Hepatic Artery Chemoembolization for 110 Gastrointestinal Stromal Tumors

Response, Survival, and Prognostic Factors

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BACKGROUND. The efficacy of hepatic artery chemoembolization (HACE) was evaluated for gastrointestinal stromal tumors (GISTs) metastatic to the liver.

METHODS. Records for patients with metastatic GIST who underwent HACE between January 1993 and March 2005 were reviewed and cross-sectional images were used to determine objective tumor response. Progression-free survival in the liver (PFS-liver) and overall survival (OS) were calculated with the Kaplan–Meier method. Patient, tumor, and treatment variables were analyzed to identify factors influencing survival.

RESULTS. Of the 110 patients identified, the radiologic response to HACE could be evaluated in 85 patients, 12 of whom (14%) demonstrated partial responses, 63 of whom (74%) demonstrated stable disease, and 10 of whom (12%) demonstrated progressive disease. PFS-liver rates were 31.2%, 8.2%, and 5.4% at 1, 2, and 3 years, respectively; the median PFS time was 8.2 months. OS rates were 62% at 1 year, 32% at 2 years, and 20% at 3 years; the median OS time was 17.2 months. Patients who had >5 liver metastases and received only 1 HACE treatment were found to have a shorter PFS compared with patients with fewer metastases or those who received ≥2 HACE sessions. Extensive liver involvement, the presence of extrahepatic metastases, and progression of liver disease after HACE were associated with poor OS. Use of imatinib prolonged OS time.

CONCLUSIONS. HACE produced a durable tumor response or disease stabilization in the majority of patients with GISTs metastatic to liver. Extent of liver disease, presence of extrahepatic disease, number of embolization treatments, and use of imatinib were found to have prognostic influence on PFS, OS, or both. ***Cancer* 2006;107:2833–41.** *© 2006 American Cancer Society.*

KEYWORDS: gastrointestinal stromal tumor, hepatic artery chemoembolization, survival, response.

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract but is relatively rare in the U.S.[1] The prognosis for patients with GISTs has reported to be dismal, mainly because of the propensity of the tumor to recur after complete resection of the primary tumor,[2] and, until recently, because of a lack of effective therapy for metastatic disease.[3] The liver is the most common site of metastasis from GISTs, with a reported incidence of 55% to 72% in patients with recurrence.[2,4] Metastatic liver disease is a major determinant of survival.[2] Surgical resection has been reported to benefit the survival of patients with liver metastases.[5,6] In the series by DeMatteo et al.[2] the 1-year and 3-year survival rates for patients who underwent hepatic resection of all visible

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disease were 90% and 58%, respectively. However, many patients have multifocal liver disease involving both liver lobes, and therefore partial hepatectomy is of unclear benefit.

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland), a new molecular targeted agent, has demonstrated efficacy against GISTs, with reported response rates of 48% to 69%.[7,8] Although the use of imatinib has resulted in a significant improvement in progression-free survival (PFS) and overall survival (OS), with a reported median PFS of 27 months and a median OS of 58 months for patients with metastatic GISTs,[9] complete response is rare and approximately half of the patients who initially demonstrate response develop disease progression within 2 years.[8]

Although some studies involving small numbers of cases have shown favorable results of hepatic artery chemoembolization (HACE) for patients with metastatic GIST, to our knowledge the role of HACE in the treatment of such patients remains unclear. Likewise, to our knowledge, prognostic factors for survival after HACE have never been studied in these patients. Herein we present our experience with the use of HACE for the treatment of liver-dominant metastatic GISTs at the University of Texas M. D. Anderson Cancer Center. We retrospectively evaluated rates of radiologic response, PFS, and OS, and analyzed patient, tumor, and treatment variables to elucidate factors that might influence survival rates.

MATERIALS AND METHODS

An electronic database was searched to identify patients with a pathologic diagnosis of leiomyosarcoma or GISTs metastatic to the liver who underwent HACE at the University of Texas M. D. Anderson Cancer Center between January 1993 and March 2005. The pathology reports of these patients were recently reviewed by a pathologist (S.K.) at our institution and patients with diagnoses of leiomyosarcoma originating at a site other than the gastrointestinal tract or mesentery or omentum and "true" gastrointestinal leiomyosarcoma proved by immunohistochemistry were excluded from the study. In addition to patients with immunohistochemically proven GISTs, patients from the early part of the study before the availability of KIT immunostaining who were diagnosed as having leiomyosarcomas arising within the gastrointestial tract or GIST without immunohistochemistry were also included in the study.

Patient demographics, tumor characteristics, extent of liver disease, and pattern of liver disease progression before HACE, treatment, percentage of the liver disease treated by HACE, and outcomes were obtained from the clinic notes in the electronic medical records and imaging studies. Approvals for this study and waiver of consent were obtained from the the University of Texas M. D. Anderson Institutional Review Board.

The patients included in this series were generally referred to HACE only if they were not candidates for surgical resection. Eligibility criteria for HACE included well-preserved hepatic (serum bilirubin levels <3 mg/dL) and renal (serum creatinine level <2 mg/dL) function, normal coagulation profiles, adequate hematologic function (white blood cell count >2000/mm^3 and platelet count >100,000/mm^3), and a performance status of 2 or better using ECOG. Patients with portal vein occlusion and no hepatopetal flow, massive ascites, encephalopathy, or active cardiac failure were excluded.

Antibiotics were not routinely used but were given in selected cases at the discretion of the referring oncologist. Preliminary angiograms of the celiac and superior mesenteric artery were performed to evaluate the arterial anatomy and to confirm the patency of the portal vein. Embolization of the entire liver in a single session was generally avoided; only 1 lobe or a portion of 1 lobe in patients with extensive liver involvement was subjected to embolization during each treatment session. The hepatic lobe with the greatest tumor burden was treated first. Two different techniques, both of which have been previously described, were utilized based on the preference of the interventional radiologist performing the procedure.[10–12] Cisplatin (at a dose of 100–150 mg) was dissolved in 10 to 15 mL of solution containing equal amounts of water-soluble iodinated contrast and sterile saline. In some patients the embolic agent (Gelfoam or 300–500 μm polyvinyl alcohol particles) was premixed with the cisplatin suspension and injected as a bolus in aliquots of 1 to 2 mL. In the rest of the patients, a small amount of embolic agent was initially injected into the artery until slowing of flow was noted, followed by the cisplatin mixture injected as a bolus in aliquots of 1 to 2 mL. This was followed by more particulate embolization to achieve substantial reduction of blood flow. In some patients the arterial catheter was left in place for infusion of 10 mg/m^2 of vinblastine over 2 hours, initiated only after a radionuclide study confirmed resumption of hepatic arterial flow without extrahepatic diversion. Patients remained in the hospital after the procedure, with the duration of hospitalization depending on the severity of symptoms and the laboratory results. Additional HACEs were performed with the goal of treating the entire liver. The timing of subsequent HACE procedures was determined by the patient's physical condition, biochemical

or tumor status, response to initial embolization, and ability to tolerate the procedure.

Follow-up abdominal imaging (computed tomography or magnetic resonance imaging) was generally performed 3 to 4 months after the first embolization, every 4 to 6 months for the first 2 years, and at least annually thereafter. The follow-up images were assessed by 2 radiologists (K.K. and S.G.) and compared with the baseline images to assess response according to the Response Evaluation Criteria in Solid Tumors (RECIST) and to document hepatic disease progression. OS was calculated from the date of first HACE to the date of death or to the date of last follow-up for patients who were alive at the time of last follow-up. PFS-liver was calculated from the date of first HACE to the date of disease progression in the liver, date of death, or date of last follow-up for patients without disease progression. All survival rates were calculated using the Kaplan-Meier method.

Correlations between patient, tumor, and treatment variables and survival were tested by univariate analysis using either the generalized Wilcoxon rank-sum test or the log-rank test. For continuing valuables, the univariate analysis was conducted using a Cox proportional hazards model. A Cox proportional hazards model was fitted to the variables as possible predictive factors of PFS-liver and OS. A stepwise selection process was used to determine the significant predictors of PFS-liver and OS. P values $<.05$ were considered statistically significant. SAS software (version 8; SAS Institute Inc., Cary, NC) and S-PLUS software (Math-Soft, Seattle, WA) were used for analyses.

TABLE 1
Patient Characteristics

Characteristic	No. of patients	Percent
Sex		
Female	45	41
Male	65	59
Primary tumor locations		
Stomach	41	37
Small intestine	49	44
Other*	20	18
Primary tumor resection		
Resected	102	93
Intact	8	7
Previous treatment		
No	62	56
Yes	48	44
Extent of liver involvement†		
≤50%	77	81
>50%–75%	14	15
>75%	4	4
Tumor size, cm†		
≤5	26	27
>5–10	43	45
>10	26	27
No. of liver lesions†		
1	10	11
2–5	36	38
>5	49	52
Extrahepatic metastases		
No	72	65
Yes	38	36
No. of embolizations		
1	42	38
≥2	68	62
	Mean	Range
Age, y	56.5	25–79
Duration of liver disease, mo	7.6	0–45

* "Other" included the large bowel (n = 8 patients); peritoneum, omentum, or mesentery (n = 11 patients); and esophagus (n = 1 patients).
† Unknown in 15 patients.

RESULTS

Patient Characteristics

Of a total of 134 patients identified as having undergone HACE for metastatic sarcomas during the study period, 110 patients (65 men and 45 women, aged 25–79 years) were classified as having GISTs and were included in the study. The primary tumor was located in the small intestine in 44% of patients and in the stomach in 37% of patients (Table 1). Thirty-eight patients (36%) had extrahepatic disease at the time of first HACE. The majority of patients in the current study (n = 62) were referred within a short period after the initial discovery of metastatic liver disease and did not receive any previous treatment; therefore, it is not possible to determine whether the liver disease was progressing in these patients. These patients were from the early study period before imatinib became available, when no effective systemic chemotherapy was available for patients with metastatic GISTs. The other 48 patients had been treated with various combinations of systemic chemotherapy (including imatinib in 6 patients), immunotherapy, or surgery (hepatectomy in 7 patients); all those patients had demonstrated radiologic evidence of disease progression before being referred for HACE. A total of 212 HACE procedures were performed (range, 1–7 sessions per patient). In 61 of the 95 patients in whom the extent of liver disease was measurable (64%), the entire liver disease was treated with HACE in 1 session (n = 13 patients) or multiple sessions (n = 48 patients). In the other 34 patients, only 50% to 75% of liver disease could be treated by HACE. Ten of these 34 patients underwent multiple treatment sessions and only the liver lobe with dominant disease was treated. The remaining 24 patients underwent only 1 HACE session for part of the liver dis-

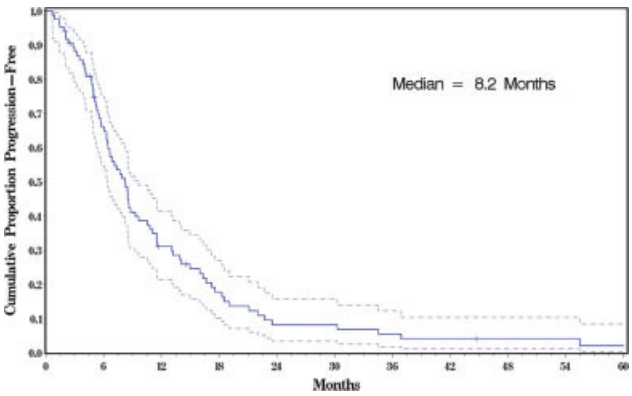

FIGURE 1. Kaplan–Meier survival curve for progression-free survival in the liver for 85 patients from the time of first hepatic artery chemoembolization (HACE) with 95% confidence intervals. The median progression-free survival time was 8.2 months.

ease, and could not undergo repeat treatments because of rapid progression of extrahepatic disease (n = 9 patients), death within 1 month after first HACE (n = 3 patients), refusal of second HACE by the patient (n = 3 patients), rapid progression of liver disease in the treated lobe (n = 3 patients), deterioration of patient's general condition (n = 4 patients), and occlusion of hepatic artery after first session (n = 2 patients).

Radiologic Response, PFS-Liver, and Prognostic Factors for PFS-Liver

Of the 85 patients for whom radiologic response could be assessed, a partial response (PR) was noted for 12 patients (14%), stable disease for 63 patients (74%), and progression of hepatic disease for 10 patients (12%). HACE resulted in PR (n = 5 patients) or disease stabilization (n = 29 patients) in 34 (71%) of the 48 patients who had been previously treated with surgery, systemic chemotherapy, or both and underwent HACE because of documented disease progression in liver.

The median PFS-liver time was 8.2 months (95% confidence interval [95% CI], 6.5–9.7 months) (Fig. 1). The number of HACE treatments and the number of liver metastases were found to be prognostic factors influencing PFS-liver in both univariate and multivariate analyses (Tables 2 and 3). Patients who underwent a single HACE procedure had a shorter median PFS-liver time compared with those who had ≥2 sessions (5.3 months vs. 9.7 months; $P = .0012$) and were 3 times more likely to experience disease progression ($P = .0001$). The median PFS-liver time was found to be shorter with an increasing number of liver metastases (22 months, 11 months, and 6 months for patients with 1, 2–5, and >5 lesions, respectively).

TABLE 2
Univariate Analysis of Progression-Free Survival-Liver

Variable	No. of patients	Median, months	95% CI	*P*
Age*	85	8.2	6.5–9.7	.7474†
Duration of liver disease*	85	8.2	6.5–9.7	.0849†
Sex				
Female	35	8.3	6.1–16.0	.3584
Male	50	8.2	6.3–8.8	
Primary tumor site				
Stomach	33	8.2	6.3–11.5	.3656‡
Small intestine	35	8.5	6.3–11.5	
Other	17	7.1	2.1–15.0	
No. of embolizations				
1	31	5.3	4.9–6.9	.0012§
≥2	54	9.7	8.3–13.2	
Embolic agent				
Gelfoam	72	8.3	6.6–9.7	.4073‡
Polyvinyl alcohol	13	6.4	4.2–16.3	
Use of vinblastine				
Yes	40	9.0	7.13–14.98	.0521‡
No	45	6.3	5.45–8.48	
Previous treatment				
No	48	6.8	5.5–10.5	.6918‡
Yes	37	8.5	6.9–11.6	
Imatinib‖				
No	74	7.9	6.3–9.3	.2918‡
Yes	11	11.1	Undefined	
No. of liver lesions				
1	9	22.0	Undefined	<.0001‡
2–5	33	11.0	7.1–14.1	
>5	43	6.3	4.8–7.4	
Tumor size, cm				
≤5	25	7.9	5.5–11.5	.9199‡
>5–10	38	7.7	5.7–10.8	
>10	22	8.9	6.3–16.3	
Extent of liver disease				
≤50%	70	8.5	11.53–21.13	.1548‡
>50%–75%	12	7.1	6.44–10.55	
>75%	3	5.3	2.33–11.57	
Extrahepatic metastases				
No	52	8.5	6.6–11.5	.2000‡
Yes	33	6.7	5.5–9.3	

95% CI indicates 95% confidence interval.
* Analyzed as a continuous variable.
† Assessed by the Wald chi-square test from a Cox proportional hazards model.
‡ Assessed by the log-rank test.
§ Assessed by the Wilcoxon rank-sum test; $P = .0942$ by the log-rank test.
‖ Given before chemoembolization in 3 patients, after chemoembolization in 6 patients, and before and after chemoembolization in 2 patients.

OS and Prognostic Factors for OS

The duration of clinical follow-up ranged from 1 to 108 months, with a median of 16.1 months. Eighteen patients were alive and 92 patients had died by the time of last follow-up. OS rates from the time of first treatment (surgery, systemic chemotherapy, or HACE) for hepatic metastatic disease were 77.1% at 1 year,

TABLE 3
Multivariate Analysis of Progression-Free Survival-Liver

Variable	Hazards ratio	95% CI	*P*
No. of embolizations			
1	2.85	1.66–4.88	.0001
≥2	1.0		
No. of liver lesions			
1	0.08	0.03–0.23	<.0001
2–5	0.42	0.25–0.69	.0006
>5	1.0		

95% CI indicates 95% confidence interval.

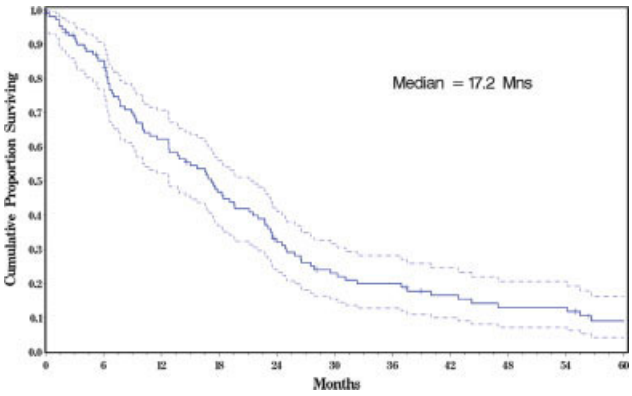

FIGURE 2. Kaplan–Meier survival curve for overall survival in all 110 patients from the time of first hepatic artery chemoembolization (HACE) with 95% confidence intervals. The median overall survival time was 17.2 months.

41.6% at 2 years, and 12.5% at 5 years with a median OS of 23.1 months (95% CI, 18.4–25.0 months). OS rates from the time of initial HACE were 62% at 1 year, 32% at 2 years, and 21% at 3 years, with a median OS time of 17.2 months (95% CI, 12.8–21.5 months) (Fig. 2). Univariate analysis identified the number of HACE procedures, presence of extrahepatic disease, extent of liver involvement, number of liver metastases, use of imatinib, and response to HACE to be factors that influenced OS (Table 4). Patients who had a single HACE treatment had a significantly shorter median OS compared with those who had ≥2 such treatments (median OS of 8.2 months vs. 22.0 months; $P = .0001$). All of these factors, except for number of embolization sessions, were also found to be significant on multivariate analysis (Table 5). Patients with extrahepatic disease had nearly 6 times the risk of death than those without ($P < .0001$). Patients with >50% but ≤75% liver involvement were at twice the risk of death of those with ≤50% liver involvement ($P = .07$), and those with >75% liver involvement were at 7 times the risk of

TABLE 4
Univariate Analysis of Overall Survival

Variable	No.	Median, months	95% CI	*P*
Age*	110	17.2	12.8–21.5	.1874[†]
Duration of liver disease*	110	17.2	12.8–21.5	.7847[†]
Sex				
Female	45	17.6	8.2–22.8	.5304[‡]
Male	65	16.6	12.8–23.5	
Primary tumor site				
Stomach	41	18.3	10.2–23.4	.6584[‡]
Small intestine	49	17.2	13.6–23.1	
Other	20	16.9	7.7–24.5	
No. of embolizations				
1	42	8.2	6.3–15.0	.0001 [§,‖]
≥2	68	22.0	17.2–24.5	
Embolic agent				
Gelfoam	96	17.4	12.8–21.5	.4022[‡]
Polyvinyl alcohol	14	7.7	4.9–56.6	
Use of vinblastine				
Yes	52	19.6	13.86–24.54	.3010[‡]
No	58	14.5	8.21–19.09	
Previous treatment				
No	62	21.1	13.7–25.0	.0803[§]
Yes	48	16.7	10.0–18.3	
Imatinib[¶]				
No	97	15.7	16.9–26.5	.0021[‡]
Yes	13	42.8	Undefined	
No. of liver lesions				
1	10	22.8	Undefined	<.0001[‡]
2–5	36	23.5	17.4–30.3	
>5	49	8.9	6.6–12.8	
Tumor size, cm				
≤5	26	18.8	13.7–24.0	.8460[‡]
>5–10	43	13.9	10.1–21.5	
>10	26	14.7	7.6–26.5	
Extent of liver disease				
≤50%	77	17.6	12.8–21.5	.0008[‡]
>50%–75%	14	16.7	4.90–24.87	
>75%	4	3.8	1.02–11.57	
Extrahepatic metastases				
No	72	22.8	15.7–25.9	<.0001[‡]
Yes	38	12.1	6.6–16.7	
RECIST response				
PR+SD	75	19.58	15.7–24.0	.0001[‡]
PD	10	8.31	3.1–12.8	

95% CI indicates 95% confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease.

* Assessed as a continuous variable.

[†] Assessed by the Wald chi-square test.[‡] Assessed by the log-rank test.

[§] Assessed by the Wilcoxon rank-sum test.

[‖] $P = .0223$ by the log-rank test.

[¶] Given before chemoembolization in 4 patients, after in chemoembolization in 7 patients, and before and after chemoembolization in 2 patients.

TABLE 5
Multivariate Analysis of Overall Survival

Variable	Hazards ratio	95% CI	*P*
Imatinib			
No	1.0		
Yes	0.126	0.041–0.390	.0003
No. of liver lesions			
1	0.279	0.098–0.797	.0172
2–5	0.616	0.346–1.097	.0997
>5	1.0		
Extent of liver disease			
≤50%	1.0		
>50%–75%	1.963	0.938–4.106	.0733
>75%	7.097	1.957–25.741	.0029
Extrahepatic metastases			
No	1.0		
Yes	5.619	2.758–11.448	<.0001
RECIST response			
PR+SD	1.0		
PD	8.403	3.373–20.935	<.0001

95% CI indicates 95% confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease.

those with ≤50% liver involvement ($P = .003$). Patients with 1 liver lesion had a lower risk of mortality than those with multiple lesions. Patients who were treated with imatinib had a superior median OS compared with those who had not been treated with imatinib (hazards ratio, 0.126; $P = .0003$). Patients who demonstrated a PR or stable disease after HACE were found to have a longer OS than did those who demonstrated progression of liver disease after HACE ($P < .0001$).

Adverse Effects

Most patients developed postembolization syndrome, which included abdominal pain, fever, nausea, and vomiting. In most cases, these symptoms were effectively managed with supportive measures. Moderate to severe adverse events occurred after 25 of the 212 HACE procedures (12%). Two patients died within 1 month after HACE and a third patient died 31 days after HACE; the causes of death were a cardiac event on Day 1, respiratory failure on Day 12, and acute respiratory distress syndrome on Day 31 after HACE, respectively. Pulmonary embolism, sepsis, severe chest pain, and hyponatremia-induced seizure occurred in 1 patient each; all of those patients recovered with medical management. Cholecystitis occurred in 2 patients, 1 of whom required a cholecystectomy. Other complications included transfusion-dependent anemia (11 patients), thrombocytopenia (1 patient), neutropenia requiring injections of granulocyte–colony-stimulating factor (3 patients), ascites (2 patients), oral candidiasis (1 patient), pleural effusion requiring thoracentesis or catheter drainage (2 patients), anasarca that necessitated diuretics and an albumin infusion (1 patient), and intratumoral hemorrhage requiring red blood cell transfusion (1 patient).

DISCUSSION

Reports on the use of HACE for the treatment of patients with metastases to the liver are scarce.[11–14] To our knowledge, the current study is the largest single-center series published to date. The radiologic response rate of 14% in our study is lower than the 70% response rate reported by Mavligit et al.[12] The cause of this discrepancy could be related to differences in patient and tumor variables, tumor response assessment criteria, and frequency of HACE sessions. In a more recent study, Rajan et al.[14] reported a response rate of 13% in their experience with HACE in 16 patients with metastatic sarcomas, including 11 GISTs. It is encouraging that a significant number of patients (71%) with documented progression of liver disease before HACE demonstrated radiologic response or disease stabilization after HACE.

One of limitations of conventional response criteria based on changes in size is the lack of a way of assessing biologic changes that reflect response to anticancer therapy.[15,16] HACE can cause substantial tumor necrosis with liquefaction without significant tumor shrinkage.[17] We observed decreases in tumor density, reflecting necrosis, without changes in tumor size in many of our patients after HACE; these cases were classified as "stable disease." Considering these observations, we speculate that our results are underestimates of the true efficacy of this treatment. Refinements to standard response criteria, such as tumor glucose metabolism by positron emission tomography (PET) are awaited. Because most of our patients are from a time period before PET became available, PET was only used in some recent patients.

Because liver metastases are an important determinant of survival for patients with metastatic GIST, time to disease progression in the liver is a critical factor in determining the efficacy of HACE. Our median PFS-liver time of 8.2 months compares favorably with the median PFS of 1–4 months reported with the use of systemic chemotherapy.[3,18] Durable response after HACE was also reported by Rajan et al.[14] and Mavligit et al.,[12] with median PFS-liver times of 8 months and 10 months, respectively. Although it would have been interesting to calculate time to treatment failure as a measure of the potential impact of HACE, lack of standardized treatment regimen and follow-up imaging in this retrospective study precluded us from doing so.

The true efficacy of HACE for improving OS is difficult to determine because of the concomitant use of other therapies, including imatinib, after disease progression in some of our patients. However, our median OS of 17.2 months from initial HACE is encouraging, and a similar OS of 13 months was reported by Rajan et al.[14] The beneficial effect of HACE for such patients is also suggested by the fact that those patients who demonstrated radiologic evidence of response or stabilization of liver disease after HACE had a survival benefit relative to those in whom the liver disease progressed despite HACE.

It is important to identify factors affecting PFS-liver and OS to allow the identification of patients who would benefit the most from this treatment. Several disease-related and treatment-related variables were found to influence the PFS-liver and OS after HACE. Patients who were able to undergo $\geq$2 HACE procedures had longer PFS-liver and OS, although the difference in OS was not statistically significant in multivariate analysis. Repeated HACE sessions have been reported to be associated with a survival benefit for patients with other malignancies.[19,20] It is not surprising that a single HACE was associated with a shorter survival because in the majority of these patients, an unfavorable clinical course (rapid progression of hepatic or extrahepatic disease, deterioration of liver function or performance status, death within a month) after the first HACE prevented these patients from undergoing additional sessions. As expected, patients with more extensive liver disease had a poor prognosis after HACE. The percentage of liver involvement has been reported to be an important prognostic factor for patients with colorectal and neuroendocrine tumors metastatic to the liver treated with HACE.[20,21] In fact, the median OS after HACE for patients with >75% involvement of the liver in our study was a dismal 3.8 months. Because most patients with >75% of the liver involved have potentially limited functional liver reserve, patients in this category may not derive any benefit from HACE.

In our retrospective analysis, 12% of the HACE procedures led to moderate to severe complications. However, many of these complications, including anemia, ascites, candidiasis, pleural effusion, albumin/furosemide infusion-dependent anasarca, and intratumoral hemorrhage are common in patients with GIST at any point in the disease process, even if they do not undergo HACE. Therefore, the true rate of complications from HACE could be much lower than 12%. Although it is most likely due to systemic absorption of cisplatin, the cause of anemia can be multifactorial: low B_{12} and folate from prior gastrectomy, low iron from gastrointestinal bleed, or anemia from chronic disease.

In the current study, the median OS time of patients who were treated with imatinib either before or after HACE was significantly longer than that of patients who did not receive imatinib (42.8 months vs. 15.7 months). At the University of Texas M. D. Anderson Cancer Center, since imatinib came into clinical use, the initial treatment for most patients with unresectable liver metastases from GIST has been imatinib. However, HACE remains a safe and effective palliative treatment for liver metastases in patients with imatinib-resistant GIST. Van Glabbeke et al.[22] reported that 12% of 934 patients with metastatic GIST were resistant to imatinib without any response and 37% progressed after initial response with a median follow-up of 25 months. Sunitinib, a newly approved multitargeted tyrosine kinase inhibitor, can be used in imatinib-resistant GIST; however, HACE offers response rates and survival benefits that appear to be comparable or superior to sunitinib for such patients.[23,24]

The current study had several limitations, largely due to its retrospective nature. The lack of a strict imaging protocol for monitoring response may have affected the response rate and PFS duration. Variations in the HACE technique, including selection of the embolic agent, and variations in the frequency of HACE may also have affected the response rate and PFS-liver. Chemoembolization has been generally defined as embolization combined with the intra-arterial administration of chemotherapy, and to our knowledge there is no consensus regarding the best chemoembolization protocol. One of the most common techniques, routinely used for hepatocellular carcinomas, involves the injection of chemotherapeutic agents emulsified with lipiodol followed by embolization with particulate agents.[25] Although some investigators also have used the same technique for metastatic liver disease,[25,26] other investigators prefer the nonoily chemoembolization for metastatic liver disease, similar to the techniques described in the current study.[10–12,27,28] Another criticism of the current study is the fact that many of our patients were from a time before KIT immunostaining came into routine use for confirming the diagnosis of GIST, and hence it is possible that a small number of our patients may have had true gastrointestinal leiomyosarcoma. A number of recent studies in which immunohistochemistry was performed on retrieved tissues in patients with an original diagnosis of leiomyosarcomas of gastrointestinal origin demonstrated that most of these tumors (90%–95%) were actually GISTs and that true leiomyosarcomas of gastrointestinal origin were rare, with most of these tumors arising from the retroperitoneum and pelvis.[29–31] Similar to the current study, a number of previous studies have

also classified leiomyosarcomas of gastrointestinal origin as GISTs without resorting to immunohistochemistry.[5,32,33] In fact, most people believe that because the majority of mesenchymal tumors of gastrointestinal origin are GISTs, older clinical and pathologic series that do not separate GISTs and leiomyosarcomas of gastrointestinal origin largely reflect GIST data.[29–31]

However, despite the shortcomings of the current study, some conclusions can still be drawn with regard to the efficacy of HACE for patients with metastatic GIST. Our findings suggest that HACE is a safe and effective treatment option for patients with metastatic GIST involving the liver for whom conventional systemic therapy has failed. Multiple HACE procedures and the use of imatinib can result in superior PFS-liver and OS, whereas a large burden of liver disease and the presence of extrahepatic disease can adversely influence PFS-liver and OS after HACE.

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