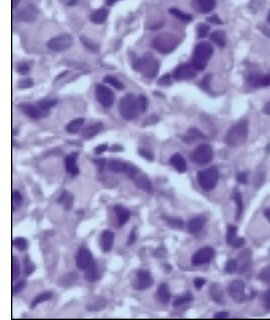


HEPATIC SURGERY FOR METASTATIC GASTROINTESTINAL NEUROENDOCRINE TUMORS

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Introduction

Gastrointestinal neuroendocrine cancers are of significant interest to clinicians and basic scientists. Although accuracy of diagnosis has improved with advances in radioimmune and hormonal assays and in the diagnosis of earlier disease by computed tomography (CT) and magnetic resonance imaging (MRI), many patients still present with hepatic metastases. In contrast to most metastatic gastrointestinal cancers, which have rapid clinical progression with a general decrease in performance status or symptoms related to visceral obstruction and pain, the progression of gastrointestinal neuroendocrine cancers is often slow and associated with clinical endocrinopathies from overproduction of gut hormones. This small subgroup of patients with metastatic neuroendocrine malignancies to the liver has become the focus of intensive multimodality therapy.

This review evaluates the role of cytoreductive hepatic surgery in the management of metastatic gastrointestinal malignancies. Over the last 2 decades, surgical techniques in both pancreatic and hepatic surgery have become reliably safe enough to broadly advocate the aggressive surgical resection of both the primary and metastatic disease, whether concomitantly or sequentially. Although clinical reports on cytoreductive surgery for these tumors are sparse, our own experience supports aggressive surgical resection in selected patients with func-

tioning metastatic neuroendocrine malignancies. Although chemotherapy has been used, low response rates are frequent because of the decreased kinetic activity of these tumors and the high degree of tumor differentiation.

Rationale for Cytoreductive Hepatic Surgery

Cytoreductive surgery, defined broadly, refers to removal or in situ destruction of any tumor to reduce clinical symptoms. Clinically, however, cytoreductive hepatic surgery refers to incomplete resection of intrahepatic tumor to reduce clinical symptoms and to enhance response to additional nonsurgical therapy.¹ Cytoreductive surgery is the major component of multimodality therapy and is generally applied to incomplete gross resections. However, complete resection of all gross tumor should be the primary aim of hepatic resection. Because the primary aim of cytoreductive hepatic surgery is to improve the quality of life, the risk:benefit ratio of resection must strongly favor cytoreduction. In this instance, increased survival is a secondary goal.

Cytoreductive surgery is primarily employed in tumors with few biologic characteristics that enhance the probability of a response to adjuvant therapy. Such tumor characteristics include the relatively long tumor doubling time, hepatic and regional lymphatics as a predominant site of metastatic disease, intrahepatic growth pattern, susceptibility to

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chemotherapy agents and embolization, associated disabling endocrinopathies, and resectability of the primary cancers despite extensive metastases. Consequently, cytoreductive surgery is typically reserved for patients with locally advanced tumors or tumors with limited distant disease and established responsiveness to chemotherapeutic agents or radiation.

Gastrointestinal neuroendocrine malignancies are particularly well suited to cytoreductive surgery. First, survival of patients with gastrointestinal neuroendocrine tumors is widely recognized as prolonged compared to other gastrointestinal malignancies.² Although few studies have examined the natural history of patients with gastrointestinal neuroendocrine cancers, this feature of neuroendocrine malignancies is widely accepted. Moreover, it is unknown whether the presence and type of endocrinopathy affects the natural history. Moertel et al³ have shown that 50% of incurable metastatic abdominal carcinoid tumors survive 5 or more years after diagnosis. Median survival of patients with unresectable hepatic metastases was greater than 3 years, and nearly 30% of these patients were alive at 5 years. Data regarding the natural history of islet cell tumors are sparse. However, Thompson et al⁴ found similar survival for patients with unresected metastatic islet cell carcinomas. Median survival of patients with hepatic metastases was 4 years, and nearly 40% were alive at 5 years after diagnosis. Clearly, the natural history of these tumors is pro-

longed even in patients with metastatic disease. Moreover, these patients suffer for longer periods of time from associated endocrinopathies.

Whether clinical endocrinopathies further affect natural history is unknown. Theoretically, uncontrolled or uncontrollable endocrinopathies should adversely affect survival. Carcinoid heart disease adds cardiac failure to gastrointestinal obstruction of mid-gut carcinoids. Gastrinomas are predisposed to gastrointestinal perforation and hemorrhage. Insulinomas can cause hypoglycemic events leading to altered states of consciousness and subsequent morbidity and mortality. VIPomas can lead to life-threatening electrolyte abnormalities associated with incapacitating diarrhea. Durable relief of such endocrinopathies should improve survival. Norton et al⁵ have shown that patients with metastatic gastrinomas had a median survival of 3.5 years, and nearly 20% of these patients survived for 10 years. However, the endocrinopathy was almost always controlled in these patients with H₂-receptor antagonists or H⁺-K⁺ ATPase inhibitors.

The clinical implication is that the therapeutic window for intervention is long and the potential to improve quality of life is great. The local growth features of the primary neuroendocrine malignancy permits resection far more frequently than other gastrointestinal malignancies of similar origin such as pancreatic ductal adenocarcinoma and small bowel adenocarcinoma.

Islet cell tumors of the pancreas are often expansile in relation to the major local visceral organs or vasculature, permitting resection of even large tumors. In contrast, carcinoids of the small intestine are associated with a desmoplastic reaction and can make resection of the primary tumor and the regional lymph nodes challenging, but they rarely preclude resection. Lastly, the severity of the endocrinopathy parallels the tumor volume. Consequently, a reduction of the bulk of the tumor mass, even when not curative, will often alleviate symptoms. Clinically, a reduction of the neuroendocrine tumor mass either completely or greater than 90% by volume has evolved as the goal for cytoreductive surgery.

The intrahepatic growth pattern of neuroendocrine metastases often permits an aggressive surgical approach. Most neuroendocrine metastases are discrete and large, and they displace but do not encase the major intrahepatic vasculature or bile ducts. Such metastases can be resected or enucleated with small margins (<1 cm) with preservation of adjacent parenchyma. From our experience, unpublished follow-up imaging data suggest that recurrences at the hepatic margins of resection are infrequent. Sclerosis of adjacent liver or adherence to intrahepatic vasculature or ducts is unusual unless preoperative arterial embolization has been performed. Some patients will have a miliary pattern of hepatic metastases with or without large dominant metastases. However, miliary metastases do not affect the resectability of larger metastases. Thus, given the

slow tumor growth rate, resection of bulky larger metastases is reasonable for palliation. Although gastrointestinal neuroendocrine cancers can be associated with an enlarged hypervascular liver, only elevated hepatic venous pressures from cardiac failure secondary to carcinoid heart disease actually precludes resection.

Resection of the primary tumor, despite incompletely resectable metastases, is important to eliminate mechanical symptoms of the primary tumor. Primary gastrointestinal carcinoids frequently cause partial gastrointestinal obstruction or

regional intestinal ischemia. Although gut carcinoids often metastasize extramurally to regional mesenteric lymph nodes, segmental enteric resection with accompanying mesentery will appropriately address the primary and regional disease. Mesenteric adenopathy, though bulky, usually displaces major mesenteric vessels to the periphery of the mesenteric mass that permits preservation of the gut vasculature. Similarly, islet cell cancers seldom encase the celiac or superior mesenteric arteries or the portal venous system. Distal islet cell cancers, however, often invade the splenic vein or spleen. This may

lead to sinistral hypertension and gastric variceal bleeding. Resection of the primary pancreatic tumor is the treatment of choice for this type of gastric bleeding.

Patients and Methods

The data analyzed in this report were accrued through a review of the English language medical literature from January 1973 through April 1999. Reports of hepatic resection for metastatic neuroendocrine malignancies were culled. The gastrointestinal neuroendocrine malignancies were

Table 1. — Summary of Outcomes From Partial Hepatectomy for Metastatic Carcinoid and Islet Cell Cancers

Author (yr)	Carcinoid	Noncarcinoid	Endocrine Symptoms	Clinical Response	Recurrence	Operative Mortality	Survival (mo)
Stephen (1972) ⁷	5	—	5	5	0	0	12-30
Davis (1973) ⁸	2	—	2	NR	1	0	18-30
Battersby (1974) ⁹	1	—	1	1	1 (resected)	0	22
Fotner (1974) ¹⁰	2	—	NR	NR	0	1	0-9
Gillett (1974) ¹¹	2	—	2	2	0	0	12
Kune (1974) ¹²	1	—	1	1	1	0	7
Lannon (1974) ¹³	1	—	1	1	1	0	8
Longmire (1974) ¹⁴	1	—	1	NR	0	1	0
Reiss (1974) ¹⁵	2	—	0	NR	1	0	36-96
Aronsen (1976) ¹⁶	1	—	1	1	1	—	96
Foster (1977) ¹⁷	7	—	7	6	5	1	7-120
Taylor (1983) ¹⁸	1	—	1	NR	1	0	46
Thompson (1983) ¹⁹	1	—	NR	NR	NR	0	47
Norton (1986) ²⁰	—	3	3	3	1	0	18-32
Stehlin (1988) ²¹	4	—	NR	NR	4	0	8-172
Akerstrom (1991) ²²	1	—	1	1	0	0	36
Wolf (1991) ²³	2	—	NR	NR	0	0	16-26
	—	2	NR	NR	1	0	11-27
Dousset (1996) ²⁴	10	—	6	6	6	0	6-36
		7	3	3	4 (2 resected)	1	0.3-108
Berney (1998) ²⁵	—	1	NR	NR	0	0	22
Sarmiento*	120	50	108	104	99	2	81 (median)

Data cited refer to number of patients.
 NR = not reported
 *Unpublished data.

stratified into two basic groups of analysis: carcinoid and noncarcinoid neuroendocrine malignancies. The latter group was composed predominantly of functioning islet cell carcinomas. Factors related to the patients and operative procedures, which were abstracted from the reports, included number of patients, resection of the primary tumor, type of hepatic resection, extent of cytoreductive procedure (partial or total gross resection), operative morbidity and mortality for the cytoreductive procedure, duration of survival, duration of clinical response, degree of clinical response (none, partial, or complete), and adjuvant or adjunctive chemotherapy. Factors related to the tumor that were abstracted from the literature review included presence or absence of clinical endocrinopathy, type of endocrinopathy, type and level of serum hormonal markers, extent of hepatic metastases, extent (stage) of primary tumor, objective response to cytoreduction by hormonal marker level or body imaging, and pattern of disease recurrence. Cumulative survival for patients with both carcinoid and noncarcinoid neuroen-

doctrine malignancies were estimated by the Kaplan-Meier method based on the duration of survival specified for each patient in each report included within our review. Statistical analyses of patient- and tumor-related factors to survival were precluded due to the small number of patients in this review and the variability in reporting. Our recent report⁶ was excluded from the analysis of the literature to reduce bias in outcome because our experience exceeded that cumulatively compiled herein.

Literature Review

Endocrinopathies

Cytoreductive hepatic surgery for metastatic carcinoid disease was performed in 164 patients (Table 1). Of these patients, 109 had symptoms of the carcinoid syndrome, and 33 had clinically evident valvular right heart disease. Specific symptoms and signs as a clinical presentation, such as flushing, diarrhea, and wheezing, were not detailed sufficiently to determine overall frequency. The preop-

erative duration of carcinoid tumor-related symptoms before cytoreduction ranged from a few weeks to 11 years. Urinary 5-hydroxyindoleacetic acid (5-HIAA) values were elevated in every patient in whom levels were obtained. Primary carcinoids arose from the small intestine in 52% of patients (Fig 1). The other primary carcinoids arose from the lung in 4% patients and were unknown in the remaining patients (ovary, pancreas, and appendix in 1 patient each). The primary site was not reported in 13 of the 164 patients.

Cytoreductive hepatic surgery for metastatic islet cell tumors was performed in 63 patients. Twenty-four (38%) of the patients with metastatic noncarcinoid gastrointestinal neuroendocrine cancers had endocrinopathies from excess hormone production. The severity of the clinical endocrinopathy was attributed to metastatic disease or overall tumor burden in each report (Fig 2). Clinical endocrinopathies varied depending on the hormone produced by the malignancy. There were 14 gastrinomas, 3 VIPomas, 10

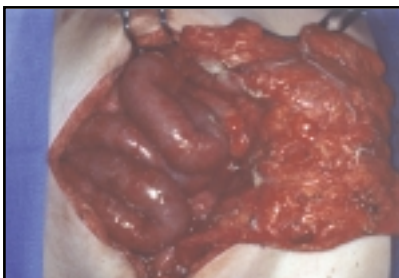


Fig 1. — Operative photograph of “primary” ileal carcinoid with ischemic ileum and right hepatic metastases showing typical intraoperative findings prior to cytoreductive surgery for carcinoid disease.

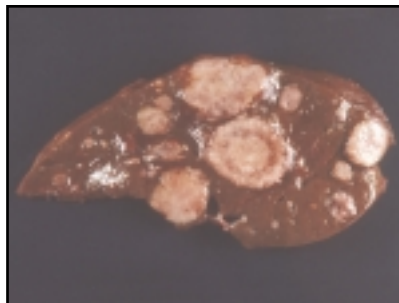


Fig 2. — Photograph of pathology specimen of large hepatic metastases from an islet cell cancer in the left liver prior to extended left hepatectomy.



Fig 3. — Resected islet cancer of the body and tail of pancreas with retroperitoneal extension involving the left renal hilus. En bloc resection of body and tail of pancreas, spleen, left kidney, and adrenal gland was performed.

glucagonomas, 23 nonfunctioning APUDomas, and 7 insulinomas. Eleven patients had overproduction of multiple hormones. In patients with multiple hormone production, only one hormone caused a clinical endocrinopathy, and symptoms of that endocrinopathy did not differ clinically from descriptions of that specific islet cell endocrine syndrome, ie, other hormones did not affect clinical presentation. Only 5 patients had cytoreduction for non-

functioning islet cell malignancies, all of them in our own series. The duration of endocrine symptoms prior to hepatectomy ranged from 18 to 42 months. Most patients had prior therapy in an attempt to control endocrinopathies either by resection of the primary tumor (Fig 3), chemotherapy, or pharmacologic agents. However, in the series at our institute, surgery was the primary therapy in 62% of patients. Hormone markers for

each endocrinopathy were obtained in most patients and were pathologically elevated in nearly all of these patients.

Orthotopic liver transplantation for metastatic neuroendocrine cancers was performed in 93 patients (Table 2). Metastatic carcinoids were present in 43% of these patients, metastatic islet cell cancers in 43%, and tumors classified only as neuroendocrine in 14%.

Table 2. — Outcome of Orthotopic Liver Transplantation in Patients With Metastatic Carcinoid and Islet Cell Cancers

Author (yr)	Carcinoid	Noncarcinoid	Not Reported	Recurrence	Operative Mortality	Survival (mo)
O'Grady (1988) ²⁶	2	—	—	1	0	7-12
Makowka (1989) ²⁷	2	—	—	0	1 (re: OLT)	2-9
	—	3	—	1	0	10-160
Ringe (1989) ²⁸	2	—	—	1	1	0.3-6
	—	1	—	0	0	5
Alsina (1990) ²⁹	1	1	—	0	13	
	—	1	—	0	0	5
Gulanikar (1991) ³⁰	1	—	—	0	0	5
Lobe (1992) ³¹	—	1	—	0	0	15
Farmer (1993) ³²	2	—	—	0	0	22-29
Schweizer (1993) ³³	—	1	—	1	0	10
Bechstein (1994) ³⁴	1	—	—	1	0	42
Frilling (1994) ³⁵	1	—	—	0	0	10
Alessiani (1995) ³⁶	—	—	9	3	0	17-61
Curtiss (1995) ³⁷	—	3	—	0	0	12-30
Routley (1995) ³⁸	6	—	—	4	0	8-67
	—	5	—	1	0	8-106
Anthuber (1996) ³⁹	2	—	—	1	1	0.3-4
	—	1	—	1	0	15
Dousset (1996) ²⁴	4	—	—	1	1 (re: OLT)	0.2-62
	—	5	—	1	3 (2 re: OLT)	0.2-17
Lang (1997) ⁴⁰	3	—	—	—	1	0.4-58
	—	5	—	2	0	47-103.5
	—	—	4	3	0	2-70
Le Treut (1997) ⁴¹	11	—	—	6 (1 resected)	0	2-77
	—	12	—	7	3	0.2-51
Caplin (1998) ⁴²	1	—	—	1	0	15
Hengst (1998) ⁴³	—	1	—	0	0	20
Savelli (1998) ⁴⁴	1	—	—	1	0	32

Data cited refer to number of patients.
OLT = operative liver transplant

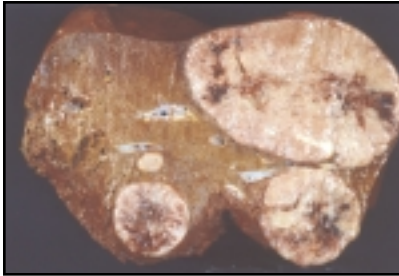


Fig 4. — Transected view of resected right liver following cytoreduction for metastatic islet cell cancer showing numerous metastases ranging from 2 mm to 4 cm.

Symptomatic endocrinopathies were present in 49% of patients. Carcinoids originated from the small intestine in 17 patients, the lung in 8, and other sites in 15. Islet cell cancers included 9 gastrinomas, 4 glucagonomas, 2 VIPomas, 2 GHRFomas, 1 insulinoma, 1 parathyroid hormone-related peptide, and 15 nonfunctioning cancers. Five patients had overproduction of multiple hormones, and the tumor type was unknown or not reported in 13 patients. The primary neuroendocrine cancer was resected prior to orthotopic liver transplantation in 29% of patients, was concurrent in 28%, and was unknown or not stated in 38%. The primary tumor was found and resected in 4 patients after orthotopic liver transplantation.

Extent of Neuroendocrine Malignancies

Primary carcinoid tumors had been resected from 0.7 to 72 months previously in 6 patients. Most of the reported resections were synchronous (76 patients). Stage of the primary carcinoid could not be determined from the literature. Hepatic metastases were

multiple in the majority of patients, but a specific number of metastases could not be tabulated because of data presentation. Hepatic carcinoid metastases range from 0.8 cm to 15 cm in greatest diameter. Few patients had concurrent extrahepatic intra-abdominal disease excluding the primary tumor. The primary islet cell carcinomas were resected previously in 5 patients and synchronously in 35 patients. As with carcinoid tumors, stage of the primary tumors at initial diagnosis could not be determined (Fig 4).

Resection of Metastatic Neuroendocrine Malignancy

Partial hepatectomy for metastatic neuroendocrine malignancies (both carcinoid and noncarcinoid) was performed overall in 227 patients, and total hepatectomy with orthotopic liver transplantation was performed in 92 patients. Partial hepatectomy was reported for 212 patients and included hemihepatectomy in 96 patients (45%), wedge resection in 34 (16%), extended lobar resections (ie, right or left hepatectomy with either contiguous or noncontiguous resection of contralateral metastases) in 30 (14%), and enucleation in 2 (5%). Five additional patients had an undefined type of major hepatic resection. The remaining patients had resection of one to three segments of the liver.

Morbidity and Mortality

The overall morbidity rate for cytoreductive hepatic surgery was 14% (29 of 212 patients). The operative mortality rate after partial

hepatectomy for metastatic carcinoid disease was 2.3% (5 of 212 patients). Excluding perioperative deaths, complications directly related to cytoreductive hepatic surgery for carcinoid tumors included postoperative liver failure in one patient and liver failure, pulmonary embolus, pleural effusion, and small bowel obstruction in another patient.

The operative mortality rate for hepatic resection for metastatic islet cell carcinomas was 1.6% (1 of 63 patients). Major postoperative morbidity for metastatic islet cell carcinoma included subdiaphragmatic bile collection, intra-abdominal hemorrhage, and subdiaphragmatic abscess. Other reported morbidity for cytoreductive hepatic surgery included biliary fistula in 2 patients, pancreatic fistula in 2 patients, and infected hematoma in 2 patients.

Eleven postoperative deaths occurred following total hepatectomy and orthotopic liver transplantation for metastatic neuroendocrine tumors. Death was attributed to irreversible rejection after 2 orthotopic liver transplantations in 1 patient, cardiac failure in 2 patients, sepsis in 3 patients, persistent intra-abdominal hemorrhage in 5 patients (associated with acute pancreatitis in 2 patients, thrombosis of the portal vein in 2 patients, and primary nonfunctioning in 1 patient). Five patients required retransplantation — 3 for chronic rejection, 1 for portal vein thrombosis, and 1 for primary nonfunction. Four of the 5 suffered operative deaths.

Survival After Cytoreductive Hepatic Surgery

The overall survival of patients with metastatic neuroendocrine tumors after partial hepatectomy is shown in Fig 5. Survival of patients following cytoreductive partial hepatectomy for malignant carcinoid tumors is shown in Fig 6. The survival rate was 71% at 5 years. Median survival could not be estimated due to the limited duration of follow-up among reports. The relationship of survival to number of metastases, margins of resection, or type of resection could not be established from the literature review. Only 43 carcinoid patients had no evidence of disease recurrence with the limits of follow-up ranging from 4 to 36 months. Four additional patients had repeat resection of recurrent disease and remained without evidence of disease recurrence. The survival rate of patients following partial hepatectomy from metastatic islet cell tumor was 82% at 5 years. Median survival could not be estimated with currently available follow-up data. There was no difference in survival after hepatic resection by type of endocrinopathy. The malignant gastrinomas and nonfunctioning APUDomas were the most common malignancy among these patients, but these tumors were the most prevalent tumors reported. Ten patients had no evidence of disease recurrence with limited duration of follow-up. Two patients had resection of recurrent tumor at 12 and 16 months and remained without evidence of disease recurrence at 60 and 108 months, respectively.

Overall survival of patients following orthotopic liver transplantation for metastatic neuroendocrine cancer is shown in Fig 7. The survival rate was 51% at 5 years, and median survival was 5.1 years. Survival after orthotopic liver transplantation for carcinoid and noncarcinoid cancers is shown in Fig 8. The

survival rate at 5 years was 44% for carcinoid tumors (with a median survival of 3.4 years) and 43% for noncarcinoid neuroendocrine cancers. Recurrence was reported in 38 patients. Death was attributed to recurrence of neuroendocrine tumor in 15 patients after liver transplantation. Recurrence was report-

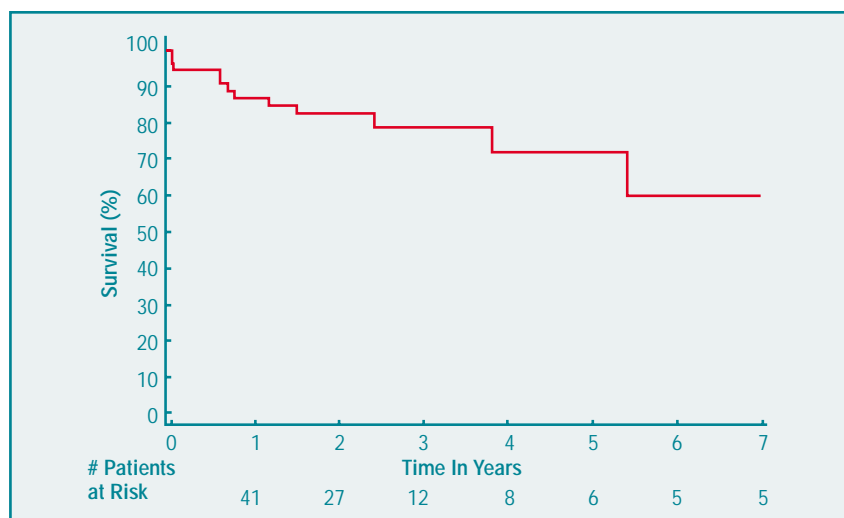


Fig 5. — Overall survival of patients with metastatic carcinoid and islet cell cancers after partial hepatectomy.

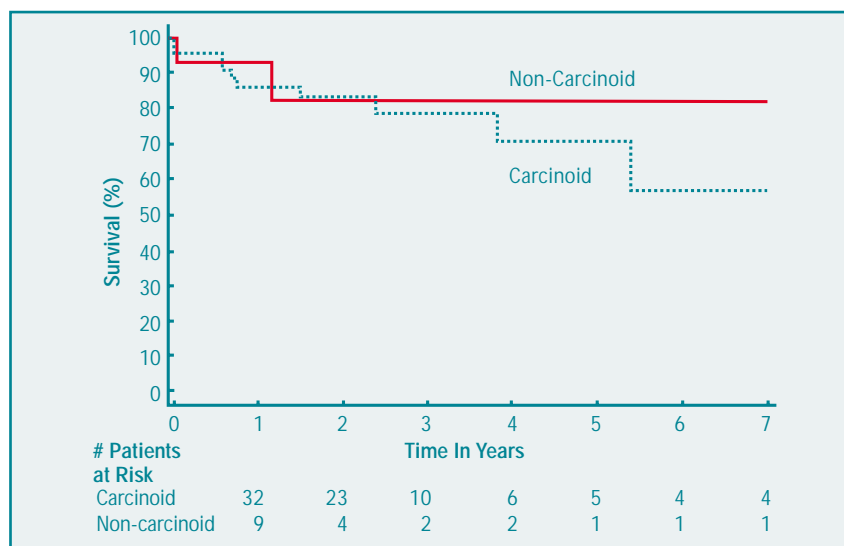


Fig 6. — Survival of patients with metastatic carcinoid and islet cell cancers after partial hepatectomy.

ed in the liver in 7 patients, bone in 11, lung in 3, and mesenteric lymph nodes in 3. One other patient had recurrence of a cholangiocarcinoma, which was diagnosed after transplantation for a neuroendocrine tumor. Death was attributed to recurrent cholangiocarcinoma.

Symptomatic Response

Symptomatic response of carcinoid syndrome resolved completely in 86% of patients undergoing partial cytoreductive hepatectomy. The duration of complete response from carcinoid syndrome ranged from 4

to 120 months. Forty-one patients had no recurrence of symptoms or objective disease (ie, normal 5-HIAA values and the absence of metastasis on imaging studies). A relationship between the onset and severity of recurrent symptoms and the extent of disease recurrence based on either 5-HIAA values or imaging studies could not be determined in this review. Clinical response to cytoreduction was incomplete in 3 patients. The duration of incomplete response could not be estimated from the literature data. Excluding operative deaths, only 1 patient selected for cytoreductive surgery failed to respond clinically.⁴⁵ Objective measurements of response to cytoreductive hepatic surgery by either 5-HIAA values or body imaging modalities were limited. In general, 5-HIAA levels were reduced following resection. However, further quantitation of 5-HIAA response was precluded due to assay variability. The mean duration of complete objective response from these patients could not be estimated because of insufficient data. Due to the time period of this literature review, a summary of objective imaging follow-up for recurrent disease was also precluded.

Symptomatic response of islet cell tumor endocrinopathies resolved completely in all 3 patients for whom a clinical response was reported. Clinical response was not stated for 3 patients, and the extent of response was not stated for 2 patients who responded. Twenty-three patients had nonfunctioning tumors. The duration of complete symptom-free response from the endocrinopathies could not be

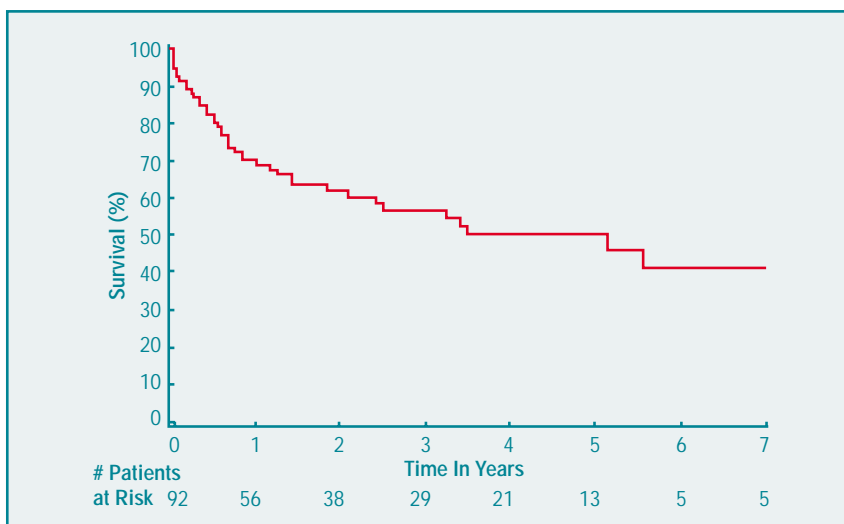


Fig 7. — Overall survival of patients with metastatic carcinoid and islet cell cancers after orthotopic liver transplantation.

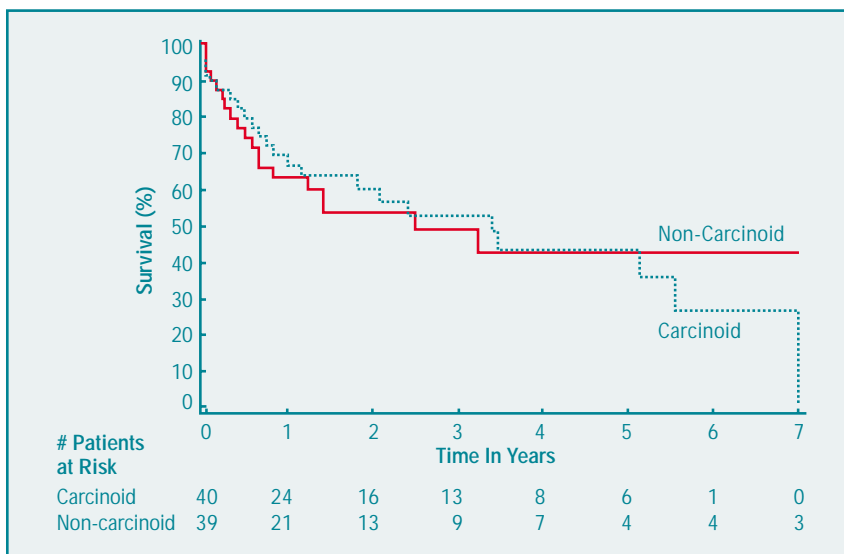


Fig 8. — Survival of patients with metastatic carcinoid and islet cell cancers after orthotopic liver transplantation.

determined. Seventeen patients had no recurrence by hormonal markers or objective imaging studies. Similar to carcinoid patients, the relationship of hormonal marker values and the onset in severity of recurrent symptoms could not be determined. Although comparison of responses after partial or complete resection is relative, reports suggest a greater degree and duration of benefit for complete resection of the metastatic disease and control of the primary tumor than for partial resection. Of those patients with endocrinopathies that persisted following resection, reduction of hormone values was documented in 2 of 3 patients. Hormonal response was not detailed in 1 patient. Meaningful analysis of "disease-free" survival based on imaging data was precluded because of the variety of abdominal imaging used in follow-up and the lack of uniform frequency of follow-up imaging.

No patient failed to respond clinically following orthotopic liver transplantation. Correlation of objective measurements of response to total hepatectomy by serum hormone values or body imaging modalities paralleled clinical response, as expected. Biochemical recurrence without clinical recurrence developed in 2 patients following liver transplantation.

Adjuvant and Adjunctive Therapy

Adjunctive therapy was performed in 65 patients. Three patients had a single recurrent hepatic nodule successfully treat-

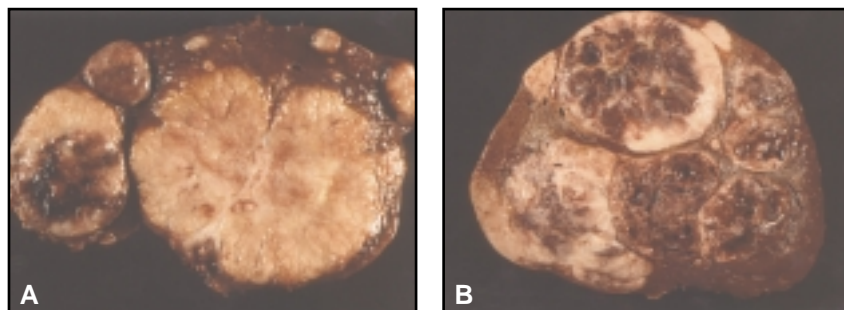


Fig 9. — Resected metastatic islet cell cancer (functioning insulinoma) in a right hepatectomy specimen, surface view (A) and transected view (B). Note metastases range from 2 mm to 4.5 cm in size. Despite residual metastases postoperatively ($\leq 3\%$ estimated preoperative hepatic tumor volume), the patient became euglycemic postoperatively and constant intravenous glucose infusions were discontinued.

ed by percutaneous alcohol injection. Twenty-one patients were treated with cytoreductive chemotherapy; and 5 underwent intra-arterial chemoembolization (Fig 9). Data are too heterogeneous to allow a proper analysis of this subset of patients.

Cryotherapy

Hepatic cryosurgery is a widely used and well-recognized modality for treatment of hepatic tumors. In 1995 Cozzi et al⁴⁶ demonstrated that hepatic cryotherapy offered adjunctive treatment for patients with neuroendocrine hepatic tumors. All 6 patients had a complete radiologic response, and they are alive and asymptomatic with a median follow-up of 24 months. There was also an 89% decrease in elevated tumor markers. Bilchik et al⁴⁷ showed that cryosurgery dramatically relieved symptoms with a significant reduction in tumor markers. The median symptom-free and overall survivals were 10 months and more than 49 months, respectively. While hepatic cryotherapy is feasible in the treatment of neuroendocrine liver metas-

tases, its role as an alternative to liver resection is not yet well supported by long-term data. Other techniques of local tumor ablation including radiofrequency ablation, percutaneous microwave coagulation, laser interstitial photocoagulation, and carbon dioxide laser remain unproven, although promising. Currently, we use radiofrequency ablation in conjunction with metastasectomy to maximally preserve functional hepatic parenchyma.

Discussion

This review suggests that cytoreductive hepatic resection for functioning metastatic neuroendocrine malignancies was efficacious in selected patients. Resection of hepatic metastases promptly relieved clinical endocrinopathies in nearly all patients, and symptomatic response often lasted many months. Perioperative morbidity and mortality were limited. Moreover, current data support further investigation of the role of hepatic transplantation in patients with isolated hepatic

metastases from gastrointestinal neuroendocrine cancers. Current data also confirm that hepatic resection, either concurrent with or subsequent to resection of the primary gastrointestinal neuroendocrine cancer, is safe.

Our own experience and that reported in this review have shown that cytoreductive surgery is safe.⁶ Admittedly, patient selection was careful, and publication bias may favor a positive patient outcome. We previously reported on operative mortality rate of 2.7% and operative morbidity rate of 24%, which does not differ from this literature review. Our overall symptomatic response rate was 90% with a mean duration of 19.3 months. Patient selection clearly influenced outcome. Reports to date may be biased toward a positive clinical response and low perioperative mortality and morbidity. Regardless of this potential, however, greater than 85% of patients had major hepatic resections (hemihepatectomy or extended hemihepatectomy), and more than 40% of patients had concurrent resection of the primary gastrointestinal neuroendocrine cancer. The fact that these collective data do not differ from the perioperative risk for major hepatic resections for other metastatic cancers and are less than the risk for resection of primary hepatic malignancies with cirrhosis supports hepatic cytoreduction for these tumors. Perioperative risk has not increased with specific endocrinopathies, with the possible exception of carcinoid heart disease. Operative repair of carci-

noid heart disease may be required prior to hepatic resection for symptomatic carcinoid syndrome in very selected patients to reduce the risk of massive hemorrhage caused by intrahepatic venous hypertension from right heart failure.⁴⁸ Finally, clinical response rates from the compiled literature were similar to our own experience.⁶ Durability of responses could not be quantitated from the list; however, our data confirmed a mean duration of response for nearly 20 months before subsequent therapy was undertaken.

Orthotopic liver transplantation for metastatic neuroendocrine cancers has been employed more frequently since our prior report. These tumors have become the primary indication for transplantation for metastatic disease. Although current results confirm that hepatic transplantation is uniformly effective for symptomatic relief, current survival data herein raise concerns over the appropriateness of such therapy for carcinoid tumors. Another independent review of 103 patients who underwent hepatic transplantation for metastatic neuroendocrine cancers found an overall 5-year survival rate of 47% but a recurrence-free 5-year survival rate of only 24%.⁴⁹ The perioperative mortality rate was 10%. Multivariate analysis showed that age greater than 50 years and transplantation with upper abdominal exenteration or Whipple's operation as adverse prognostic factors. Perhaps more accurate preoperative staging with octreotide scanning and MRI will permit better patient selection for hepatic

transplantation. Nonetheless, if future socioeconomic factors and organ availability permit hepatic transplantation in patients with metastatic cancer, this option for improved quality of life in these previously end-stage patients with neuroendocrine cancers may be more widely accepted.

There is no consensus on adjunctive chemotherapy or biotherapy for patients with malignant neuroendocrine tumors. These therapies are usually reserved for patients with advanced, inoperable, or residual disease. In practice, chemotherapy is usually withheld until all surgical options have been exhausted. Combination chemotherapy with streptozotocin and 5-fluorouracil or doxorubicin is still considered the first-line treatment for malignant neuroendocrine tumors.⁵⁰⁻⁵² The majority of patients treated had metastatic carcinoid tumor and, in general, the outcome has been disappointing.^{53,54} However, in patients with predominantly anaplastic neuroendocrine tumors in advanced stages, good tumor response rates with a combination of cisplatin and etoposide can be achieved.⁵⁵

Neuroendocrine gastrointestinal tumors express somatostatin receptors in 80% to 90% of patients, and somatostatin analogues have become important in the treatment of those patients. Although objective tumor regression occurs in only 10% to 20% of patients, stabilization of tumor growth is achieved in nearly half of the patients with a duration of 8 to 16 months.⁵⁶

Interferon alfa has been used as an alternative to somatostatin analogues. A median biochemical response rate of 44% and a tumor response rate of 11% have been observed.⁵⁷ The current medical management of neuroendocrine tumors is based on the use of chemotherapy for more highly proliferating tumors, such as malignant endocrine pancreatic tumors and foregut carcinoids, while biotherapy, including interferon alfa and somatostatin analogues, is used in slow-growing tumors, such as midgut carcinoids.⁵¹

Clear guidelines for patient selection are evolving. In general, if both the primary neuroendocrine cancer and its regional and hepatic metastases are resectable based on preoperative imaging studies, exploration for resection is clearly the treatment of choice. Conversely, if neither the local extent of the primary and regional neuroendocrine cancer or its hepatic metastasis is resectable, medical treatment is advised. However, most patients present clinically between these two extremes. Indeed, most patients will have resectable primary tumors but incompletely resectable or ablatable hepatic metastases. If hepatic metastases are multiple and bilobar, the decision for cytoreductive surgery is more complex. In general, if an expected 90% or greater of the hepatic disease can be removed with the primary and regional disease, then exploration is advised. If less than 90% of the hepatic metastases with the primary tumor are resectable or ablatable, then

cytoreductive surgery is currently not indicated because the duration and degree of symptomatic response following such surgery is expectedly brief. However, if effective adjunctive treatments become available, cytoreduction to a lesser degree may become indicated.

Accurate imaging is essential for evaluating potential candidates with neuroendocrine carcinoma for hepatic resection. In general, MRI with contrast enhancement is the single most accurate imaging modality for hepatic metastases from neuroendocrine tumors. MRI accurately and clearly defines these hypervascular metastases and their relationship to the intrahepatic vasculature. Moreover, MR cholangiography can be obtained concurrently if indicated. Imaging of the primary tumor depends on the site of origin with enteroclysis best for carcinoid tumors and rapid contrast enhanced CT for most islet cell carcinomas. Whether octreotide scanning should be routinely employed in all patients with metastatic neuroendocrine carcinomas is currently unknown. To date, most reports addressing cytoreductive hepatic surgery have not employed octreotide scanning as an option for resection. Although imaging of patients with metastatic neuroendocrine carcinomas with octreotide scanning probably would have a high positivity rate, the responses to date obtained after cytoreductive surgery without octreotide scanning would question its necessity because treatment is primarily palliative. Perhaps octreotide scanning should be routinely used in

patients prior to hepatic transplantation given the socioeconomic impact of this therapy.

Perioperative preparation of patients with neuroendocrine carcinoma is similar to that for patients for other hepatic malignancies, except that control of the endocrinopathy preoperatively is important. Our data have shown that for patients with malignant carcinoid tumors, preoperative antihormonal therapy with a somatostatin analogue is essential to prevent carcinoid crisis at the time of resection. Preoperative preparation with 150 to 500 μg of somatostatin on call to the operating room prevents hemodynamic instability intraoperatively (unpublished data, M Warner, D. Nagorney). Similarly, control of other neuroendocrine tumors with adequate glucose monitoring for insulinomas and H_2 -receptor antagonists or $\text{H}^+\text{-K}^+$ ATPase inhibitors for gastrinomas are essential.

Conclusions

Hepatic resection for metastatic neuroendocrine tumors is done primarily for palliative purposes. The intent of surgery is to resect or ablate 90% or greater of the hepatic disease. Consequently, ablative technology (cytoablative or thermal [microwave or radiofrequency] units) should be available for adjunctive intraoperative use. Hepatic tumors are approached as any metastatic tumor with the intent to resect all gross tumor with a tumor-free margin. All bulky disease is resected or ablated.

Cholecystectomy is routinely performed to eliminate potential complications from future hepatic arterial embolization or use of somatostatin analogues. Regional lymphadenectomy of the hepatoduodenal ligament, portal vein, and hepatic and celiac arteries is performed for all islet cell cancers and selected carcinoids. Excision of gross nodal disease during partial hepatectomy will ensure optimal long-term hepatic blood flow and reduce the risk of subsequent extrahepatic bile duct obstruction.

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