Hepatic Arterial Embolization and Chemoembolization for the Treatment of Patients with Metastatic Neuroendocrine Tumors

Variables Affecting Response Rates and Survival

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BACKGROUND. The objective of this study was to determine the prognostic variables that influence response and survival in patients with metastatic neuroendocrine tumors who are treated with hepatic arterial embolization (HAE) or chemoembolization (HACE).

METHODS. Patients with metastatic neuroendocrine tumors who underwent HAE or HACE were included in this retrospective study. Follow-up imaging studies were compared with baseline imaging to determine the radiologic response. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed to assess the prognostic variables that affected response and survival.

RESULTS. The study included 69 patients with carcinoid tumors and 54 patients with pancreatic islet cell carcinomas. Patients who had carcinoid tumors had a higher response rate (66.7% vs. 35.2%; $P = 0.0001$) and had longer PFS (22.7 mos vs. 16.1 mos; $P = 0.046$) and OS (33.8 mos vs. 23.2 mos; $P = 0.012$) compared with patients who had islet cell carcinomas. For patients with carcinoid tumors, multivariate analysis identified male gender as the only independent risk factor for poor survival ($P = 0.05$). Octreotide was predictive marginally for PFS ($P = 0.06$). Patients who were treated with HAE had a higher response rate than patients who were treated with HACE ($P = 0.004$). For patients with islet cell carcinoma, an intact primary tumor, $\geq 75\%$ liver involvement, and extrahepatic metastases were associated with reduced OS in the univariate analysis; the presence of bone metastases was the only risk factor ($P = 0.031$) in the multivariate analysis. Patients who were treated with HACE had a prolonged OS (31.5 mos vs. 18.2 mos) and improved response (50% vs. 25%) compared with patients who were treated with HAE, although the differences did not reach statistical significance.

CONCLUSIONS. Patients with carcinoid tumors had better outcomes than patients with islet cell carcinomas. The addition of intraarterial chemotherapy to HAE did not improve the outcome of patients with carcinoid tumors, but it seemed to benefit patients with islet cell carcinomas. In patients who had carcinoid tumors, male gender predicted a poor outcome, and a trend toward prolonged PFS was observed in patients who received concomitant octreotide. An intact primary tumor, extensive liver disease, and bone metastases were associated with reduced survival in patients with islet cell carcinomas. ***Cancer* 2005;104:1590–602.** © *2005 American Cancer Society.*

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Carcinoid and pancreatic islet cell carcinomas have a predilection for metastasizing to the liver. The presence of liver metastases is associated with a poor prognosis. Surgical resection of the liver metastases is possible in < 10% of patients.[1–5] Systemic chemotherapy has limited effectiveness for patients with carcinoid tumors.[1–5] Although interferon also has been used, recent randomized trials suggest response rates of only 4–7%.[5,6] Among patients with islet cell carcinomas, objective response rates of 30–70% have been reported with streptozocin-based chemotherapy.[1–5] However, few second-line options are available. Somatostatin analogues are effective in controlling the symptoms in many of these patients; however, the disease can become refractory to treatment.[7]

Many reports have shown that hepatic arterial embolization (HAE) can reduce tumor size and hormone output, resulting in palliation of symptoms.[8–24] Moertel et al.[22] found that patients who were treated with a combination of hepatic arterial occlusion and systemic chemotherapy had a higher response rate than patients who were treated with arterial occlusion alone. Because hepatic metastases derive most of their blood supply from the hepatic artery, regional delivery of chemotherapy offers pharmacokinetic advantages over systemic administration. This has prompted many investigators to use hepatic arterial chemoembolization (HACE), which combines embolization and intraarterial delivery of chemotherapy.[15,17–19,21,23]

Although several studies have documented the beneficial effects of HAE and HACE in these patients,[8–24] doubt remains whether chemoembolization offers any therapeutic advantage over particulate embolization alone. Clinical and treatment variables that affect the response rates and survival duration in these patients have not been characterized well. In the current study, we reviewed our experience with HAE and HACE for liver metastases from carcinoid tumors and islet cell carcinomas and evaluated the response rates and the durations of progression-free survival (PFS) and overall survival (OS) in these patients. We also analyzed various patient, disease, and treatment variables to assess their influence on the response rates and survival durations.

MATERIALS AND METHODS

We retrospectively evaluated the medical records of all patients who had histologically confirmed carcinoid tumors and pancreatic islet cell carcinomas metastatic to the liver and who underwent HAE or HACE at The University of Texas M. D. Anderson Cancer Center between January 1992 and December 2000. Approval for this study was obtained from the Institutional Review Board. Electronic medical records, pathology reports, and imaging studies were used to collect patient demographic, pathology, treatment, and outcome data. The presence of extrahepatic metastases was based on available imaging data, which included bone scans, octreoscans, magnetic resonance imaging (MRI), or computed tomography (CT) scans; in many patients, imaging studies were performed at an outside institution. In all patients, the diagnosis was made by staff pathologists from our institution based on histologic and immunohistochemical examination of pathologic specimens. All functional as well as nonfunctional pancreatic neuroendocrine tumors were labeled as islet cell tumors. The location of the primary tumors in patients who had a histologic diagnosis of carcinoid included small bowel (n = 43 patients), bronchus (n = 9 patients), and others (n = 17 patients).

The choice of HAE or HACE was based on the discretion of the referring physician. For most patients, only one lobe of the liver was subjected to embolization during each treatment session. In patients with extensive liver involvement, only a small portion of the liver lobe was subjected to embolization during each session. Patients with extensive disease in the untreated portion of the liver or inadequate hormonal response underwent additional embolization sessions. In patients who were treated with HAE, the hepatic artery was catheterized, and the embolic agent (polyvinyl alcohol particles or gelfoam powder) was injected until substantial slowing of the blood flow was achieved. In patients who underwent HACE, the chemotherapeutic agent was administered followed by the embolic material. In patients with hormonal symptoms, octreotide was injected subcutaneously before the embolization. The patients were hospitalized for 2–5 days after the procedure, depending on the severity of symptoms and the laboratory results.

Follow-up abdominal imaging studies (CT or MRI) generally were obtained 3–4 months after the first embolization, then every 4–6 months for the first 2 years, and at least annually thereafter. We compared follow-up CT or MRI studies with the baseline imaging studies to determine the objective tumor response in the liver based on the World Health Organization criteria: A complete response (CR) was defined as the complete disappearance of all recognizable tumor in the liver, a partial response (PR) was defined as a reduction ≥ 50% in tumor size, a minor response (MR) was defined as a reduction < 50% but ≥ 25%, in tumor size, stable disease (SD) was defined as a reduction or progression of disease < 25%, and progressive disease (PD) was defined as an increase ≥ 25% in tumor size over that measured at the time of maximal tumor shrinkage or as the appearance of new lesions. For

statistical analysis, patients who achieved a CR or a PR were considered responders. The size of the liver metastases was determined by multiplying the longest dimension of the tumor mass by its greatest perpendicular dimension, as measured on CT or MRI studies. In patients who had multiple liver lesions, up to five lesions were selected based on their size and suitability for accurate repeated measurements.

Patient characteristics and other variables were compared between tumor groups. Chi-square or Fisher exact tests were used to compare differences in discrete or categorical variables, and the Wilcoxon rank-sum test was used for continuous variables. PFS was defined as the duration from the date of the initial embolization procedure to the date of progression for patients who showed radiologic evidence of disease progression in the liver or to the date of death or last follow-up for patients who did not progress. OS was defined as the duration from the date of the initial embolization procedure to the date of death or to the date of the last follow-up for patients who remained alive at the time of last follow-up.

Survival analyses were performed separately for each tumor group. All survival durations were calculated using the Kaplan–Meier method. The log-rank test was used to compare cumulative survival between groups. Univariate Cox proportional hazards regression models were fit to evaluate the predictive effect of each factor alone. Multivariate Cox models were fit to assess the predictive effects of factors simultaneously. The multivariate models assessed included the treatment variable (HAE vs. HACE) and those variables that had a P value < 0.1 in the univariate analyses for either tumor group. The probability of a PR was modeled using univariate and multivariate logistic regression techniques. A Hosmer and Lemeshow goodness-of-fit test was assessed for each model. Statistical significance was defined as $P \leq 0.05$. Analyses were performed using SAS software (SAS/STAT User's Guide, version 8, 1999; SAS Institute, Inc., Cary, NC) and S-PLUS software (S-PLUS 2000, Professional Release 3, 1988–2000; Data Analysis Products Division, MathSoft, Inc., Seattle, WA).

RESULTS

Patient Characteristics

Sixty-nine patients with carcinoid tumors and 54 patients with pancreatic islet cell carcinomas were included in the current study. Patient demographics, tumor characteristics, and treatment details for both patient groups are summarized in Table 1. Patients who had carcinoids were significantly older and were more likely to have been treated with octreotide, but they were less likely to have received prior systemic chemotherapy than patients who had islet cell carcinomas. Seventy-four percent (51 of 69 patients) of the group with carcinoid tumors had carcinoid syndrome, whereas 37% (20 of 54 patients) of the group with islet cell tumors had functional tumors (9 gastrinomas, 6 insulinomas, 3 vipomas, and 2 glucagonomas). Among the patients with carcinoid tumors, the indications for HAE/HACE included carcinoid syndrome in 45 patients, mass-related signs and symptoms in 9 patients, and rapid tumor growth in 15 patients. In patients with islet cell carcinomas, HAE/HACE was performed to control hormonal symptoms in 12 patients, to control mass-related signs and symptoms in 12 patients, and to control rapid tumor growth in 21 patients; in the remaining 9 patients, the indication was not clear from available clinical information.

Among the patients with carcinoid tumors, the patient, tumor, and treatment variables were similar between the HAE group and the HACE group (Table 2). Among the patients with islet cell tumors, patients in the HACE group were more likely to have undergone primary tumor resection, had less extensive liver involvement, and had more embolization sessions compared with patients in the HAE group. In the carcinoid group, the extent of liver disease ($<$ 25% involvement: 7 patients vs. 4 patients; 25–50% involvement: 6 patients vs. 10 patients; 50–75% involvement: 12 patients vs. 16 patients; $>$ 75% involvement; 4 patients vs. 10 patients; $P = 0.37$) and the incidence of extrahepatic metastatic disease (72% vs. 67.5%; $P = 0.79$) did not differ significantly between patients who had their primary tumor removed and patients who had an intact primary tumor, respectively. In the islet cell group, the extent of liver disease ($<$ 25% involvement: 6 patients vs. 9 patients; 25–50% involvement: 7 patients vs. 11 patients; 50–75% involvement: 3 patients vs. 10 patients; $>$ 75% involvement: 1 patient vs. 7 patients; $P = 0.44$) and the incidence of extrahepatic disease (47% vs. 62%; $P = 0.38$) also did not differ significantly between the respective groups.

OS

Figure 1 shows the OS curves, which were obtained using the Kaplan–Meier method, plotted as a function of the tumor type; eight patients (four patients in each group) were lost to follow-up for this analysis. The median duration of OS for patients with carcinoid tumors was 33.8 months, whereas that for patients with islet cell carcinomas was 23.2 months ($P = 0.012$). The overall cumulative 1-year, 2-year, and 5-year OS rates for patients with carcinoid tumors were 95.3%, 68.6%, and 28.6%, respectively, and the same rates for patients with islet cell carcinomas were 68.8%, 48.7%, and 13.7%, respectively.

TABLE 1
Patient Characteristics by Tumor Type

	Carcinoid tumors (n = 69)		Islet cell carcinomas (n = 54)		
Patient characteristic	**No.**	**%**	**No.**	**%**	***P* value**
Gender					0.37
Female	30	43.5	28	51.9	
Male	39	56.5	26	48.2	
Primary tumor resection					0.26
Resected	29	42.0	17	31.5	
Intact	40	58.0	37	68.5	
Previous treatment					0.0002
No	46	66.7	16	32.0	
Yes	23[a]	33.3	34[b]	68.0	
Octreotide					0.0020
No	29	42.0	38	70.4	
Yes[c]	40	58.0	16	29.6	
Extent of liver involvement					
≤ 25%	11	15.9	15	27.8	0.11
> 25–50%	16	23.2	18	33.3	
> 50–75%	28	40.6	13	24.1	
> 75%	14	20,.3	8	14.8	
Extrahepatic metastases					
No	21	30.4	23	42.6	0.19
Yes	48	69.6	31	57.4	
Treatment					
HAE	42	60.9	32	59.3	1.00
HACE	27	39.1	22	40.7	
Age (yrs)					
Median	59.0		51.5		0.0009
Range	42–79		25–74		
Duration of liver disease (mos)					
Median	18.0		14.5		0.69
Range	1–144		1–120		
No. of embolizations					
Median	2		2		0.31
Range	1–4		1–10		

HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.

[a] This included systemic chemotherapy in 20 patients, intraarterial chemotherapy in 2 patients, and partial hepatectomy and RFA in 1 patient.

[b] This included systemic chemotherapy in 32 patients and partial hepatectomy plus previous hepatic arterial embolization 2–3 years earlier in 2 patients.

[c] Octreotide was used for control of hormonal signs/symptoms in most patients.

In patients with carcinoid tumors, predictive effects for OS were found for gender, extent of liver disease, and presence of bone metastases using univariate analysis (Table 3). Men were nearly 2.5 times more likely to die than women (median OS: 33.2 mos vs. 57.3 mos; $P = 0.03$). The median survival was 20.1 months in patients with > 75% liver involvement and was 86.4 months in patients with ≤ 25% liver involvement ($P = 0.05$). Extrahepatic disease was marginally predictive: Patients who had extrahepatic metastases had a shorter OS compared with patients who did not have such metastases (33.2 mos vs. 86.4 mos; $P = 0.08$). The presence of bone metastases decreased survival significantly (26 mos vs. 86.4 mos; $P = 0.02$). In the multivariate model, only male gender remained predictive for poor survival (Table 4) (relative risk = 2.55; $P = 0.05$).

In patients with islet cell carcinomas, univariate analysis for OS showed predictive effects for primary tumor resection, extent of liver disease, and extrahepatic metastases (Table 3). Patients with intact primary tumors were > 2.5 times more likely to die than patients with resected tumors ($P = 0.017$). Patients with > 75% liver disease were 3 times more likely to die ($P = 0.049$) than patients with ≤ 25% liver involvement. Patients with extrahepatic metastases were 2.8 times more likely to die than patients without extrahepatic metastases ($P = 0.009$). Decreased survival was noted in patients with bone

TABLE 2
Patient Characteristics by Treatment Type

Patient characteristic	No. of carcinoid tumors (%)			No. of islet cell carcinomas (%)		
	HAE (n = 32)	HACE (n = 22)	P value	HAE (n = 42)	HACE (n = 27)	P value
Gender						
Female	18 (42.9)	12 (44.4)	1.00	16 (50.0)	12 (54.6)	0.79
Male	24 (57.1)	15 (55.6)		16 (50.0)	10 (45.4)	
Primary tumor resection						
Resected	17 (40.5)	12 (44.4)	0.81	6 (18.8)	11 (50.0)	0.02
Intact	25 (59.5)	15 (55.6)		26 (81.3)	11 (50.0)	
Previous treatment						
No	26 (61.9)	20 (74.1)	0.43	8 (26.7)	8 (40.0)	0.37
Yes	16 (38.1)	7 (25.9)		22 (73.3)	12 (60.0)	
Octreotide						
No	18 (42.9)	11 (40.7)	1.00	20 (62.5)	18 (81.8)	0.15
Yes	24 (57.1)	16 (59.3)		12 (37.5)	4 (18.2)	
Extent of liver involvement						
< 25%	5 (11.9)	6 (22.2)	0.25	8 (25.0)	7 (31.8)	0.05
25–50%	13 (31.0)	3 (11.1)		7 (21.9)	11 (50.0)	
50–75%	16 (38.1)	12 (44.4)		10 (31.3)	3 (13.6)	
> 75%	8 (19.1)	6 (22.2)		7 (21.9)	1 (4.6)	
Extent of liver involvement						
≤ 75%	34 (81.0)	21 (77.8)	0.77	25 (78.1)	21 (95.5)	0.12
> 75%	8 (19.1)	6 (22.2)		7 (21.9)	1 (4.6)	
Extrahepatic metastases						
No	12 (28.6)	9 (33.3)	0.79	14 (43.8)	9 (40.9)	1.00
Yes	30 (71.4)	18 (66.7)		18 (56.3)	13 (59.1)	
Median age (yrs)	58	60	0.59	52	51.5	0.44
Median duration of liver disease (mos)	18	15	0.34	23	10.5	0.47
Median no. of embolizations	2	2	0.50	2	3	0.03

HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.

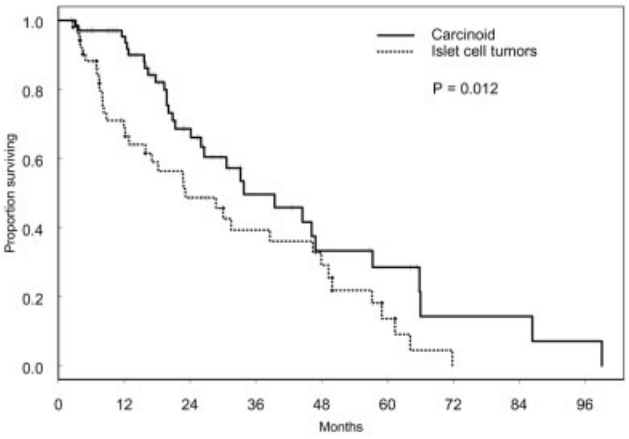

FIGURE 1. These Kaplan–Meier curves for overall survival were calculated according to tumor type. The median survival of patients with carcinoid tumors was significantly longer compared with the median survival of patients with islet cell carcinomas (33.8 mos vs. 23.2 mos, respectively; $P = 0.012$).

metastases and in patients with extrahepatic metastases to other sites (lymph nodes, spleen, peritoneum, and lung). However, in the multivariate model, only metastases to bone remained predictive for survival (Table 4) ($P = 0.03$).

Progression-Free Survival

The median duration of PFS for patients with carcinoid tumors was 22.7 months, whereas that for patients with islet cell carcinomas was 16.1 months ($P = 0.046$) (Fig. 2). The use of octreotide was predictive only marginally for PFS in the carcinoid cohort (Tables 5, 6). Patients who received octreotide had a longer PFS than did patients who did not (23.9 mos vs. 18.3 mos; $P = 0.06$). For patients with islet cell carcinomas, predictive effects for PFS were not found for any of the factors investigated in either the univariate model or the multivariate model (Tables 5, 6).

Response Rates

All patients were evaluable for assessment of radiologic response. Two-thirds (46 of 69 patients) of the group with carcinoids responded radiologically, compared with 35.2% (19 of 54 patients) of the group with islet cell carcinomas ($P = 0.0001$). None of the 69

TABLE 3
Univariate Analysis for Overall Survival

	Carcinoid tumors (n = 69)					Islet cell carcinomas (n = 54)				
Variable	No.	Median (mos)	RR	95% CI[a]	P value	No.	Median (mos)	RR	95% CI[a]	P value
Age (continuous)[b]	69		6.34	0.49–82.7	0.16	54		1.40	0.41–4.77	0.59
Duration of liver disease (continuous)[b]	69		0.90	0.64–1.27	0.56	48		0.89	0.70–1.14	0.37
Gender										
Female	30	57.3	1.00			28	30.0	1.00		
Male	39	33.2	2.44	1.08–5.49	0.03	26	18.2	0.79	0.40–1.56	0.49
Primary tumor										
Resected	29	46.2	1.00			17	46.4	1.00		
Intact	40	26.0	1.79	0.84–3.85	0.13	37	15.9	2.57	1.18–5.61	0.017
Previous treatment										
No	46	44.5	1.00			16	49.9	1.00		
Yes	23	26.6	1.70	0.75–3.83	0.20	34	22.8	1.27	0.57–2.85	0.56
Octreotide										
No	29	44.5	1.00			38	28.7	1.00		
Yes	40	33.2	1.32	0.60–2.91	0.48	16	12.0	1.69	0.83–3.45	0.15
Treatment										
HAE	42	33.2	1.00			32	18.2	1.00		
HACE	27	33.8	1.00	0.47–2.17	0.99	22	31.5	0.71	0.36–1.40	0.33
Extent of liver disease										
≤ 25%	11	86.4	1.00			15	46.4	1.00		
> 25–50%	16	29.9	3.73	0.76–18.2	0.10	18	18.2	1.51	0.56–4.11	0.42
> 50–75%	28	39.4	2.86	0.64–12.8	0.17	13	38.6	1.54	0.53–4.47	0.43
> 75%	14	20.1	5.01	1.00–25.0	0.05	8	15.9	3.01	1.01–9.02	0.049
Extent of liver disease										
≤ 75%	55	33.8	1.00			46	30.0	1.00		
> 75%	14	20.1	1.85	0.78–4.36	0.16	8	15.9	2.23	0.96–5.20	0.06
Extrahepatic metastases										
No	21	86.4	1.00			23	46.4	1.00		
Yes	48	33.2	2.44	0.91–6.51	0.08	31	17.0	2.80	1.29–6.06	0.009
Other sites	33	33.8	1.93	0.68–5.51	0.22	23	18.2	2.74	1.20–6.27	0.02
Bone	15	26.0	3.66	1.23–10.87	0.02	8	12.9	2.92	1.13–7.59	0.03
No. of embolizations (continuous)	69		1.21	0.74–2.00	0.45	54		1.04	0.88–1.23	0.68

RR: relative risk; 95% CI: 95% confidence interval; HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.

[a] Values shown are the lower and upper limits for a 95% confidence interval on the relative risk.

[b] Log transformation.

patients with carcinoid tumors had a CR. A PR was observed in 46 patients (67%), an MR was observed in 6 patients (8.7%), SD was observed in 11 patients (16%), and PD was observed in 6 patients (8.7%). In the islet cell carcinoma group, a PR was observed in 19 patients (35%), an MR was observed in 1 patient (2%), SD in was observed 32 patients (59%), and PD was observed in 2 patients (4%).

In the univariate analyses, the method of treatment and the extent of liver disease were predictive of radiologic response in the carcinoid cohort (Table 7). Treatment remained predictive for response in multivariate analysis (Table 8); patients who received HAE, compared with patients who received HACE, were six times more likely to respond ($P = 0.002$). The extent of liver disease was predictive only marginally; patients with ≤ 75% liver involvement were almost 4 times more likely to respond as patients with > 75% liver involvement ($P = 0.06$).

In the univariate analyses, primary tumor resection was predictive of radiologic response in the islet cell carcinoma group (Table 7). The method of treatment was predictive only marginally; patients who received HACE showed a higher response rate (50% vs. 25%; $P = 0.06$). In a multivariate model that contained the variables primary tumor resection, treatment, and extent of liver involvement, primary tumor resection remained predictive for response (Table 8); patients

TABLE 4
Multivariate Cox Proportional Hazards Model for Survival

	Carcinoid tumors (n = 69)				Islet cell carcinomas (n = 54)			
Variable	**No.**	**RR**	**95% CI[a]**	***P* value**	**No.**	**RR**	**95% CI[a]**	***P* value**
Gender								
Female	30	1.00			28	1.00		
Male	39	2.55	0.99–6.58	0.05	26	0.78	0.34–1.76	0.54
Primary tumor								
Resected	29	1.00			17	1.00		
Intact	40	1.43	0.57–3.57	0.45	37	2.01	0.86–4.69	0.11
Treatment								
HAE	42	1.00			32	1.00		
HACE	27	1.54	0.63–3.81	0.35	22	0.91	0.37–2.24	0.84
Extent of liver disease								
≤ 25%	11	1.00			15	1.00		
> 25–50%	16	5.37	0.90–32.11	0.07	18	1.54	0.54–4.42	0.42
> 50–75%	28	2.75	0.52–14.48	0.23	13	0.91	0.25–3.24	0.88
> 75%	15	2.28	0.37–14.20	0.38	8	1.67	0.47–5.95	0.43
Extrahepatic metastases								
No	21	1.00			23	1.00		
Other sites	33	1.70	0.57–5.04	0.34	23	2.20	0.90–5.42	0.09
Bone	15	2.50	0.64–9.67	0.18	8	3.23	1.09–9.53	0.03

RR: relative risk; 95% CI: 95% confidence interval; HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.
[a] Values shown are the lower and upper limits for a 95% confidence interval on the relative risk.

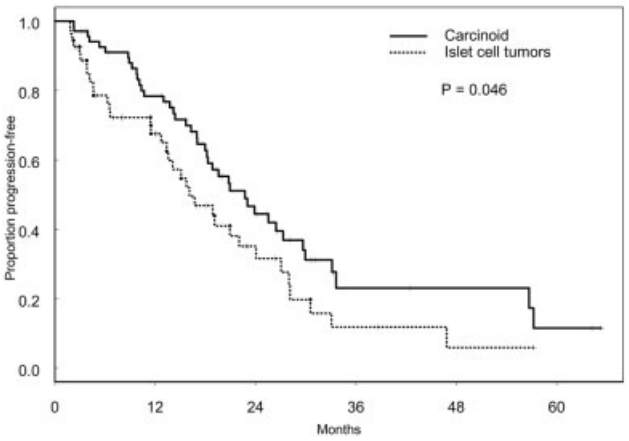

FIGURE 2. These Kaplan–Meier curves for progression-free survival were calculated according to tumor type. The median progression-free survival for patients with carcinoid tumors was significantly longer compared with the median progression-free survival for patients with islet cell carcinomas (22.7 mos vs. 16.1 mos, respectively; $P = 0.046$).

who had resected tumors were 3.5 times more likely to respond ($P = 0.05$).

Adverse Effects

Most patients experienced some degree of postembolization syndrome, which generally lasted 48–72 hours. Serious adverse events were noted after 25 embolization sessions (8.5%) in 19 patients. Hepatorenal syndrome occurred in seven patients, and sepsis occurred in six patients. One patient experienced transient myelosuppression, one patient developed anasarca and bilateral lower limb edema, one patient developed transient cortical blindness, and one patient developed necrotizing cholecystitis that required cholecystectomy. Hepatic abscess formation necessitating catheter drainage occurred in two patients, and one patient died of myocardial infarction 3 days after the procedure. Patients who had > 75% liver involvement had a higher incidence of major complications compared with patients who had up to 75% liver involvement (27.3% vs. 12.9%); however, this difference was not statistically significant ($P = 0.11$). The incidence of complications in the HACE and HAE treatment groups were 20% and 12%, respectively ($P = 0.31$).

DISCUSSION

Previous reports have suggested that the natural history of metastatic neuroendocrine tumors is unpredictable, and the reported median survival in these patients after embolization treatment ranges from 13–80 months.[8–24] Most of these studies have not taken into account the different biologic behavior, natural history, and prognosis of carcinoids and pancreatic islet cell carcinomas, and both types have been evaluated as a single cohort, thus making comparative

TABLE 5
Univariate Cox Proportional Hazards Models for Progression-Free Survival

	Carcinoid tumors (n = 69)					Islet cell carcinomas (n = 54)				
Variable	No.	Median (mos)	RR	95% CI[a]	P value	No.	Median (mos)	RR	95% CI[a]	P value
Age (continuous)[b]	69		4.08	0.57–29.20	0.16	54		1.15	0.39–3.38	0.80
Duration of liver disease (continuous)[b]	69		0.96	0.73–1.28	0.80	48		1.17	0.89–1.54	0.27
Gender										
Female	30	23.0	1.00			28	15.1	1.00		
Male	39	20.8	1.36	0.73–2.54	0.34	26	16.7	0.86	0.44–1.68	0.67
Primary tumor										
Resected	29	22.7	1.00			17	16.7	1.00		
Intact	40	20.8	0.78	0.42–1.45	0.43	37	14.1	1.66	0.78–3.53	0.19
Previous treatment										
No	46	25.5	1.00			16	28.0	1.00		
Yes	23	20.8	1.13	0.58–2.19	0.71	34	15.1	1.92	0.85–4.35	0.12
Octreotide										
No	29	18.3	1.00			38	16.7	1.00		
Yes	40	23.9	0.55	0.30–1.03	0.06	16	11.5	1.48	0.70–3.12	0.31
Treatment										
HAE	42	20.9	1.00			32	14.1	1.00		
HACE	27	23.9	1.00	0.53–1.86	0.99	22	18.9	0.78	0.39–1.57	0.49
Extent of liver disease										
≤ 25%	11	23.9	1.00			15	18.9	1.00		
> 25–50%	16	26.4	0.78	0.28–2.16	0.63	18	15.7	1.72	0.69–4.34	0.25
> 50–75%	28	20.8	1.23	0.50–3.05	0.65	13	16.1	1.29	0.51–3.25	0.59
> 75%	14	16.3	1.62	0.60–4.38	0.34	8	6.6	1.69	0.55–5.15	0.36
Extent of liver disease										
≤ 75%	55	23.0	1.00			46	16.1	1.00		
> 75%	14	16.3	1.59	0.75–3.34	0.23	8	6.6	1.29	0.49–3.37	0.61
Extrahepatic metastases										
No	21	18.2	1.00			23	15.7	1.00		
Yes	48	23.0	0.79	0.41–1.51	0.47	31	18.9	0.99	0.51–1.95	0.98
No. of embolizations (continuous)	69		0.77	0.52–1.15	0.21	54		0.84	0.66–1.07	0.16

RR: relative risk; 95% CI: 95% confidence interval; HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.
[a] Values shown are the lower and upper limits for a 95% confidence interval on the relative risk.
[b] Log transformation.

TABLE 6
Multivariate Cox Proportional Hazards Model for Progression-Free Survival

	Carcinoid tumors (n = 69)				Islet cell carcinomas (n = 54)			
Variable	No.	RR	95% CI[a]	P value	No.	RR	95% CI[a]	P value
Octreotide								
No	29	1.00			38	1.00		
Yes	40	0.55	0.30–1.02	0.06	16	1.42	0.67–3.04	0.36
Treatment								
HAE	42	1.00			32	1.00		
HACE	27	0.95	0.51–1.78	0.87	22	0.83	0.41–1.68	0.60

RR: relative risk; 95% CI: 95% confidence interval; HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization.
[a] Values shown are the lower and upper limits for a 95% confidence interval on the relative risk.

evaluation impossible. In the current study, which is one of the largest single-center series to date, patients with carcinoid tumors had better outcomes than patients with islet cell carcinomas, as evidenced by higher radiologic response rates and longer median PFS and OS durations. In the study by Eriksson et al.,[11]

TABLE 7
Univariate Logistic Regression for Radiologic Response

	Carcinoid tumors (n = 69)					Islet cell carcinomas (n = 54)				
Variable	No.	CR + PR (%)	OR	95% CI[a]	P value	No.	CR + PR (%)	OR	95% CI[a]	P value
Age (continuous)	69		0.99	0.94–1.05	0.85	54		1.03	0.98–1.07	0.29
Duration of liver disease (continuous)	69		1.00	0.98–1.02	0.81	48		1.00	0.98–1.03	0.92
Gender										
Female	30	66.7	1.00			28	46.4	1.00		
Male	39	66.7	1.00	0.36–2.75	1.00	26	23.1	0.35	0.11–1.12	0.08
Primary tumor										
Resected	29	75.9	1.00			17	58.8	4.44		
Intact	40	60.0	0.48	0.17–1.38	0.17	37	24.3	1.00	1.31–15.11	0.02
Previous treatment										
No	46	69.6	1.00			16	50.0	1.00		
Yes	23	60.9	0.68	0.24–1.94	0.47	34	26.5	0.36	0.10–1.25	0.11
Octreotide										
No	29	65.5	1.00			38	34.2	1.00		
Yes	40	67.5	1.09	0.40–3.01	0.86	16	37.5	1.15	0.34–3.89	0.82
Treatment										
HACE	27	44.4	1.00			22	50.0	3.00		
HAE	42	81.0	5.31	1.80–15.67	0.003	32	25.0	1.00	0.94–9.54	0.06
Extent of liver disease										
≤ 25%	11	63.6	1.00			15	33.3	1.00		
> 25–50%	16	81.3	2.48	0.43–14.34	0.31	18	38.9	1.27	0.30–5.33	0.74
> 50–75%	28	71.4	1.43	0.33–6.26	0.64	13	38.5	1.25	0.27–5.89	0.78
> 75%	14	42.9	0.43	0.09–2.17	0.31	8	25.0	0.67	0.10–4.58	0.68
Extent of liver disease										
> 75%	14	42.9	1.00			8	25.0	1.00		
≤ 75%	55	72.7	3.56	1.06–11.97	0.04	46	37.0	1.76	0.32–9.71	0.52
Extrahepatic metastases										
No	21	66.7	1.00			23	34.8	1.00		
Yes	48	66.7	1.00	0.34–2.97	1.00	31	35.5	1.03	0.33–3.19	0.96

CR: complete response; PR: partial response; OR: odds ratio; 95% CI: 95% confidence interval; HACE: hepatic arterial chemoembolization; HAE: hepatic arterial embolization.
[a] Values shown are the lower and upper limits for a 95% confidence interval on the odds ratio.

TABLE 8
Multivariate Logistic Regression for Radiologic Response

	Carcinoid tumors (n = 69)				Islet cell carcinomas (n = 54)			
Variable	No.	OR	95% CI[a]	P value	No.	OR	95% CI[a]	P value
Primary tumor								
Intact	40	1.00			37	1.000		
Resected	28	2.34	0.70–.82	0.17	17	3.54	0.9–12.81	0.05
Treatment								
HACE	27	1.00			22	2.12		
HAE	42	6.41	1.97–20.84	0.002	32	1.00	0.60–7.51	0.24
Extent of liver disease								
> 75%	14	1/00			8	1.00		
≤ 75%	55	3.73	0.96–14.56	0.06	46	1.05	0.16–6.85	0.96

OR: odds ratio; 95% CI: 95% confidence interval; HACE: hepatic arterial chemoembolization; HAE: hepatic arterial embolization
[a] Values shown are the lower and upper limits for the 95% confidence interval on the odds ratio.

the median survival in patients with carcinoid tumors (80 mos) was higher than that in patients with islet cell carcinomas (20 mos). Moertel et al.[22] also reported a longer median survival (27 mos vs. 9 mos) in patients who had carcinoid tumors, compared with patients who had islet cell carcinomas, treated with emboliza-

TABLE 9
Reported Series of Hepatic Artery Chemoembolization and Hepatic Artery Embolization in Patients with Metastatic Carcinoid Tumors and Islet Cell Carcinomas

Carcinoid tumors				Islet cell carcinomas			
HACE		HAE		HACE		HAE	
Study	% CR + PR (no.)	Study	% CR + PR (no.)	Study	% CR + PR (no.)	Study	% CR + PR (no.)
Hazarizadeh et al., 1992[15]	50.0 (4/8)	Hanssen et al., 1989[16]	71.0 (5/7)	Carrasco et al., 1983[9]	100.0 (3/3)	Carrasco et al., 1983[9]	50.0 (3/6)
Rusznieweski et al., 1993[18]	33.3 (6/18)	Moertel et al., 1994[22]	69.6 (16/23)	Mavligit et al., 1993[23]	80.0 (4/5)	Moertel et al., 1994[22]	82.0 (14/17)
Therasse et al., 1993[19]	35.0 (6/17)	Wangberg et al., 1996[20]	42.5 (17/40)	Kim et al., 1999[17]	50.0 (7/14)	Eriksson et al., 1998[11]	17.0 (2/12)
Kim et al., 1999[17]	25.0 (4/16)	Eriksson et al., 1998[11]	38.0 (11/29)	Dominguez et al., 2000[10]	57.0 (4/7)	Ajani et al., 1988[8]	60.0 (12/20)
Dominguez et al., 2000[10]	50,0 (4/8)	Carrasco et al., 1983[9]	83.0 (5/6)	Rusznieweski et al., 1993[18]	0.0 (0/5)		
Roche et al., 2003[21]	43.0 (6/14)	Loewe et al., 2003[24]	73.0 (16/22)				
Drougas et al., 1998[12]	6.7 (1/15)						
Average	32.0 (31/96)	Average	55.0 (70/127)	Average	53.0 (18/34)	Average	56.0 (31/55)

HAE: hepatic arterial embolization; HACE: hepatic arterial chemoembolization; CR: complete response; PR: partial response.

tion or ligation of the hepatic artery. Similar findings also have been reported in the surgical literature.[25,26] In the study by Nave et al.,[25] which involved liver resection for metastatic disease, patients with islet cell carcinomas did not survive the first 5 postoperative years, whereas the 5-year survival rate of patients with metastatic carcinoids was 58%.

To our knowledge, the prognostic factors for survival or PFS in patients with metastatic neuroendocrine tumors who are treated with HAE/HACE have not been studied previously. Male gender emerged as the only independent predictor of a poor outcome in patients with metastatic carcinoid tumors, with a relative risk of 2.76. Similar findings also have been reported in other studies.[27–29] In a study by McDermott et al.[27] that involved 188 patients with gastrointestinal carcinoids, women had a better prognosis than men, with a 5-year survival rate of 66% compared with 47% for men. In another study that involved 31 patients with carcinoids, the 10-year survival rate was 13% for men and 83% for women ($P = 0.0032$).[28]

It has been shown that octreotide analogues are effective in improving the clinical symptoms related to these tumors by inhibiting the release of polypeptides. Anecdotal reports suggest that octreotide analogues also may have an inhibitory effect on tumor growth.[5] Several studies have shown that the combination of HAE/HACE with systemic octreotide leads to radiologic, biochemical, and clinical response in patients with metastatic neuroendocrine tumors, and HAE/HACE can be effective even in patients who have octreotide-refractory symptoms.[11,12,14] Although we did not find that the use of octreotide was a statistically significant variable in predicting response or survival in either group of patients, it was predictive marginally for PFS in the carcinoid group. Patients with metastatic carcinoid tumors who received octreotide had a longer PFS compared with patients who did not receive octerotide (23.9 mos vs. 18.3 mos; $P = 0.06$). To our knowledge, this association has not been reported previously, and prospective randomized trials are needed to assess whether concomitant use of octreotide with HAE/HACE offers any benefit in these patients.

Since the report by Moertel et al.[22] demonstrated a greater regression rate and a longer duration of regression with systemic chemotherapy after hepatic arterial occlusion than with occlusion alone, many authors have favored HACE over HAE for the treatment of metastatic neuroendocrine tumors. Although no previous study has compared HAE with HACE in the treatment of metastatic neuroendocrine tumors, a compilation of results from various studies reported in the literature indicates that, although there is no difference in the response rates for the two treatment methods for patients with islet cell carcinomas, patients with carcinoid tumors may show a higher response rates to HAE compared with HACE (Table 9). However, we must point out that direct comparison between these studies is problematic because of the marked heterogeneity in the patient groups, differences in the treatment protocols, and the different methods used to report response.

In the current study, the addition of intraarterial chemotherapy to embolization did not improve the OS or PFS in patients with carcinoid tumors, and it actually had a deleterious effect on the radiologic response rate (44.4% vs. 81%; $P = 0.004$). In contrast, a tendency to-

ward prolonged survival (31.5 mos vs. 18.2 mos) and improved response rate (50% vs. 25%) was noted in patients with islet cell carcinomas who received HACE compared with patients who received HAE. However, these results must be viewed with caution, because the HAE group had a greater proportion of patients with unresected primary tumors and more extensive liver involvement than the HACE group in the islet cell tumor cohort. At least theoretically, it is not unreasonable to expect that intraarterial chemotherapy will be more effective in patients with islet cell carcinomas, because carcinoid tumors generally are resistant to systemic chemotherapy, whereas islet cell carcinomas generally demonstrate a better response.[1–5]

In our series, there was a clear tendency toward a worse outcome in patients who had > 75% liver involvement by metastatic disease; this was noted in both tumor types in the univariate analysis for OS. The radiologic response rate also was correlated with the extent of liver disease in patients with carcinoid tumors; patients with ≤ 75% liver involvement were 3.5 times more likely to respond ($P = 0.06$) than patients with > 75% liver involvement. In the report by Kress et al.,[30] a trend toward longer survival was noted in patients with tumor burdens < 50%, and the majority of patients with tumor burdens > 75% died from 30 days to 6 months after chemoembolization; those authors concluded that patients with tumor burdens > 75% of the liver do not benefit from HACE. In fact, a tumor burden > 50% liver has been used as an exclusion criterion by many authors. However, we were able to treat many patients with > 75% liver involvement successfully and safely by treating only a small portion of the liver in each embolization session; in this category, a response rate of 43% and an OS of 20.1 months was achieved in the carcinoid group, whereas patients in the islet cell carcinoma group showed a response rate of 25% and an OS of 16 months. These results suggest that, although the median survivals and response rates are lower in patients with > 75% liver disease, many of these patients can benefit from embolization.

In this study, the prognosis for patients with islet cell carcinomas who underwent resection of their primary tumor was better compared with the prognosis for patients who had an intact primary tumor (OS: 46.4 mos vs. 15.9 mos; $P = 0.017$; univariate analysis). Although the multivariate analysis also showed a trend toward improved survival in the patients who had resected primary tumors, the trend did not reach statistical significance. In the carcinoid group, although patients with resected primary tumors had a longer OS than patients with intact primary tumors (46.2 mos vs. 26 mos), this difference was not statistically significant ($P = 0.13$). Complete resection of the primary tumor as a favorable prognostic variable in patients with islet cell carcinomas also has been reported in other studies.[31–33] For their series of 50 patients with pancreatic neuroendocrine tumors, Chu et al.[31] found 5-year survival rates of 63% for the group that underwent resection of the primary tumor and 22% for the group that did not ($P = 0.001$). In another study, patients in the resected group had a 3-year survival rate of 100% compared with 34% for patients who had biopsy and chemotherapy.[32] Chu et al.[31] pointed out that these findings may be related to selection bias, because it is likely that patients who could not undergo resection of their primary tumor had more advanced disease. Although we cannot rule out the possibility that the patients with resected primary tumors may have had less local tumor burden, we did not find any statistically significant difference in the extent of liver involvement or the incidence of extrahepatic metastatic disease between the two groups both among patients with carcinoid tumors and among patients with islet cell carcinomas. The preponderance of evidence from the literature and the results of our own study suggest that, when feasible, the primary tumor in patients with islet cell carcinomas should be resected.

Most authors believe that the most common cause of death in these patients is liver failure from tumor progression and that extrahepatic metastatic disease has no significant effect on the outcome.[25,34] In the current study, however, the presence of extrahepatic bone metastases was an independent prognostic variable for reduced survival in patients with islet cell carcinomas. A few previous studies have shown that the development of bone metastases in patients with gastrinomas is predictive of a poor prognosis.[35,36] In the carcinoid group, univariate analysis also showed decreased survival in patients who had bone metastases compared with patients who had no extrahepatic disease (26 mos vs. 86.4 mos; $P = 0.02$).

A major limitation of the current study is the retrospective design. Because of the retrospective, nonrandomized nature of the study, there are limited numbers of patients in some of the subgroups for meaningful statistical analysis. In addition, the lack of a uniform imaging protocol for the detection of extrahepatic metastatic disease and variability in the frequency of follow-up imaging may have affected the survival and response analyses. Despite such difficulties, however, we still can draw some conclusions with regard to the use of HAE/HACE in patients with metastatic neuroendocrine tumors.

Our current analyses suggest that patients who have pancreatic islet cell carcinomas have a poor prognosis compared with patients who have carcinoid tumors after treatment with HAE/HACE. On the basis of the results of

the current study and a review of the literature, we believe that, although chemoembolization has not shown any therapeutic benefit over particulate embolization alone in patients with metastatic carcinoid tumors, patients with islet cell carcinomas seem to benefit from the addition of intraarterial chemotherapy to embolization. These results need to be validated in prospective, randomized studies and may change with the development of newer chemotherapeutic agents. In patients with carcinoid tumors, male gender has a negative effect on survival, and the concomitant use of octreotide seems to be beneficial in prolonging PFS. Intact primary tumor, extensive liver disease, and bone metastases are associated with an unfavorable outcome in patients with islet cell carcinomas.

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