HIAA values in 19 patients were available for comparison to the preembolization studies and were correlated with the symptomatic response.

Results

The results of the study are given in Table 1. Twenty-three of the 25 patients could be evaluated: 20 (87%) experienced symptomatic improvement and were considered responders, one patient (4%) did not respond, and two patients (9%) died of complications from the embolization. Two patients could not be evaluated: both underwent a single episode of hepatic artery embolization and were subsequently lost to follow-up. The median follow-up time for the 21 patients who could be evaluated and survived the procedure was 16 months (range: 1–50 months).

The median duration of the response in the 20 responders was 11+ months (range: 1–50 months). Responses were subjectively categorized as excellent in 14 (70%) and moderate in 6 (30%) patients. Objective correlation of the symptomatic response with hepatic imaging or urine 5-HIAA values was available in 18 patients. In 17 of the 18 responders who had follow-up hepatic imaging, there was a decrease in the extent of the hepatic metastases (Figs. 1 and 2); in the remaining patient, the hepatic metastases did not change significantly but there was a decrease in urine 5-HIAA values. The urine 5-HIAA values decreased after embolization in all 18 responders for whom this test was available; the mean of the lowest values was 41% (range: 8–67%) of the preembolization levels. Objective documentation of the response by either hepatic imaging or urine 5-HIAA excretion testing was not available for two responders, both of whom were lost to follow-up 1 month after their first embolization.

Four of the 20 responders experienced a recurrence of symptoms an average of 14 months (range: 9–23 months) after the first embolization. These patients had not been embolized for a mean of 9 months (range: 8–11 months) before relapse. One patient responded to subsequent embolizations; one's tumor continued to progress, one remained stable, and one was lost to follow-up.

Systemic chemotherapy administered to two patients after the start of embolotherapy did not yield any response. One patient who also received intraarterial chemotherapy in conjunction with embolization could not be evaluated.

Fifteen patients are alive at a median of 16 months (range: 1–50 months), and eight patients died at a median of 8 months (range: 5 days–22 months) after their first embolization.

All patients suffered the postembolization syndrome consisting of abdominal pain, nausea, vomiting, and fever, usually lasting from 3 to 10 days after the first embolization. These symptoms, however, decreased in severity with subsequent embolizations so that by the third episode, most of the patients had an uneventful postembolization course. The first embolization also precipitated intense episodes of flushing in most of the patients, and five of these also experienced hypertensive crises that did not usually last beyond the procedure. These five patients required administration of antihypertensive agents for control of the hypertension.

Discussion

Embolization of the hepatic artery resulted in improvement of the carcinoid syndrome in 20 (87%) of the 23 patients who could be evaluated, with a median duration of response of 11+ months. Excluding the two patients (9%) whose deaths were precipitated by the procedure, only one of 21 patients failed to respond to embolization. The response rate in our series is comparable to that reported in other series [24–

TABLE 1: **Results of Hepatic Artery Embolization in 25 Patients with the Carcinoid Syndrome**

Case No. (age, gender)	Primary Site	No. of HAEs	5-HIAA Level		Hepatic Imaging	Response Duration (months)	Survival (months)
			First	Lowest			
RESPONDERS							
1 (44, M)	Small bowel	8	105	27	Improved	39	39 (a)
2 (65, F)	Small bowel	3	60	21	Improved	25	25 (a)
3 (60, F)	Small bowel	7	302	99	Improved	21	21 (a)[a]
4 (66, M)	Small bowel	4	97	23	Improved	16	16 (a)
5 (45, M)	Small bowel	5	423	35	Improved	50	50 (a)
6 (42, F)	Small bowel	5	429	116	Improved	16	16 (a)
7 (33, F)	Small bowel	3	191	101	Improved	38	38 (a)
8 (69, F)	Small bowel	2	323	134	Improved	2	2 (a)
9 (53, F)	Small bowel	2	165	110	Improved	1	1 (a)
10 (54, F)	Small bowel	3	89	54	Improved	11 LTF	22 (d)
11 (59, M)	Small bowel	1	325	NA	NA	1	LTF[b]
12 (69, F)	Small bowel	1	163	NA	NA	1	LTF
13 (66, M)	Cecum	5	279	150	Improved	14 LTF	18 (a)
14 (23, F)	Pancreas	2	21	10	Unchanged	1	6 (d)
15 (65, M)	Bronchus	6	127	23	Improved	34	40 (a, p)
16 (57, M)	Bronchus	2	41	17	Improved	2	2 (a)
17 (68, M)	Bronchus	2	228	123	Improved	4	4 (a)
18 (58, M)	Bronchus	2	230	149	Improved	1	1 (a)
19 (50, M)	Unknown	3	39	21	Improved	2	2 (a)
20 (57, M)	Unknown	6	338	85	Improved	12 LTF	16 (d)
NONRESPONDERS AND PATIENTS WHO COULD NOT BE EVALUATED							
21 (49, M)	Small bowel	3	147	>147	Progression		8 (d)
22 (62, M)	Small bowel	1	1113			LTF	11 (d)
23 (59, F)	Small bowel	1	239			LTF	
24 (59, M)	Small bowel	1	230			Death post-HAE	
25 (51, M)	Unknown	1	399			Death post-HAE	

Note.—HAE = hepatic artery embolization; 5-HIAA = 5-hydroxyindoleacetic acid; a = alive; d = dead; p = progressive disease; NA = not available; LTF = lost to follow-up.
[a] progression of extrahepatic disease.
[b] refused further HAE.

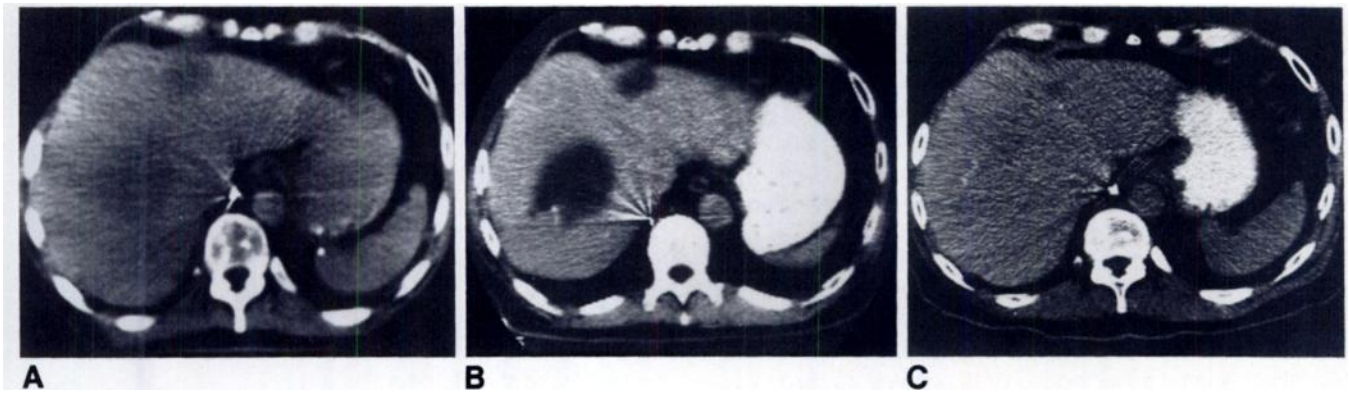

Fig. 1.—**A**, CT before embolization. Hepatic metastases in right lobe and medial segment of left lobe. **B**, CT 1 month after first embolization. Hepatic metastases have become more apparent because of decrease in their attenuation coefficient due to necrosis. Better definition of margins. **C**, CT after three embolizations, 9 months after first treatment. Lesion in right lobe is barely discernible even at low-window level. Other metastasis is considerably smaller.

26], which usually consisted of single episodes of embolization. Although the median duration of the response in these other series is not clear, it is logical to assume that longer periods of clinical remission can be achieved through periodic embolizations.

The results of hepatic artery embolization compare favorably with those achieved by surgical devascularization of the liver. In a review of the literature through 1982, Moertel [4] found 32 cases of surgical ligation of the hepatic artery for treatment of the carcinoid syndrome. Eighteen patients (56%) experienced striking improvement or complete clinical remission, whereas seven (22%) died in the postoperative period. In another series of 10 patients with metastatic carcinoid tumors who underwent ligation of the hepatic artery [7], eight showed symptomatic improvement with a decrease in the urinary excretion of 5-HIAA to less than 50% of the pretreatment levels. The median duration of response was 5 months. There was one postoperative death.

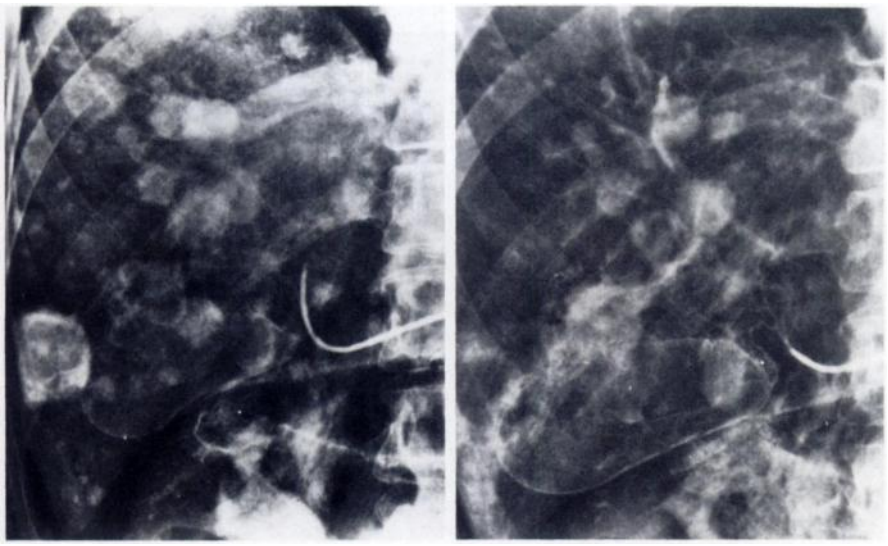

Fig. 2.—**A**, Parenchymal phase of right hepatic arteriogram before embolization. Many metastases in right lobe. **B**, Parenchymal phase of right hepatic arteriogram after one embolization, 2 months later. Hepatic metastases have decreased in vascularity, size, and number.

More recently, occlusion of the hepatic artery by surgical ligation or embolization combined with systemic chemotherapy (doxorubicin, dacarbazine, 5-fluorouracil, and streptozotocin) was reported to result in striking or complete symptomatic relief of the carcinoid syndrome in nine of 10 patients [40]. The median duration of response was 6+ months.

Chemotherapeutic agents alone have generally not been as effective in controlling the symptoms or the hepatic metastases of the carcinoid syndrome. The best reported results have been achieved with a combination of methotrexate and cyclophosphamide, yielding a response in six of 11 patients [12]. However, this same drug combination did not result in any responses in a larger series [19]. The combination of 5-fluorouracil and streptozotocin administered at 6-week and 10-week intervals yielded response rates of 33% in 42 patients [15] and 22% in 86 patients [20], respectively. The combination of streptozotocin and doxorubicin resulted in four responses in a group of 10 patients [17].

After proximal embolization of the hepatic artery such as that performed with stainless steel coils (which is analogous to surgical ligation), the peripheral hepatic arterial circulation is almost instantly reconstituted through collateral vessels. This effect is used advantageously to redistribute blood flow to a single vessel when arterial infusion of chemotherapy is performed in the presence of aberrant hepatic arteries [46]. On the other hand, we have observed that embolization with particulate embolic materials, such as Ivalon or Gelfoam, produces a longer-lasting arterial occlusion and thus results in a much greater antineoplastic effect. Within approximately 72 hr, however, intrahepatic collateral vessels reconstitute the hepatic arterial circulation. Since most of the blood supply to hepatic neoplasms is derived from the hepatic artery [47–49], this prolonged period of decreased arterial flow induces varying degrees of necrosis of the carcinoid metastases. The viability of the normal liver parenchyma is maintained by the portal vein, which is responsible for approximately 75% of the liver's blood supply [50]. A liver biopsy performed during resection of the primary tumor in one of our patients who had three embolizations demonstrated total necrosis of the metastatic neoplasm.

The first embolization was usually limited to a single lobe, depending on the extent of the hepatic metastases and general clinical condition of each patient. We assumed that if extensive parenchymal necrosis occurred, hepatic function would be preserved by the nonembolized lobe. Subsequent embolizations involved both lobes of the liver. Although a single embolization usually results in striking improvement of the carcinoid syndrome and reduction of the urine 5-HIAA levels, it does not result in complete necrosis of the hepatic metastases and, therefore, the procedure needs to be repeated at frequent intervals. After two or three monthly embolizations, 6-month intervals between subsequent embolizations are probably adequate to maintain remission. The four patients who relapsed had not been embolized for periods of 8 to 11 months. On the other hand, some of our patients continued in symptomatic remission for longer periods of time without further embolizations. Therefore, the frequency at which the embolizations are performed is primarily dictated by the patient's symptoms.

Each catheterization of the hepatic artery results in some degree of endothelial injury which, combined with the decreased flow resulting from the embolization, predisposes different segments of the hepatic artery to thrombosis. This may be an impediment to subsequent catheterizations. However, embolizations may still be performed by advancing the catheter through the thrombus [51] or by catheterizing the collateral pathways that reconstitute the hepatic arterial circulation beyond the occluded segment [52].

Our patients were not routinely premedicated to counteract the effects of the active substances released during the embolization. However, some of the patients were being treated with cyproheptadine at the time of the embolization.

None of the patients received prophylactic antibiotics, and no infectious complications occurred. Bradykininergic crises with intractable hypotension did not occur in any of our patients. Infarction of the gallbladder was probably responsible for most of the pain experienced by our patients in the postembolization period, but this event appears to be self-limiting and otherwise well tolerated [53, 54].

Two patients, in whom hepatic function was already severely impaired by metastatic disease, died of hepatic failure worsened by the embolization within 7 days of the procedure. In retrospect, these two patients should not have been candidates for embolization because of their extensive hepatic metastatic disease. In a previous review of 310 patients treated with hepatic artery embolization for a variety of hepatic neoplasms at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, we observed that 18 patients died of hepatorenal failure in the immediate postembolization period. All 18 patients were distinguished by the extent of their hepatic metastatic disease: replacement of more than 50% of the liver by tumor, serum lactic dehydrogenase above 425 mU/ml, serum glutamic oxaloacetic transaminase above 100 mU/ml, and bilirubin above 2 mg/dl. These conditions were observed in only two of 292 patients who survived the immediate postembolization period (unpublished data). Therefore, we now feel that embolization is contraindicated in patients who fulfill all the criteria listed above.

Hepatic artery embolization provides the most effective treatment for the hepatic metastases and carcinoid syndrome. This procedure yields the highest response rates and when repeated periodically will maintain clinical remissions for prolonged periods of time. However, the eventual occlusion of the main trunks of the hepatic artery and its collaterals will not allow continuation of the embolizations indefinitely. Because of the usually prolonged course of the disease, it is difficult to determine the impact of hepatic artery embolization on survival. Moreover, the extrahepatic disease that remains untreated could eventually determine the clinical outcome. Therefore, the need remains for more effective chemotherapeutic agents.

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