Surgical Treatment of Advanced-Stage Carcinoid Tumors

Lessons Learned

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Objective: To evaluate clinical outcomes in a large group of advanced-stage carcinoid patients (stage IV) following multimodal surgical therapy.

Summary Background Data: Patients with advanced-stage carcinoid have traditionally experienced poor 5-year survival (18%–30%). Few recent series have evaluated a large number of patients treated with aggressive surgical rescue therapy.

Methods: This single-center retrospective review analyzes the records of 82 consecutive carcinoid patients treated by the same 2 surgeons, from August 1998 through August 2004 with a 3- to 72-month follow-up.

Results: Surprisingly, one third of 26 (32%) patients were found to have intestinal obstructions; 10 being moribund at presentation. Mesenteric encasement with intestinal ischemia was successfully relieved in 10 of 12 cases. Five of eighty-two "terminal" patients were rendered free of macroscopic disease. Karnofsky performance scores improved from 65 to 85 ($P < 0.0001$). Two- and four-year survival for patients with no or unilateral liver metastases ($n = 23$) was 89%, while 2- and 4-year survival for patients with bilateral liver disease ($n = 59$) was 68% and 52% ($P = 0.072$), respectively.

Conclusion: We think that all patients with advanced-stage carcinoid should be evaluated for possible multimodal surgical therapy. Primary tumors should be resected, even in the presence of distant metastases to prevent future intestinal obstruction. The "wait and see" method of management of this slow-growing cancer no longer has merit. We offer an algorithm for the surgical evaluation and management of these patients.

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Although rare, carcinoid tumors are the most common type of neuroendocrine tumors. Earlier reports of the 5-year survival in patients with metastatic disease ranged from 18% to 30%.[1–3] In later series, patients treated with aggressive surgical therapy had improved survivals ranging from 50% to 80%.[4–6]

Many clinicians prefer to avoid surgery in patients with carcinoid because of its propensity toward slow growth. However, the most common cause of death in patients with carcinoid is progression of advanced metastatic disease.[7] Outcome data for salvage debulking procedures for patients with advanced disease are lacking. We report our experience with salvage therapy in 82 patients diagnosed with advanced-stage carcinoid, operated upon at our institution by the same 2 surgeons from August 1998 through August 2004.

PATIENTS AND METHODS

This is a retrospective review of 82 consecutive advanced-stage carcinoid patients referred to our center who underwent surgical treatment with the intent to palliate their disease. Data were obtained from review of inpatient and outpatient medical records and clinical follow-up at 3 to 72 months.

Diagnosis and Extent of Disease

Diagnosis was based on histopathologic documentation of carcinoid tumor obtained by biopsy or surgical specimen. 5-Hydroxyindolacetic acid (5-HIAA) and chromogranin-A levels were obtained as dictated by clinical presentation. All patients underwent CT scanning of the chest, abdomen, and pelvis as their radiologic staging along with ^{111}In-pentetreotide whole body scanning (octreoscan) as part of their metastatic evaluation.

Treatment/Procedures

All symptomatic patients were treated with continuous infusion octreotide intravenously intraoperatively and postoperatively to prevent carcinoid crisis.

The majority of patients were on monthly octreotide depot treatment preoperatively, especially those with pain or carcinoid syndrome. Liver lesions were addressed with radiofrequency ablation (RFA), hepatic resections (both anatomic and nonanatomic), or combination therapy. Debulking (removal of extraintestinal tumor) procedures involved resections of the stomach, mesenteric node-bearing tissue, small intestine, colon, pancreas, or uterus. Major vessel encasement (portal vein, celiac, or superior mesenteric vessels) was not considered an absolute contraindication to resection. Whenever possible, the gallbladder was removed to negate the possibility of future gall stone development associated with long-term octreotide therapy.

RFA of Liver Metastasis

RFA was used in a large number of patients as an adjunct technique. The technique was applied percutaneously, laparoscopically, or most frequently via open approach at the time of staging laparotomy. Patients were treated with RF3000 generator system (R for Radiotherapeutics Corp, Mountainview, California). The LeVeen needle electrode (2.5 cm or 3.5 cm diameter) was placed into the tumor under ultrasound guidance. Multiple sites of deployment were used for tumors greater than 3.5 cm in diameter.

Outcome Measures

Primary outcome measures were symptom control and improvement in physical performance status (Karnofsky scoring system). Resolution of an intestinal obstruction was considered a specific end point. Survival was calculated according to Kaplan-Maier actuarial survival. Changes in quality of life and physical performance status were documented with follow-up clinical visits and/or phone conversations.

RESULTS

Patient and Tumor Characteristics

There were 39 (47.5%) men and 43 (52.5%) women with a median age of 57 years (range, 14–76 years) (Table 1). There were 19 (23%) foregut, 54 (66%) midgut, and 4 (5%) hindgut carcinoids. Five patients (6%) had primaries that were indeterminable. Twenty-seven (33%) patients were referred without any prior surgical intervention. That included 14 (17%), which had undiscovered primary tumors and were explored with the purpose of resection their primary tumor. Eleven (79%) of these were diagnosed. An additional 8 (10%) patients presented with prior surgical intervention, but without known primary source, 6 (7%) of which were diagnosed upon exploration. Fifty-five (67%) patients in all were explored elsewhere, most referred after their cases were terminated because the tumor was deemed unresectable. Mean time from initial diagnosis to presentation at our center was 53.8 months (range, 5–204 months).

TABLE 1. Patient and Tumor Characteristics

Patient Characteristics	
Gender	
Male	39 (47.5%)
Female	43 (52.5%)
Time to presentation	
53 mo	(5–204)
Median age (range)	
57	(14–76)
Clinical complaint	
Syndrome	59 (72%)
Intestinal Obstruction	26 (32%)
Abdominal Pain	27 (33%)
Weight Loss	27 (33%)
Patient Characteristics at Presentation	
No prior surgery	27 (33%)
Unknown primary	14 (51%)
Explored elsewhere	55 (67%)
Unknown primary	8 (15%)
Total unknown primary	22 (27%)
Tumor Characteristics Confirmed at Operation	
Foregut	19 (23%)
Midgut	54 (66%)
Hindgut	4 (5%)
Unknown	5 (6%)

Patients had multiple and often overlapping complaints at presentation. An octreotide-refractory pain-diarrhea-flushing triad was present in 23 (28%) patients. Surprisingly, 26 (32%) patients were found to have intestinal obstruction (partial or complete) due to tumor, the tumor-associated desmoplastic reaction, or simple adhesions; 14 patients (53%) were undiagnosed preoperatively. Twenty-seven patients (33%) had abdominal pain that was difficult to control even with narcotic analgesics, with mesenteric encasement present in 12 (14%) patients. A total of 59 patients (72%) presented with some component of the carcinoid syndrome, including diarrhea, flushing, wheezing, and palpitations. A total of 27 (33%) patients presented with weight loss attributed to their disease.

Surgical Strategy

A multidisciplinary team consisting of surgeons, interventional radiologists, medical oncologists, and gastroenterologists met for review of presenting patients to discuss options for treatment and outline a plan (Fig. 1). Treatment options included exploratory laparotomy/laparoscopy, liver resection, and/or RFA (open, laparoscopic, or percutaneous), cholecystectomy if not previously performed, decompression

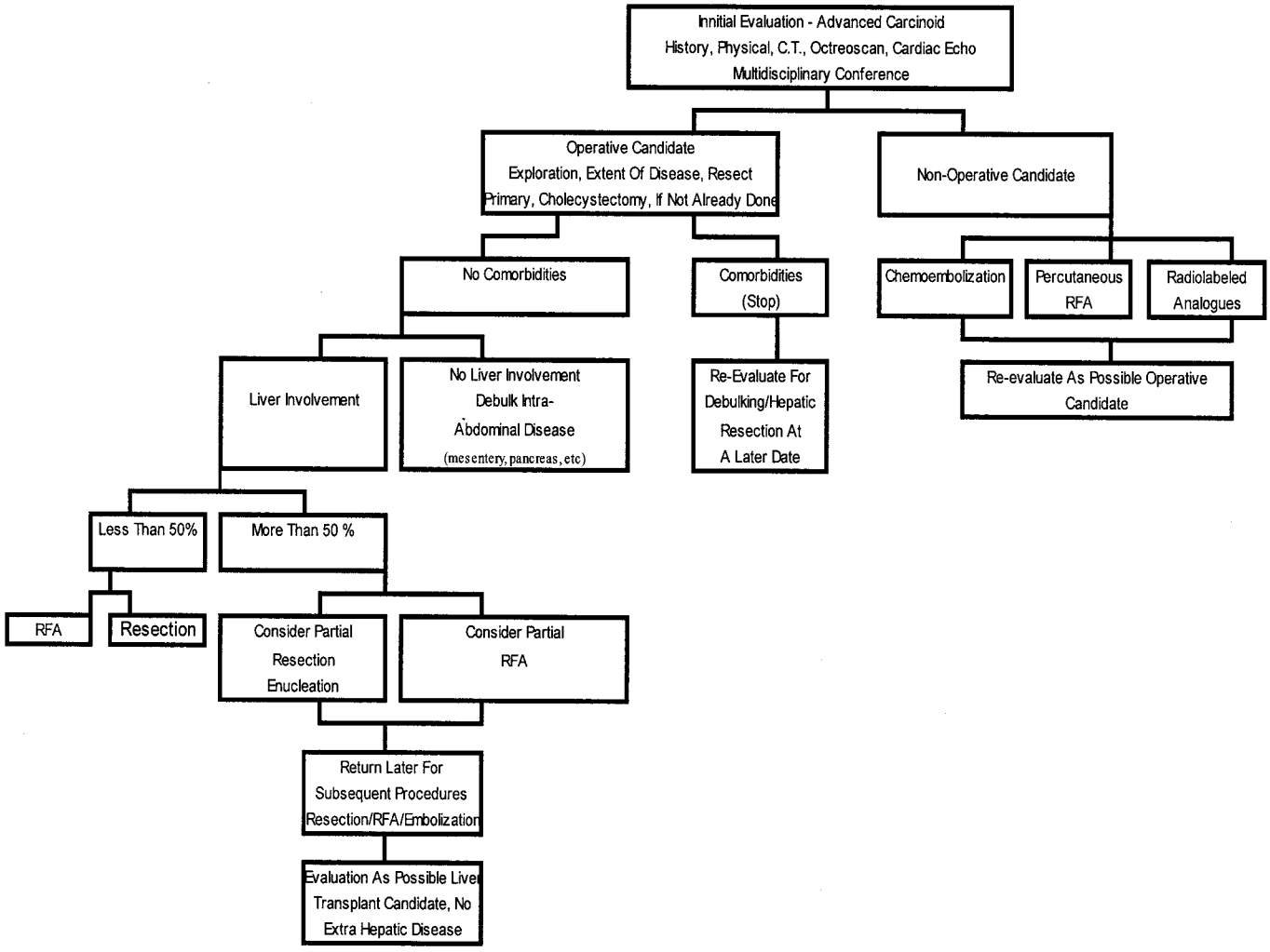

FIGURE 1. Suggested algorhythm for surgical strategy with advanced stage carcinoid.

of mesenteric encasement, pancreatic resection, small intestinal resection or diversion, in some cases takedown of a previous intestinal bypass for "unresectable obstructions," percutaneous hepatic artery chemoembolization preoperatively or postoperatively, and high-dose radiolabeled somatostatin analogs.

All patients underwent a surgical intervention with intent to determine the extent of disease, identify the primary tumor if not previously known or removed, perform cholecystectomy if not already done, and debulk hepatic or other visceral metastases by resection, RFA, or in combination. Pancreatic resections included Whipple procedures and distal pancreatectomies and required resection and replacement of the portal vein on four occasions. Hysterectomy or partial gastrectomy was performed when contiguous tumor involvement was present. Removal of mesenteric tumor encasing the mesenteric vessels was possible in 10 of 12 (83%) patients. Eighteen (22.7%) patients underwent second hepatic debulking procedures, most commonly RFA. Seven (8.5%) underwent a third or more repeat hepatic debulking procedure.

Extent of Disease

Extensive small bowel involvement was present in 39 of 82 (47.6%) cases (Table 2). Mesenteric/peritoneal/retroperitoneal extension of tumor or the tumor-associated desmoplastic reaction was encountered in 39 of 82 (47.6%) cases.

TABLE 2. Operative Findings

Finding	No. (%)
Mesenteric/peritoneal retroperitoneal extension	39 (47.6)
Vascular encasement	12 (14)
Intestinal obstruction	26 (32)
Upstaged/downstaged (total)	11/2 (16)

TABLE 3. Outcomes

Outcome	Value
Mean Karnofsky Index	65 (pre) to 85 (post) ($P < 0.0001$)
Narcotic cessation	20/23 (87%)
Weight gain	17/27 (63%)
Carcinoid syndrome	53/59 (89.8%)
5-HIAA ($n = 34$) (average decrease)	53%
Obstruction relieved	25/27 (93%)
Vascular encasement	10/12 (83%)

Overgrowth of tumor into the mesentery with mesenteric vascular encasement was observed in 12 of 82 (14.6%) patients. Liver metastases were present in 65 (79%) patients, with multilobar involvement in 59 (72%). Eleven (13.4%) patients were upstaged and 2 (2.4%) were down-staged as a result of exploration. Three patients whose syndrome was not tumor related, but rather the result of intestinal obstruction, were found to have little or no residual carcinoid tumor and were found to be free of disease. One patient, previously deemed unresectable, was rendered free of disease after Whipple procedure and portal vein replacement.

Outcome

The mean follow-up time for all patients was 22.8 months (range, 3–72 months) (Table 3). Seventy-five (91.5%) patients showed significant improvement in their symptoms. Mean preoperative and postoperative Karnofsky physical performance scores were 65 and 85, respectively ($P < 0.0001$). Twenty-four of 26 (92%) patients undergoing 28 procedures for intestinal obstruction were significantly relieved of their obstruction. One patient had a fatal recurrence at 2 months at an outside institution, and another had a late pelvic abscess that proved fatal. Fifty-three of 59 (89.8%) patients presenting with symptoms of carcinoid syndrome had improvement, including 3 who had concomitant obstruction. All 27 patients with refractory pain had significant relief postoperatively, with 20 patients successfully weaned off narcotics. When present ($n = 34$), 5-HIAA or chromogranin-A levels decreased by an average of 53%. There were 2 patients operated upon for bleeding, and 2 for obstructive jaundice, each having resolution with operative intervention. Of 27 patients presenting with weight loss, 17 (63%) had postoperative weight gain with maintenance postoperatively. Five patients (6%) referred as terminal have no clinical evidence of disease. Operative 30-day mortality was 0%. Overall survival was 66% (3–72 months) with a median actuarial survival of 51.2 months, as measured from the time of intervention. Twenty-five (33%) patients went on to die of their disease; 3 died of unrelated causes (stroke, anaphylaxis, sudden cardiac arrest). Disease-specific actuarial survival at 2 and 4 years was 70% and 55%, respectively (Kaplan-Meier) (Fig. 2). For patients with none or unilateral liver metastases ($n = 23$), actuarial survival at 2 and 4 years was 89%. For those with bilateral liver disease ($n = 59$), 2- and 4-year survival was 68% and 52%, respectively ($P = 0.072$) (Fig. 3). Two-year survival by site of primary tumor origin was 58%, 79%, and 79% for foregut, midgut, and hindgut tumors but fell to 36%, 60%, and 67% at 4 years, respectively (Fig. 4).

For patients with metastases to the mesentery, peritoneum, and retroperitoneum, actuarial 2- and 4-year survival rates were 64% and 44% versus 77% and 61%, without those metastases respectively ($P = 0.15$) (Fig. 5).

Complications

The total number of minor complications (<30 days) was 32 (39%) (Table 4). There were 14 major complications

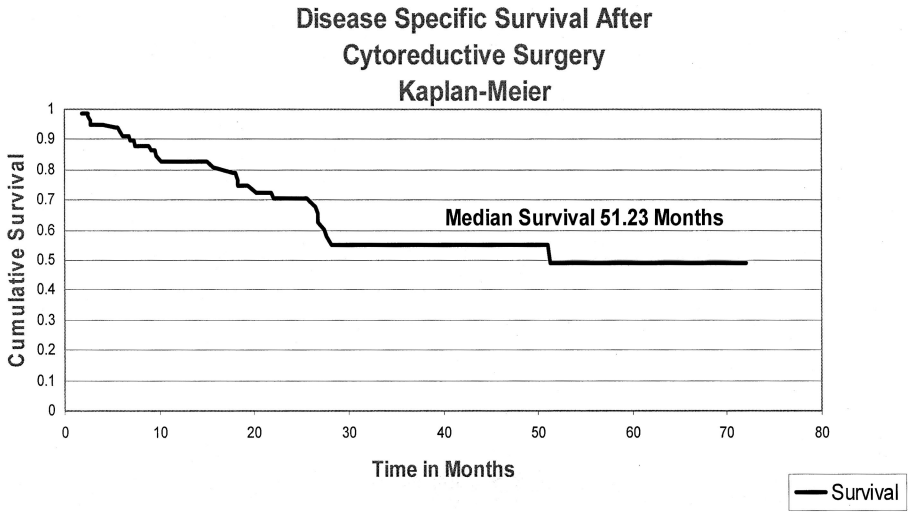

FIGURE 2. Overall and median survival.

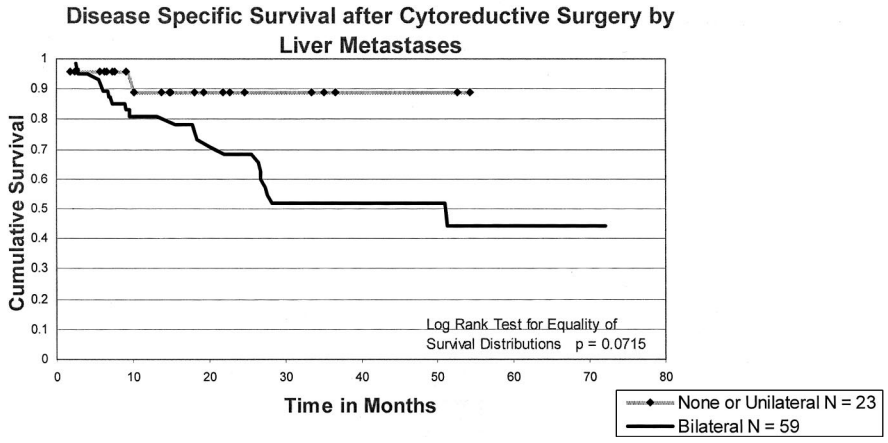

FIGURE 3. Survival band on unilateral or bilateral liver metastases.

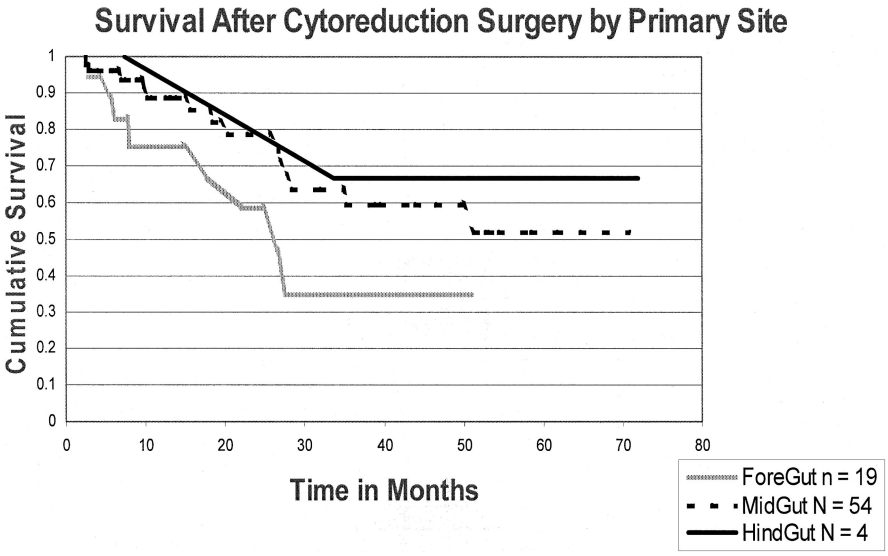

FIGURE 4. Survival stratified to primary site of origin.

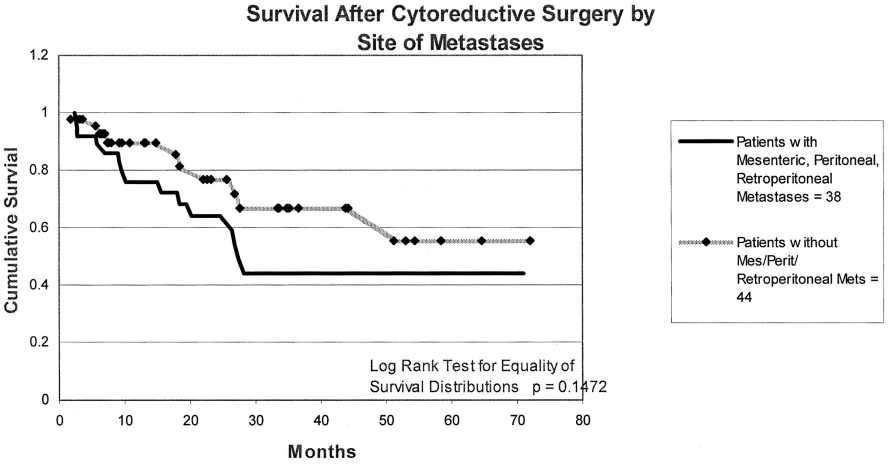

FIGURE 5. Survival by presence or abscence of extra hepatic metastases.

TABLE 4. Complications

Complications	
Major complications	
Pleural effusion/pneumonia	6
Abscess	4
Bile fistula	2
Postoperative bleeding	2
Minor complications	32

in 10 (12%) patients. Four (22%) of the18 patients who underwent a second operation had complications. Two (28%) of 7 patients had 2 complications after a third or more operations (10 procedures). The most common complications in descending order were pleural effusion (6), abscess (4), bile leak (2), and bleeding (2). Two patients had major late (30–90 days) complications (abscess, 1 fatal), and 1 had fatal recurrence of obstruction at 2 months.

DISCUSSION

This paper represents our first long-term analysis of a large group of carcinoid patients with advanced-stage disease, accrued over a relatively short and recent time frame. We believe this to be the first large-scale report of rescue surgical therapy for patients with advanced neuroendocrine tumors. While carcinoid tumors usually are considered to have a protracted and indolent course, clinical presentation at our center tended to be in the late stages of the disease and often dramatic. A significant number of patients develop intra-abdominal progression with disabling symptoms, and often life-threatening complications (such as intestinal obstruction, ischemia, or perforation).[8] A large proportion of the patients had carcinoid disease/symptoms for greater than 4 years prior to presentation, with the average time from diagnosis to referral of 53.8 months (median, 33.2 months). We were surprised to find that one sixth of our patients presented with previously unrecognized intestinal obstructions, often being deemed nonsalvageable terminal cancer patients relegated to high-dose narcotic therapy and/or hospice care. In the majority of these cases, release of the obstruction allowed return to full-time activity and provided us with an opportunity to address their liver metastases concurrently or at a later date. Some patients, who had their symptoms of pain and intermittent diarrhea ascribed to the carcinoid syndrome, were completely relieved by the surgical cure of their obstruction.

Bilobar hepatic disease is no longer a contraindication for palliative resection.[9] Five-year survival rates in excess of 70% are now reported after hepatic resection compared with 29% to 50% survival without resection.[8,10]

We routinely use continuous intravenous preoperative, intraoperative, and postoperative octreotide therapy (100–1000 μg IV bolus 1 hour prior to a procedure and an infusion of 50–500 μg/hour) for all procedures and for chemoembolizations, as suggested in the consensus report on somatostatin analog use in management of these tumors.[11] We have not had a patient who developed carcinoid crisis when we used this approach.

Two important findings were discovered with an unexpected frequency, namely, intestinal obstruction and mesenteric vessel encasement. The mesenteric encasement was thought to be previously unresectable in 6 of 12 (50%) of the patients we explored. Mesenteric lymphadenectomy has been shown in other series to double life expectancy and relieve symptoms.[7,9] The presence of mesenteric, peritoneal, or retroperitoneal seeding did not lead to a statistically significant decrease in survival (Fig. 5) and should not be considered an absolute contraindication to exploration.

The extent of disease was best evaluated by open laparotomy. Many of our patients (16%) were either upstaged (13.4%) or downstaged (2.4%) as a result of unexpected findings at laparotomy.

An additional small number of patients ($n = 5$; 3.7%) were rendered clinically free of disease by surgery. This included a group of patients who were previously considered to be nonsalvageable by their referring physicians.

We have had recent experience in placing intra-arterial hepatic ports for infusional chemotherapy as described by Diaco et al.[12] These hepatic artery ports are used for 5-day infusions of 5-fluorouracil in patients with extensive bilobar hepatic carcinoid. These infusions are followed by chemoembolization. Early results of this technique are promising, and some patients have had significant reduction in their tumor burden. We hope to render these patients resectable.

Our laboratories have been examining the in vitro angiogenic response of patient-specific tumors to a battery of conventional and experimental agents to determine if patient-specific therapy for these malignancies is possible. We have used our in vitro angiogenesis assays to test conventional antiangiogenic agents and novel agents such as Epothilone B in over 50 different carcinoid tumors from these same patients.[13] It is our hope that the results of these studies can be used to guide patient-specific antitumor therapy in the future.

CONCLUSION

Patients with advanced-stage carcinoid tumors present unique surgical challenges. However, these patients also offer surgeons a unique opportunity to provide significant improvements in both quality of life and patient survival. We propose that the management of stage IV neuroendocrine tumors should include surgical resection of the primary tumor when possible, prophylactic cholecystectomy, and staged debulking

as comorbidities allow. Medical control of symptoms should include somatostatin analogs and consideration for interferon. By using a multimodality approach to this disease, including cytoreductive techniques, patients can remain symptomatically well controlled and enjoy prolonged survival. Multiple, sequential procedures are justified to prolong symptom control and to maximally reduce tumor burden. This can be accomplished with acceptable complication rates. We recommend early surgical debulking for relief of symptoms and prolongation of survival.[9] The traditional "wait-and-worry" method of management of this disease no longer has merit. Early, aggressive surgical intervention is warranted. The selection of appropriate therapies for advanced-stage carcinoid patients using a multidisciplinary team approach is optimal. Combining aggressive surgery with patient-specific chemotherapeutic and antiangiogenic interventions should yield optimal results in these patients.

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Discussions

DR. COURTNEY M. TOWNSEND, JR. (GALVESTON, TEXAS): During the chemoembolization, others have reported the use of the simultaneous infusion of octreotide to cause intratumoral slowing of vascular flow in order to improve the efficiency of chemoembolization. Has that in fact been used in your case? And do you plan to use that in the treatment of patients who use the intrahepatic catheter for the chemotherapy?

DR. BRADLEY PUTTY (BILOXI, MISSISSIPPI): At the time of chemoembolization, we use continuous infusion octreotide mainly to prevent the carcinoid crisis. Some of these patients have rather dramatic responses to their chemoembolization. And that is the main reason we have been using it to prevent periprocedural complications.

DR. LESLIE H. BLUMGART (NEW YORK, NEW YORK): A brief comment. We have been using embolization for a wide variety of tumors and have not used chemoembolization. I don't know what the evidence for using chemoembolization is at all in this disease. We use polyvinyl alcohol and no chemotherapy, and the results are comparable to those reported by other groups.

DR. ROBERT C.G. MARTIN, II (LOUISVILLE, KENTUCKY): Dr. Boudreaux, nice talk. I just had a quick question. With this succession of patients, did you see any type of survival advantage based on histologic factors? We are beginning to see that not all carcinoids are behaving the same, and with this number of patients were you able to delineate any type of factors, preoperatively, most importantly, to not decide on who we should operate on, but who we shouldn't operate on?

DR. MICHAEL A. CHOTI (BALTIMORE, MARYLAND): I enjoyed the presentation. One question or problem we often face in the operating room is this mesenteric mass. What is resectable? What will make the patient have short bowel? When can you peel it off? And how many feet of small bowel can you take? Can you give us some tips as to when we approach this mesenteric nodal mass in the operating room when you decide that it will come out and when you decide that it won't?

DR. BRADLEY PUTTY (BILOXI, MISSISSIPPI): I will try to address the questions in order. First, Dr. Blumgart mentioned the issue of bland embolization versus chemoembolization. As our medical and angiographical colleagues have emphasized as evidenced elsewhere in the literature, not every institution performs chemoembolization in the same manner, and it is difficult to make comparisons between institutions.

As Dr. Boudreaux mentioned, a lot of it does depend on the skill of the angiographer, but it also depends on the different agents used. And at our own institution, we have not found comparable results to be favorable with the bland embolization as compared to our embolization with 5-FU and cisplatin.

Regarding the survival based on histological features, we found that vascular invasion as evidenced on the pathological evaluation is a poor prognostic feature.

Regarding the mesenteric mass and discovering what is resectable, we found that this is a difficult question to address, especially because going into the operating room you frequently do not know; you don't have a good handle on the degree to which the tumor has spread and involved the mesentery and the small bowel.

Frequently, we have patients presenting having undergone extensive bowel resections in the past. So we found that in approaching such a case, beginning a case early in the morning and planning on being there a better part of the day, you can carefully dissect the mass off the vessels.

And then as far as those lesions that are involving the bowel and causing constriction secondary to a desmoplastic reaction or multiple metastases within the bowel wall, then simply limited resection is in order. And in those cases where you cannot resect enough without relegating the patient to a short bowel syndrome, we perform a bypass.