

# Cytoreductive Surgery in Patients with Advanced-Stage Carcinoid Tumors

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The role of aggressive surgical resections as well as criteria for resectability in patients with advanced carcinoid tumors is not clearly defined. Thirty patients (17 male and 13 female) who were previously diagnosed to have "unresectable carcinoid disease" were treated using a multimodality approach over a period of 2 years. Extensive liver involvement was present in 28 of 30 (93%) of the cases. Small bowel involvement was noted in 22 of 30 (73%), and peritoneal/retroperitoneal/mesenteric invasion was observed in 15 of 30 (50%) of the cases. Three patients had remote metastases (brain, bone, and eye). Twenty of 30 (66%) patients had carcinoid syndrome with severely disabling symptoms. Eight patients (26%) had small bowel obstruction. All patients underwent at least one surgical exploration/intervention. Radiofrequency ablation (RFA) of one or more liver lesions was performed as an adjunct in 22 of 30 (73%) patients. Six patients (20%) had a second surgical procedure. There were 11 complications in eight patients (27%) after the initial operation. Median hospital stay for patients who underwent RFA only, RFA/liver resection, and liver resection with abdominal tumor debulking were 2, 4, 8, and 16 days respectively. Twenty-five of 30 patients (83%) showed symptomatic improvement. Mean pre- and postoperative Karnofsky physical performance scores were 55 and 85 respectively ( $P < 0.02$ ). Small bowel obstruction was due to adhesions in five patients. All patients with intestinal obstruction had complete relief of their symptoms postoperatively. 5-Hydroxyindolacetic acid levels decreased by 50 per cent in all patients with follow-up determinations available. Aggressive surgical exploration and tumor debulking could be performed with significantly improved symptomatic outcome and relatively minor complications. Longer follow-up is needed for assessment of effect on survival.

CARCINOIDS ARE THE MOST common neuroendocrine tumors. The biological behavior of these tumors is heterogeneous and the clinical presentation may vary from asymptomatic incidental findings to extensive metastatic disease with refractory carcinoid syndrome.

The overall 5-year survival rate of all types of carcinoid tumor was reported to be approximately 50 per cent in the largest series in the literature.<sup>1</sup> Although extent of disease (EOD) dictates the overall prognosis<sup>2,3</sup> many patients with metastatic disease may live for years with indolent disease.<sup>4</sup>

Therapeutic options in patients with advanced carcinoid disease range from control of symptoms only with octreotide to radical and repetitive cytoreductive

procedures.<sup>5-7</sup> The role of aggressive surgical treatment remains controversial. However, a number of studies have shown clinical benefit with aggressive approaches.<sup>8-10</sup>

## Patients and Methods

This is a retrospective analysis of 30 consecutive advanced-stage carcinoid cases treated at the Memorial Medical Center (New Orleans, LA) between 1998 and 2001. All patients underwent surgical treatment with palliative intent. Data were obtained from review of inpatient and outpatient medical records and clinical follow-up.

## Diagnosis and EOD Determination

Diagnosis was based on histopathologic documentation of carcinoid tumor obtained via biopsy or surgical specimen. 5-Hydroxyindolacetic acid (5HIAA) and chromogranin-A levels were obtained as the clinical presentation dictated. All patients underwent CT of chest, abdomen, and pelvis as their initial radiologic

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assessment. The majority of patients underwent  $^{111}\text{In}$ -pentetretotide whole-body scanning as part of their metastatic workup. Ultrasonography of abdomen and liver was utilized when appropriate. The ultimate EOD definition was based on preoperative imaging studies as well as operative exploration.

#### *Treatment Procedures*

Patients with pain or carcinoid syndrome remained on octreotide treatment to control symptoms. Liver lesions were addressed either with radiofrequency ablation (RFA) or hepatic resections. The types of hepatic resections performed were nonanatomic enucleations, segmentectomy, right hepatectomy, and left hepatectomy. Debulking procedures involved the resection of stomach, small bowel, colon, and pancreas with restoration of gastrointestinal continuity. Debulking is defined as incomplete removal of extraintestinal tumor growth. Major vessel encasement was not considered an absolute unresectability criterion. Patients with inaccessible metastases or recurrences were accrued into institutional high-dose  $^{111}\text{In}$ -pentetretotide infusion therapy protocol.

#### *RFA of Liver Metastases*

RFA was utilized in most patients as an adjunct technique. The technique was applied percutaneously, laparoscopically, or (as in vast majority of the cases) using an open approach. The technique of RFA was similar to that described in the literature.<sup>11</sup> Briefly: The patients were treated using RF 3000 generator system (Radio Therapeutics Corp., Mountain View, CA). The Le Vein needle electrode was placed in the tumor under ultrasound guidance and the multiple array was deployed to deliver a maximum power of 90 W. Multiple sites of deployment were used in tumors larger than 2.5 cm in diameter.

#### *Outcome Measures*

Primary outcome measures were symptomatic control and improvement in physical performance status. Because of the short follow-up time survival was not assessed as an end point. Physical performance status assessment was made using the Karnofsky scoring system. Resolution of an intestinal obstruction was considered as a specific end point. Change in quality-of-life and physical performance status were documented with follow-up clinical visits and/or phone conversations with the patients and their referring physicians.

### **Results**

#### *Patient and Tumor Characteristics*

Thirty patients with advanced carcinoid tumors underwent surgical exploration/resection and/or RFA.

There were 17 men and 13 women with a median age of 45 (range 14–76). Patient complaints at presentation were multiple and overlapping. The most common presenting picture was carcinoid syndrome. Abdominal pain-diarrhea-flushing triad refractory to octreotide treatment was present in 20 patients (66%). Abdominal pain difficult to control with narcotic analgesics was encountered in 14 patients (47%). Weight loss was present in two cases (7%). Eight patients (27%) presented with small bowel obstruction. Obstruction was due to adhesions in five of eight patients (63%). Primary tumor location was identified to be the small bowel in 19 patients (64%). Other sites of tumor origin were appendix in one (3%), rectum in one (3%), pancreas in one (3%), and lung in two (7%). The site of tumor origin could not be clearly determined in six patients (20%). At the time of their first evaluation at our institution 15 patients (50%) had undergone a prior surgical resection. Eleven patients (37%) were referred with advanced disease without any prior intervention. Three patients (10%) had an exploration/biopsy procedure, and one (3%) had previous tumor embolization. All patients with carcinoid syndrome were being treated with octreotide for control of symptoms.

#### *Extent of Disease*

Extensive small bowel involvement was present in 22 of 30 (73%) cases. Mesenteric/peritoneal/retroperitoneal extension of disease was encountered in 27 of 30 cases (90%). The liver was involved in 28 of 30 (93%) cases. Metastatic spread to the liver was multiple-bilobar in 23 of 28 (83%), multiple-right lobar in one of 28 (3%), solitary-right or left lobar in four of 28 (14%) of these cases. Overgrowth of tumor into the mesentery encasing the mesenteric vessels was observed in five (17%) patients. Remote metastatic disease was identified on imaging studies before surgical intervention in three (10%) patients. Patient and tumor characteristics are shown in Table 1.

#### *Surgical Strategy*

All patients underwent a surgical exploration/intervention (laparoscopic or open) to determine the EOD and with the intent to palliate. Carcinoid symptoms refractory to maximal medical management were the most common indication. Seventeen patients (57%) had RFA and/or a hepatic resection procedure alone as the initial surgical intervention. Ten patients (33%) had combined hepatic and abdominal procedures performed. The remaining three patients (10%) had nonhepatic abdominal procedures. Hysterectomy and partial resections of pancreas and/or stomach were performed when contiguous involvement of the tumor

TABLE 1. Patient and Tumor Characteristics

Men:women	17:13
Median age (range)	45 (14-76)
Clinical findings	
Carcinoid syndrome	20 (66%)
Abdominal pain	14 (47%)
Small bowel obstruction	8 (27%)
Weight loss	2 (7%)
Primary tumor location	
Small bowel	19 (64%)
Lung	2 (7%)
Rectum	1 (3%)
Appendix	1 (3%)
Pancreas	1 (3%)
Unknown	6 (20%)
Anatomic site involved	
Small bowel	22 (73%)
Mesentery	13 (43%)
Retroperitoneum	6 (20%)
Peritoneum	8 (20%)
Liver	28 (93%)
Multiple, bilobar	23
Multiple, right lobe	1
Solitary, right lobe	3
Solitary, left	1

was present. All restrictive bowel adhesions were carefully released. Removal of the mesenteric tumor encasing the vessels in three patients (10%) was accomplished by incising the peritoneum longitudinally over the mesenteric vessels and carefully dissecting the vessels from the tumor. Six patients (20%) had a second and three patients (10%) had a third operation. Details of the surgical procedures performed are given in Table 2. Median hospital stays for patients who underwent RFA only, RFA-liver resection, and liver resection-small bowel resection-tumor debulking were 2.4, 8, and 16 days respectively.

#### Outcome

The mean follow-up time for all patients was 11 months (range 6-36 months). Twenty-five patients (83%) showed significant symptomatic improvement. Mean pre- and postoperative Karnofsky physical performance scores were 55 and 85 respectively ( $P < 0.02$ ). Clinical condition remained unchanged in two patients (7%), and three patients (10%) died of progressive disease. Small bowel obstruction was due to

TABLE 2. Surgical Procedures and Complications

Patient	First Procedure	Complication	Second Procedure	Complication
1	RFA + LR(L)			
2	RFA + LR(L) + SR(L)			
3	RFA + LR(R)	CHD injury	Whipple	
4	RFA + LR(R) + SBR	Bleeding		
5	RFA + LR(R) + SR(L) + SBR	Wound infection		
6	RFA + LR(L)			
7	RFA + SR(L)			
8	RFA + SR(L)			
9	RFA + SR(R)			
10	Lysis of adhesions			
11	LR(L) + SR(R)	Bile leak		
12	LR(R)	Pleural effusion	Whipple	
13	LR(R) + SBR			
14	SR(R) + MD + SBR			
15	MD			
16	RFA (laparoscopic)		RFA + SR(R&L)	
17	RFA (laparoscopic)			
18	RFA + MD + Celiac block	Pleural effusion, liver abscess		
19	RFA + SBR			
20	RFA + SBR + MD			
21	RFA + SBR + MD			
22	RFA + SBR + MD	Pleural effusion, neuralgia, ileus	RFA + LR(R) + SR(L)	Wound infection
23*	RFA + hysterectomy		RFA + SBR + MD	Liver abscess
24*	RFA		RFA	
25*	SBR			
26	RFA + SBR			
27	SR(L) + pancreas, gastric resection			
28	RFA + SR(L)	Pelvic abscess		
29	RFA			
30	RFA			

SBR, small bowel resection; LR, lobe resection; L, left; R, right; SR, segmental resection; MD, mesenteric debulking.

\* Patients who underwent a third surgical procedure.

adhesions in five of eight (63%) patients. All eight patients with intestinal obstruction had complete relief postoperatively. 5HIAA levels decreased by 50 per cent in all patients with follow-up determinations available.

#### Complications

The total number of complications was 13. There were 11 complications in eight patients (27%) after the initial operation. Two of six patients (33%) who underwent a second operation had complications. The complications specific to RFA procedure were pleural effusion, liver abscess, and intercostal neuralgia. Other operative complications included wound infection, pelvic abscess, bleeding, common hepatic duct injury, bile leak, and prolonged ileus. Complications are listed in Table 2.

#### Discussion

Carcinoid tumors usually have a protracted course. Early presentation might be indolent and some might not be biologically aggressive tumors. However, a significant number of patients show intra-abdominal progression of disease and develop liver metastases with disabling symptoms.

An effective chemotherapy regimen for carcinoid tumors is not available.<sup>7</sup> The mainstay of management of these patients remains to be the control of symptoms with octreotide. Carcinoid tumors, like many other apudomas, express somatostatin receptor type-2 (sst-2). The hormone production and release can be controlled by sst-2-preferring somatostatin analogs (*i.e.*, octreotide). Octreotide has clinically proven to be effective in decreasing the hormone production by carcinoid tumors. However, complete and sustained control of symptoms can rarely be achieved. A novel approach for systemic therapy of carcinoid tumors is *in situ* radiation using radiolabeled somatostatin analogs. The antitumor actions of radiolabeled somatostatin analogs are multiple and complex. Receptor-specific cytotoxic effects of <sup>111</sup>Indium-labeled sst-2-preferring somatostatin analogs have been demonstrated in *in vitro* models.<sup>12</sup> Clinical trials utilizing radiolabeled somatostatin analogs are underway.<sup>13</sup>

The control of hepatic disease has been a prime objective because the endocrine complications of carcinoid tumors stem from the presence of liver metastases. Nonsurgical means of targeting liver metastases include hepatic artery embolization and chemoembolization techniques. Limited but encouraging results have been reported utilizing these interventional techniques alone or in conjunction with systemic chemotherapy.<sup>5,7</sup>

Surgical resection has been used with both curative

and palliative intent in the management of advanced carcinoid tumors. However, liver resection for cure is possible in a very small number of cases, and the effect of cytoreductive surgery on survival has never been evaluated prospectively. Data on management of advanced carcinoid tumors have been combined in the overall experience with data on cytoreductive surgery for neuroendocrine tumors. The Mayo Clinic experience with hepatic resections of neuroendocrine tumors revealed symptom relief in 90 per cent of the patients with a 19.3-month duration of response.<sup>9</sup> The overall 4-year survival was 73 per cent, which compared favorably with an expected survival of 30 to 40 per cent of institutional historic controls. The operative mortality was 2.7 per cent. The report concluded that surgery was safe and provided excellent palliation of symptoms. These authors predicted that cytoreductive surgery would prolong survival if more than 90 per cent of the gross metastatic disease could be removed.<sup>9</sup> A second large study reporting the Memorial Sloan-Kettering Cancer Center experience in 85 cases of neuroendocrine metastatic liver disease included 41 carcinoid patients. One-, three-, and five-year survival rates after hepatic resections were 94, 83, and 76 per cent respectively. Operative mortality rate was 6 per cent. This report concluded that surgical resection provided excellent palliation of pain and hormonal symptoms and in selected patients prolonged survival.<sup>10</sup> Søreide et al.<sup>8</sup> reported a series of 75 carcinoid patients who were treated primarily with planned repetitive surgical resections. These authors demonstrated that abdominal debulking and liver resections were associated with threefold to fourfold increase in survival. First operation in these patients was associated with a major complication rate of 10 per cent and an operative mortality of 2 per cent. The first reoperation, however, had significantly increased morbidity and mortality with incidences of 33 and 14 per cent respectively.<sup>8</sup>

RFA is an evolving technique for treatment of primary and metastatic liver lesions. This technique is increasingly being used for treatment of carcinoid liver metastases. Objective radiologic and tumor marker responses with this technique have been demonstrated. The technique can be applied percutaneously or laparoscopically.<sup>14,15</sup>

Our series represents one of the largest in reference to the time frame in which the patients were treated. We report our surgical strategy and techniques, operative mortality and morbidity, and success in palliation. The survival benefit is the subject of our ongoing prospective study.

The initial assessment of EOD was done using CT scan of chest and abdomen and Octreoscan (<sup>111</sup>In-pentetreotide) whole-body imaging. The complete

staging, however, was based on surgical exploration. This yielded the optimal assessment of EOD as well as resectability. Hepatic disease was approached by RFA and resections. Extrahepatic disease was aggressively debulked.

Two important surgical pathologies found to be associated with the patients were surprisingly high incidence of benign small bowel obstruction secondary to adhesive bands from a prior operation and the propensity of mesenteric vessel encasement by mesentericointestinal lesions. The patients with obstructive symptoms had complete relief of their clinical picture by adhesiolysis or removal of the obstructing lesion. All these patients were thought to have terminal disease and were placed on high doses of narcotics at the time of their referral. Two of these eight patients were completely disease free after the surgical intervention. In a significant number of cases a subclinical obstruction was responsible for or at least contributed to the pain the patients were experiencing. Mesenteric involvement is another cause of abdominal pain, diarrhea, and weight loss. The mesenteric encasement from carcinoid tumors unlike that from other malignant tumors is more in the form of constrictive entrapment rather than actual tumor invasion of the vessel wall. Therefore the generally accepted unresectability criterion with major vessel encasement does not necessarily apply in carcinoid cases. A careful surgical dissection and relief of the involved vessels is often technically achievable. The benefit from dissectional removal of mesenteric carcinoid tumors has been reported in the literature.<sup>16</sup>

A significant proportion of the patients had a remarkable improvement in their physical performance status. This was achieved with relatively minor and certainly treatable complications and with no operative mortality. Utilization of RFA has decreased the need for extensive hepatic resections and related morbidity/mortality. Objective responses could be documented by CT and 5HIAA levels. Most follow-up imaging and tumor marker studies were performed at the referring institutions.

We conclude that surgical exploration and aggressive tumor debulking with the adjunct use of RFA could be accomplished with relatively minor complications but significantly improved symptomatic out-

come and thus is warranted in patients with advanced-stage carcinoid disease.

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#### DISCUSSION

**RAYMOND P. BYNOE, M.D., F.A.C.S.** (Columbia, SC): The authors addressed a disease process that is not only difficult to diagnose but also to treat. Carcinoid disease can be indolent in its progression; therefore at the time of presentation advance intra-abdominal involvement may be present. Fortunately surgically treated patients with carci-

noid tumors have an overall favorable 83.5 per cent 5-year survival rate. The authors have a survival of 90 per cent for this retrospective review.

This paper is a retrospective review of 30 patients with advanced carcinoid disease treated at Memorial Medical Center in New Orleans over a 3-year period. All the patients included in this study had tissue confirmation of carcinoid. The authors stated chemical analysis, 5-HIAA, was per-

formed as clinically indicated. An initial CT scan was performed on all patients and most had whole-body scanning performed.

The most common presentation in this patient population was carcinoid syndrome, abdominal pain, and flushing. All 30 patients had extensive mesenteric, gastrointestinal, pancreatic, and/or hepatic involvement. Sixty-six per cent of this study group was refractory to medical management, which included octreotide therapy. The majority of this subset of patients had metastatic hepatic disease.

Nave et al. published data which demonstrated a 63 per cent 5-year survival in patients with liver metastasis greater than 2 cm and 23 per cent survival in lesions less than 2 cm. This is felt to be related to the anatomic *versus* nonanatomic hepatic resection.

The treatments outlined in the paper include one or more of the following: 1) Debulking procedures to restore gastrointestinal continuity with and without medical therapy, 2) radiofrequency ablation and/or hepatic resection for liver lesion, and 3) those with inaccessible metastasis received an institutional high-dose infusion  $^{111}\text{In}$ -pentetreotide protocol.

The authors demonstrated that the aggressive surgical approach in the treatment of encasement of mesenteric vasculature with resectional debulking of the tumor without resection of the bowel is beneficial. Ohrvall et al. also reported this technique in their paper with similar results. This process spares this patient population the potential complication of short bowel syndrome. An interesting finding in eight patients presenting with abdominal pain only had had adhesive bands from previous surgery as the cause of their obstruction. These patients responded well to lysis of adhesion postoperatively.

The authors were able to further demonstrate an improved quality of life by using the Karnofsky physical performance scores for the study patients treated with an aggressive approach. This aggressive surgical regime resulted in a reasonably low morbidity and mortality. Miller et al. showed similar results in their patient population.

Several interesting points merit further discussion.

Aggressive surgical resection for palliative treatment was recommended. 1) What delineates aggressive resection? 2) Could you delineate what subset of patients would benefit from what procedures?

Although 66 per cent of this population was refractory to medical therapy (octreotide treatment) other patients in this study did respond to medical therapy. Is aggressive resection appropriate for this smaller group of patients that responded to octreotide especially if liver lesions are present?

The study indicated improved quality of life demonstrated by increase in Karnofsky scores postoperatively. Did the scores improve the same percentage for all treatment groups or did one group respond better than another?

If radiofrequency ablation is important in the treatment of the hepatic lesion: 1) How did the authors determine which hepatic lesions were amenable to radiofrequency ablation (based on size, location, or endocrine activity of the tumor)? 2) Is there any additional benefit to treating medically controlled patients with a small hepatic lesion in this fashion?

The authors report a 50 per cent decrease in the 5HIAA levels in the study group. Could the authors elaborate as to how the different surgical treatment affected this analysis—particularly in performing hepatic tumor debulking with anatomic and nonanatomic resection and RFA?

A number of patients had combined procedures for their hepatic disease. Could the authors elaborate on the patients' responses? How did the four patients who required additional surgery present? In view of the recently published data with chemoembolization for hepatic metastasis and carcinoid was this a consideration as adjuvant therapy with RFA and conventional hepatic resection?

I would like to ask the authors are there any data on the long-term follow-up of their study population?

**JAMES V. SHARP, M.D.** (Lake City, FL): In spite of the fact that many people consider them benign, carcinoids are cancers. Cancers should, therefore, be excised widely. The disease is, in general, worse than most physicians' acknowledgment; I think that carcinoids should almost be considered as bad as a sarcoma.

**SEZA A. GULEC, M.D.** (Closing Discussion): An aggressive resection essentially means expanding the limits of resection. Contiguous organ involvement in most gastrointestinal cancers is a relative contraindication for resection because the prognosis of these patients is usually poor. However the situation is completely different in patients with carcinoid tumors. One can accomplish significant symptomatic improvement with extensive resections despite an advanced stage of the disease. A whole number of operations ranging from partial organ resections to a Whipple procedure can be performed. Most patients benefit from an extended cytoreduction. Liver resections and RFA target the patients with severe carcinoid symptoms. Nonhepatic procedures on the other hand help the patients with obstruction, abdominal pain, malabsorption, and malnutrition problems. Most striking improvements in Karnofsky scores are observed in patients who present with intestinal obstruction. Half of the patients with obstruction in our series were initially referred to hospice. All of these patients were able to return a reasonable physical performance status after a surgical intervention relieving their bowel obstruction. Aggressive cytoreduction is indicated even in patients who are responding to medical treatment. The outcome of surgery is more favorable in this group of patients simply due to a better preoperative functional status. Small lesions with bilobar distribution could be better approached by RFA, whereas a solitary lesion could be best treated with a resection. The hormonal status of the tumor does not affect the decision in choosing RFA *versus* resection. Both the clinical and radiologic response to RFA is more favorable with small lesions. Chemoembolization before a hepatic resection may cause an extensive inflammatory reaction around the liver and thus may complicate the surgical dissection. Therefore we do not use chemoembolization routinely before surgery. However it is a technique that we use in selected cases. The effect of aggressive cytoreduction on survival can be discussed after the long-term data are acquired and analyzed.

