

Results of a Single-Center Experience With Resection and Ablation for Sarcoma Metastatic to the Liver

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Hypothesis: A subset of patients with sarcoma liver metastasis may benefit from hepatic resection and/or ablation.

Design: Retrospective review of prospectively collected cancer center database records.

Patients and Methods: Sixty-six patients who underwent hepatic resection and/or open radiofrequency ablation of metastatic sarcoma between July 1, 1996, and April 30, 2005, were identified from the database. Clinicopathologic, operative, recurrence, and long-term survival data were analyzed.

Results: The primary sarcoma site was the abdomen or retroperitoneum (n=22), stomach (n=18), small or large bowel (n=17), pelvis (n=4), uterus (n=3), or other (n=2). Tumor pathologic types included gastrointestinal stromal tumor (n=36), leiomyosarcoma (n=18), and sarcoma not otherwise classified (n=12). Thirty-five patients underwent resection, 18 underwent resection plus

radiofrequency ablation, and 13 underwent radiofrequency ablation only. With a median follow-up of 35.8 months, 44 patients (66.7%) had recurrence (intrahepatic only, n=16; extrahepatic only, n=11; both, n=17). Treatment with radiofrequency ablation (either alone or combined with resection) ($P=.002$) and lack of adjuvant chemotherapy ($P=.01$) predicted shorter disease-free survival. The 1-, 3-, and 5-year overall survival rates were 91.2%, 65.4%, and 27.1%, respectively. Patients with gastrointestinal stromal tumor who were treated with adjuvant imatinib mesylate had the longest median survival (not reached) ($P=.003$).

Conclusions: Long-term survival can be achieved following surgical treatment of sarcoma liver metastasis, especially in patients with gastrointestinal stromal tumor. Patients with sarcoma liver metastasis should be evaluated by a multidisciplinary team, as recurrence is common and adjuvant therapy may prolong survival.

Arch Surg. 2006;141:537-544

RESECTION OF LIVER METASTASES arising from neuroendocrine or colorectal carcinoma is a well-established and effective treatment modality with reported 5-year survival rates of 30% to 76% in patients with liver-only disease.¹⁻⁹ In contrast, the role of hepatic surgery for sarcoma metastasis to the liver remains ill defined. Most studies on hepatectomy for sarcoma metastasis are limited by small patient numbers,¹⁰⁻¹⁷ inclusion of patients with other noncolorectal metastatic carcinomas,¹⁸⁻²⁰ or short median follow-up.¹⁹ In addition, few studies^{21,22} have investigated the role of radiofrequency ablation (RFA) either alone or in combination with resection for sarcoma liver metastasis. As such, the prognosis of patients with metastatic sarcoma treated surgically remains uncertain.

Unlike extremity and trunk soft tissue sarcomas, metastasis to the liver from primary visceral and retroperitoneal sarcomas is common. In fact, 20% to 60% of pa-

tients with visceral or retroperitoneal sarcomas will develop hepatic metastases.²³⁻²⁶ Unfortunately, metastatic sarcoma to the liver is generally not sensitive to chemotherapy or chemoembolization,²⁷⁻²⁹ and the median survival from the time of diagnosis of liver metastases is only 14 months.²⁴ Therefore, surgery remains the only treatment option that provides the possibility of cure for these patients.

Because the prognosis of patients with sarcoma metastasis to the liver is not well defined, the objective of the current study was to assess the efficacy of surgery—including resection and/or RFA—in a large cohort of patients with metastatic liver sarcoma at a single institution. Additionally, we sought to determine which clinicopathologic factors were associated with disease-free and overall survival. Identification of prognostic factors could help to identify subsets of patients with sarcoma liver metastasis who may potentially benefit from hepatic resection and/or RFA.

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Table 1. Clinical and Pathologic Features of 66 Patients

Variable	Value*
Age, median, y	54
Sex	
Female	33 (50.0)
Male	33 (50.0)
Status of metastatic disease	
Primary	55 (83.3)
Recurrent	11 (16.7)
Primary tumor site	
Abdomen or retroperitoneum	22 (33.3)
Stomach	18 (27.3)
Small or large bowel	17 (25.8)
Pelvis	4 (6.1)
Uterus	3 (4.5)
Other	2 (3.0)
Primary tumor pathologic type	
Gastrointestinal stromal tumor	36 (54.5)
Leiomyosarcoma	18 (27.3)
Sarcoma not otherwise classified	12 (18.2)
Tumors, median, No.	3
>3 Metastases	43 (65.1)
Largest tumor size, median, cm	3.9
Tumor >3 cm	32 (48.5)
Tumor location	
Unilobar	31 (47.0)
Bilobar	35 (53.0)

*Values are expressed as patients, number (percentage), unless indicated otherwise.

METHODS

Between July 1, 1996, and April 30, 2005, 66 patients with sarcoma metastatic to the liver underwent surgical treatment (resection, RFA, or a combination of both modalities) at The University of Texas M. D. Anderson Cancer Center, Houston. Only patients with histologically confirmed sarcoma metastases treated with curative intent were included in the current study. Patients were evaluated with a baseline history and physical examination, serum laboratory tests, computed tomography or magnetic resonance imaging of the abdomen and pelvis, and chest radiography.

Following surgery, all of the patients were regularly followed up and prospectively monitored for recurrence with computed tomography or magnetic resonance imaging of the abdomen as well as chest radiography every 3 to 4 months up to 2 years and then every 6 months thereafter.

SURGICAL RESECTION

At the time of laparotomy, intraoperative hepatic ultrasonography was performed to identify, count, and characterize the nature and vascular proximity of the metastatic lesions. The location of the metastases and their relationship to surrounding vascular and biliary structures dictated whether a formal anatomic resection was performed. In general, the extent of surgery was determined by the estimated hepatic functional reserve, which was assessed by a combination of preoperative liver biochemistry, the distribution of the metastatic lesions within the liver, and the predicted remnant liver volume after resection. Resection was classified as less than a hemihepatectomy (eg, segmentectomy or subsegmentectomy), hemihepatectomy, or extended hepatectomy (≥5 liver segments).³⁰

Radiofrequency ablation of hepatic lesions was performed at the time of laparotomy according to a previously described standardized treatment algorithm.³¹⁻³³ Intraoperative ultrasonography was used to place the RF needle into the lesions to be treated by RFA. Radiofrequency ablation was administered using the RF 2000 or 3000 generator system (Boston Scientific Co, Natick, Mass), a LeVein monopolar needle electrode (4.0-cm maximum array diameter), and 4 dispersive grounding pads applied to the patient's skin. The LeVein needle electrode is a 15-gauge, 12- to 15-cm insulated cannula that contains 10 to 12 individual hook-shaped electrode arms that are deployed in situ. For tumors smaller than 2.5 cm in diameter, the multiple array was deployed into the center of the tumor. For larger lesions, the array was first deployed at the most posterior interface ultrasonographically between the tumor and normal liver parenchyma and subsequently withdrawn and redeployed at 1.5-cm intervals in the tumor. Each tumor or area within a large tumor was treated with a 1-phase application of RF power before retracting the multiple array and repositioning or removing the needle electrode. The electrode was optimally positioned to achieve complete destruction of the tumor and at least a 1-cm zone of normal liver parenchyma when possible.

DATA COLLECTION

The following data were collected for each patient: demographics; tumor pathologic type, number, and size; operative and complication details; chemotherapy details; disease status; date and site of recurrence; date of and status at last follow-up; and date of death. Gastrointestinal stromal tumors (GISTs) and tumors designated as gastrointestinal leiomyosarcoma tumors before 1993 were grouped together.³⁴ For the purposes of data analyses, the data were recorded as follows: clinical features as present or absent; tumor size as smaller than or equal to 3 cm vs larger than 3 cm; tumor location as unilobar vs bilobar; and number of lesions resected or ablated. Tumor size and number were defined by the resection specimen and/or by intraoperative ultrasonographic measurement. Data on recurrence were categorized as intrahepatic only, distant only, or both intrahepatic and distant.

STATISTICAL ANALYSES

All of the data are presented as percentages of patients or the median value with ranges. The χ^2 test was used to assess differences in variables. Recurrence and survival were measured from the date of metastectomy. Actuarial survival curves were constructed according to the Kaplan-Meier method, and the log-rank test was used to assess the association of clinicopathologic and treatment variables with recurrence and survival. Statistical significance was set at $P < .05$.

RESULTS

CLINICOPATHOLOGIC CHARACTERISTICS

Table 1 shows the clinicopathologic features of the 66 patients in the study. The median patient age was 54 years (range, 21-78 years). The median number of treated lesions was 3 (range, 1-20 treated lesions), and the median size of the largest lesion was 3.9 cm (range, 1.2-16.0 cm). Most patients (n=35 [53.0%]) had bilobar disease. Surgery was performed for initial metastatic disease in 55 patients (83.3%) and for recurrent disease in 11 patients

Table 2. Details of Surgical Treatment

	Patients, No. (%)
Type of surgical treatment (n = 66)	
Resection only	35 (53.0)
RFA only	13 (19.7)
RFA plus resection	18 (27.3)
Type of surgical resection (n = 53)	
Wedge	15 (28.3)
Segmentectomy	16 (30.2)
Hemihepatectomy	18 (34.0)
Extended hepatectomy	4 (7.5)

Abbreviation: RFA, radiofrequency ablation.

(16.7%). The primary sarcoma site was abdomen or retroperitoneum (n=22 [33.3%]), stomach (n=18 [27.3%]), small or large bowel (n=17 [25.8%]), pelvis (n=4 [6.1%]), uterus (n=3 [4.5%]), or other (n=2 [3.0%]). Tumor pathologic types included GIST (n=36 [54.5%]), leiomyosarcoma (n=18 [27.3%]), and sarcoma not otherwise classified (n=12 [18.2%]).

At the time of the operation, surgical treatment was resection alone in 35 patients (53.0%), RFA alone for tumors in unresectable locations in 13 patients (19.7%), and resection of large or dominant lesions combined with RFA of smaller lesions (an approach used in patients otherwise considered unresectable) in 18 patients (27.3%) (**Table 2**). Of the 53 patients who had a surgical resection, most of them (n=38 [71.7%]) had an anatomic resection and a minority (n=15 [28.3%]) had a nonanatomic resection. Specifically, the extent of hepatic resection was a wedge resection in 15 patients (28.3%), a segmentectomy in 16 (30.2%), a hemihepatectomy in 18 (34.0%), and an extended hepatectomy in 4 (7.5%).

On final pathologic analysis of the 53 patients who had a resection, no patient had a positive margin; the margin status was negative by 1.0 to 9.0 mm in 22 patients (41.5%) and at least 1.0 cm in 30 (56.6%). Data on margin status were unavailable in 1 patient (1.9%). Patients with fewer than 3 tumors (78.6%) were more likely to have at least a 1.0-cm surgical margin than patients who had more than 3 tumors (48.4%) ($P=.04$). Tumor size and the extent of surgical resection did not predict margin status ($P=.46$). Patients who underwent less than a hemihepatectomy were more likely to be treated with RFA (54.2%) compared with patients who had a more extensive resection (22.7%) ($P=.03$).

The perioperative complication rate was 15.2%. The median length of stay was 7 days (range, 2-22 days). Three patients died within 90 days of treatment, for a perioperative mortality rate of 4.5%.

The majority (n=52 [78.8%]) of patients received some form of chemotherapy, with most patients receiving both preoperative and postoperative therapy. Specifically, 38 patients (57.6%) received preoperative chemotherapy prior to surgical treatment of the hepatic sarcoma metastases. The type of preoperative chemotherapy that was administered varied considerably. Most patients received either imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, NJ) (n=15 [39.5%]) or adriamycin-based

Table 3. Sites of Recurrence After Hepatic Resection in 44 Patients

Location	Patients, No. (%)
Liver	33 (50.0)
Lung	15 (34.1)
Local recurrence at primary tumor site	9 (20.5)
Peritoneum	3 (6.8)
Bone	2 (4.5)

therapy (n=14 [36.8%]); 2 patients received adriamycin alone and 12 received adriamycin in combination with another agent [ifosfamide, n=9; dacarbazine, n=2; or 5-fluorouracil and gemcitabine hydrochloride, n=1]. One patient received gemcitabine hydrochloride alone whereas 2 received gemcitabine hydrochloride plus taxotere. Other preoperative therapies included the monoclonal α -v/ β -3 antibody vitaxin (n=2) and temozolomide (n=1). Three patients underwent preoperative chemoembolization with cisplatin. Of the 38 patients who received preoperative chemotherapy, 27 (71.1%) also received postoperative treatment. Of the 28 patients (42.4%) who did not receive preoperative chemotherapy, 14 (50.0%) received postoperative treatment. Postoperative regimens used to treat these 14 patients also varied considerably; they included imatinib mesylate (n=11 [78.6%]), adriamycin plus taxotere (n=1 [7.1%]), gemcitabine hydrochloride plus taxotere (n=1 [7.1%]), and cisplatin (n=1 [7.1%]). In total, of the 36 patients with GIST, 26 received imatinib mesylate and 10 did not.

PATTERNS OF RECURRENCE

With a median follow-up of 35.8 months, 44 (66.7%) of 66 patients had developed recurrent disease: 16 patients (24.2%) with intrahepatic-only disease, 11 (16.7%) with distant-only disease, and 17 (25.8%) with a combination of intrahepatic and distant metastases. The median time to development of recurrence was 13.5 months (range, 1.2-59.1 months). The most common site of distant metastatic failure was the lung (15 [53.6%] of 28 patients with distant disease) (**Table 3**).

Statistical analyses revealed that a history of RFA was associated with risk of recurrence. Patients who were treated with RFA only (11 [84.6%] of 13 patients) or resection plus RFA (16 [88.9%] of 18 patients) were more likely to have recurrence compared with patients who underwent resection alone (20 [57.1%] of 35 patients) (each $P<.05$). In those patients who did have recurrence, however, the pattern of recurrence did not differ based on the surgical method of treatment (31.3% of patients who underwent resection alone and had liver-only recurrence vs 37.1% of patients who underwent RFA with or without resection and had liver-only recurrence; $P=.76$). Other factors, including type of surgical resection, primary tumor pathologic type, primary tumor site, initial vs recurrent metastatic disease, number of tumors treated, number of lesions ablated, pathologic margin status, tumor number, and tumor size, did not affect the chance of overall recurrence (all $P>.05$).

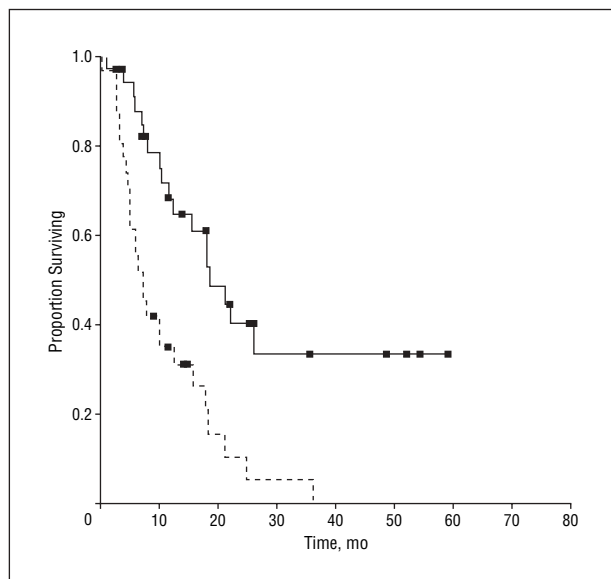


Figure 1. Effect of treatment on disease-specific survival. Patients with liver metastases from sarcoma who were treated with resection alone (solid line) had significantly longer disease-free survival than patients who underwent radiofrequency ablation either with or without resection (dashed line).

In addition to overall recurrence, analyses were performed to determine which factors, if any, were associated with an increased risk of intrahepatic recurrence. No examined factor was specifically associated with an increased risk of local recurrence ($P = .65$).

DISEASE-FREE SURVIVAL

The 1-, 3-, and 5-year actuarial disease-free survival rates were 52.1%, 20.6%, and 16.4%, respectively. On univariate analysis, a number of factors were associated with a decrease in disease-free survival, including lack of adjuvant chemotherapy and treatment with RFA. Specifically, in the entire study population, a history of chemotherapy—either preoperative or postoperative—was associated with an improved disease-free survival (22.7 months with no chemotherapy vs 36.3 months with chemotherapy; $P = .01$). However, when disease-free survival was stratified by tumor pathologic type (GIST vs non-GIST), history of chemotherapy—specifically treatment with imatinib mesylate—was only associated with an improved disease-free survival in patients with GIST ($P = .03$).

Patients who were treated with RFA either alone or as a combined modality with resection also had a shorter disease-free interval (7.4 months) than patients who underwent resection alone (18.6 months) ($P = .002$) (**Figure 1**). All of the other examined factors were not associated with disease-free survival (all $P > .05$).

OVERALL SURVIVAL

The median overall survival was 47.2 months, and the 1-, 3-, and 5-year actuarial overall survival rates were 91.2%, 65.4%, and 27.1%, respectively (**Figure 2**). Univariate analyses revealed several factors that were associated with overall survival. Patients with sarcoma me-

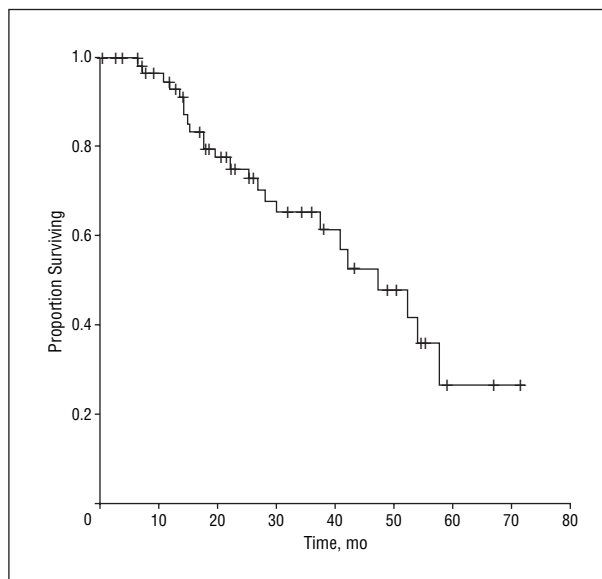


Figure 2. Overall survival in patients with liver metastases from sarcoma in the entire population (resection only, radiofrequency ablation only, and resection plus radiofrequency ablation). The median overall survival was 47.2 months.

tastasis smaller than or equal to 3 cm tended to have a longer overall survival (not reached) than patients with larger metastasis (overall survival, 42.1 months) ($P = .11$). Similarly, patients who were treated with resection alone tended to have a better overall survival (54.0 months) compared with patients who underwent RFA (either alone or in combination with hepatic resection) (overall survival, 33.2 months) ($P = .19$).

Sex, age, tumor distribution (unilateral vs bilateral), number of metastases, and width of surgical margin did not predict survival (all $P > .05$). Whether surgery was for recurrent disease or for initial metastatic disease also did not influence survival. In general, patients who were treated with chemotherapy had a longer median overall survival (51.8 months) than patients who underwent surgery alone (median overall survival, 18.4 months) ($P = .02$). More specifically, patients with GIST who were also treated with imatinib mesylate had a significantly longer median survival (not reached) compared with all of the other patients (median survival, 37.1 months) ($P = .003$) (**Figure 3**).

COMMENT

Although the role of metastectomy in patients with pulmonary metastases from sarcoma is well reported and accepted,^{35,36} the role of metastectomy for sarcoma metastatic to the liver remains poorly defined. Only a few institutions have described large series^{17,25} of patients who have undergone hepatic resection for sarcoma metastatic to the liver. To our knowledge, however, the current study is the first to examine the prognosis and outcome of patients with hepatic sarcoma metastases who were treated with hepatic resection, RFA, or a combination of both modalities. Unlike previous studies, the current study also specifically examines the impact of chemotherapy—in particular, imatinib mesylate—on the

prognosis of patients with sarcoma liver metastasis. As such, we are able not only to evaluate the feasibility and safety of each treatment strategy but also to more directly assess the effect of chemotherapy on disease-specific survival.

Previous studies on hepatic resection for sarcoma metastases either have been anecdotal^{11,15,16,37} or have failed to find many prognostic factors that were predictive of survival.²⁵ Similar to the findings of the current study, DeMatteo et al²⁵ found that clinicopathologic characteristics such as sex, age at hepatectomy, tumor number, and margin status were not prognostic of disease-specific survival. Whether the hepatectomy was being performed for recurrent disease or initial metastatic disease also did not influence survival in either study.

In the study by DeMatteo et al,²⁵ history of complete surgical resection was one of the only significant prognostic factors that predicted a better disease-specific survival. In that study, survival was also predicted by the extent of hepatectomy, with those patients who had a major liver resection having a longer median survival than patients who had lesser resections.³⁸ In the current study, every patient underwent a complete resection. Although the extent of the surgical resection did not influence survival, history of RFA (either alone or in combination with resection) was associated with a significantly decreased disease-free survival and a trend toward decreased overall survival. Radiofrequency ablation has become a widely used ablative technique to provide treatment for patients who are not candidates for hepatic resection.^{21,39-41} Although RFA has been mostly used as an isolated, alternative therapy, it can be combined with hepatic resection.³² By combining RFA with resection, more patients may become candidates for surgical treatment, as the surgeon can resect larger tumors while ablating residual smaller lesions. In the current study, RFA was used alone in patients who had lesions that were in unfavorable locations or who were judged to be unable to tolerate a major parenchymal resection. Those patients who were treated with RFA alone (84.6%) or in combination with surgical resection (88.9%) had a significantly higher rate of recurrence (90.9%) compared with patients who underwent resection alone (57.1%) (both $P < .05$). Although direct comparisons between patients who undergo resection alone, RFA alone, and a combination of RFA and resection are difficult, these results imply that patients who harbor disease that cannot be adequately treated with resection alone are at an increased risk of recurrence.

Interestingly, unlike previous studies²⁵ that did not specifically analyze the effect of chemotherapy, we found that patients with GIST who had received imatinib mesylate had the longest median survival. Because of the traditionally poor results with surgery alone, chemotherapy has been used in an attempt to extend survival in patients with metastatic sarcoma.^{27,28,38} Prior to the landmark discovery of the *c-kit* proto-oncogene,⁴² the clinical approach to metastatic sarcoma—regardless of histologic subtype—generally included a variety of chemotherapeutic agents, including dacarbazine, mitomycin C, adriamycin, ifosfamide, and cisplatin.^{25,43,44} This is reflected in the current study, as patients with GIST

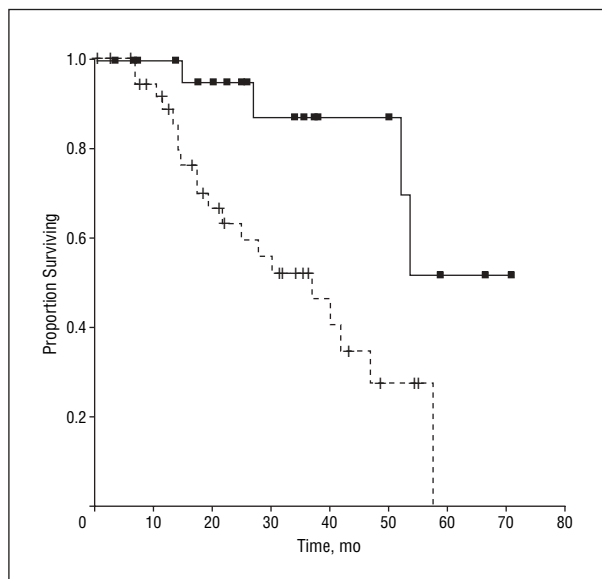


Figure 3. Relationship of tumor pathologic type and imatinib mesylate therapy to survival in patients with liver metastases from sarcoma. Patients with gastrointestinal stromal tumors who were treated with imatinib mesylate (solid line) had better overall survival compared with all of the other patients regardless of histologic subtype or chemotherapy treatment (dashed line).

represented a sequential cohort whereby patients treated at the beginning of the study were more likely to receive non-imatinib mesylate therapy compared with those treated more recently. Unfortunately, the overall response rates to these chemotherapy agents were usually less than 10% to 15%, with partial response rates of 0% to 10%.⁴³⁻⁴⁵ Lang et al¹⁷ found that the long-term outcome after liver resection for hepatic metastases from leiomyosarcoma was superior to those after chemotherapy and chemoembolization. Our data appear to corroborate the previous findings that conventional chemotherapy has a limited therapeutic role in patients with liver metastasis from non-GIST sarcomas. In the current study, chemotherapy did not predict disease-specific survival in patients with non-GIST sarcoma. Specifically, patients with non-GIST sarcoma who were treated with chemotherapy had a similar disease-free survival compared with patients who did not receive chemotherapy. These data need to be interpreted with caution, however, as the number of patients with non-GIST sarcomas ($n=30$) was small. Therefore, the study may have lacked the statistical power to identify a clinical effect of chemotherapy if one in fact did exist.

Conventional chemotherapy had been traditionally unsuccessful in the treatment of metastatic GIST disease.⁴⁶ However, in 1998, Hirota et al⁴² discovered gain-of-function mutations in exon 11 of the *c-kit* proto-oncogene. The cell-surface transmembrane receptor *c-kit* that has tyrosine kinase activity and is the protein product of the *c-kit* proto-oncogene is expressed by most GIST tumors.⁴⁷ The constitutively activated *c-kit* receptor tyrosine kinase stimulates the proliferation and enhances the survival of neoplastic GIST tumor cells.⁴⁷ These findings led to the application of imatinib mesylate—an orally bioactive tyrosine kinase inhibitor—as targeted therapy for GIST. Prior to imatinib mesylate, the me-

dian survival was reported to be 19 months in patients with metastatic GIST and only 12 months in patients who also had local recurrences.²⁵ The introduction of imatinib mesylate–targeted therapy for GIST has, however, substantially impacted the clinical treatment and prognosis of metastatic GIST.^{46,47} Phase I and II studies of imatinib mesylate for the treatment of metastatic GIST demonstrated objective response rates that approached 70% with minimal associated toxicity. Although initial reports noted a durable response for imatinib mesylate,⁴⁷ it has subsequently become evident that with extended follow-up, tumor recurrence or progression can occur despite an initial response to imatinib mesylate therapy.^{46,48,49} For this reason, surgical resection should remain the mainstay of treatment for GIST liver metastasis. In the current study, patients with GIST who were resected and treated with imatinib mesylate had the longest disease-free and overall survival. These data serve to emphasize that resection of liver metastasis in patients with GIST should be considered in the era of targeted imatinib mesylate therapy, as this cohort of patients appears to have a particularly favorable prognosis. Results of future trials such as the Radiation Therapy Oncology Group S-0132 trial will help to further elucidate the role of imatinib mesylate as adjuvant therapy in patients with potentially resectable metastatic GIST.

Selection of appropriate patients for hepatic resection of metastatic sarcoma must be individualized and must include an extensive evaluation of the extent of the disease. Metastatic GIST and non-GIST sarcomas have important clinical differences that should be considered at the time of treatment. Although the majority of patients have recurrence, resection of metastatic sarcoma to the liver may improve disease-free and overall survival in selected patients. We currently recommend that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection. Resection, however, should be performed as part of a multidisciplinary approach in conjunction with systemic therapy, as this may result in prolonged survival for patients, especially in those patients with GIST who can be offered targeted therapy with imatinib mesylate.

Accepted for Publication: January 28, 2006.

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Previous Presentation: This paper was presented at the 113th Scientific Session of the Western Surgical Association; November 8, 2005; Rancho Mirage, Calif; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

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DISCUSSION

Mark Talamonti, MD, Chicago, Ill: Upon my review of the manuscript and the presentation today, I feel the authors reach 3 important conclusions, each of which I would like to explore in more detail.

First, the ability to undergo a complete resection of all gross disease was the single most important prognostic factor affecting disease-free and overall survival rates. Therefore, when considering patients with sarcoma metastases for hepatic resection, the surgical imperative would be unequivocally to resect all gross disease to whatever extent is necessary, including extended hepatectomy and complex bilobar resections. These same authors from M. D. Anderson have also recently reported their experience with preoperative portal vein embolization to induce contralateral lobe hypertrophy before hepatic resections

for hepatocellular carcinomas with the same objective: complete margin negative resections. Therefore, my first question, how many of the patients in your resection arm underwent such preoperative preparation prior to formal hepatic resections? In the title of your paper, the question is, "Hepatic sarcomas: resection or ablation?" The answer would seem to be resection, yes; ablation, no. Based on the results of the current series, do the authors now consider patients for portal vein embolization preoperatively to optimize the chances of a potentially curative resection, albeit with its greater complexities and risks of complications, rather than RFA, which would seem to be clearly more palliative in nature?

This also leads to my second observation and question. Dr Pawlik referred to statistically significant differences in disease-free survival when comparing potentially curative complete resections with the more likely palliative RFA and RFA plus surgery groups. While it is interesting to present the results of these 2 groups, they might not really be comparable. I think the latter 2 groups might be more appropriately compared to patients undergoing nonoperative forms of liver-directed therapy such as embolization, chemoembolization, and intralesional therapies. Data from interventional radiologists at the same institution report similar median survivals and overall survival rates with nonoperative liver-directed treatments. So my second question to the authors is what criteria did you use in your management algorithm to choose patients for RFA plus or minus surgery vs other forms of nonoperative liver-directed therapies?

Finally, the authors confirm previous findings that conventional chemotherapy has limited therapeutic benefit in patients with non-GI [gastrointestinal] stromal metastases. On the other hand, patients with GIST metastases who were resected and treated with Gleevec had the longest disease-free and overall survival rates. Can you give us more insight into how you treated patients preoperatively or postoperatively with Gleevec and resection? If you treated preoperatively, how long did you treat with Gleevec and how did you monitor treatment responses before deciding to operate? If given postoperatively as an adjunct to potentially curative resection, what criteria were used to determine if patients were to receive Gleevec, and how soon after surgery was it started?

Dr Vauthey: Your first question relates to the approach to patients with extensive liver involvement with metastatic sarcoma and whether or not we treated some of these patients with extended resection. In this series, 8 patients had extended hepatectomy and none of them had portal vein embolization. We have not reviewed the films specifically in response to this question, and I cannot tell you how many patients who underwent resection plus radiofrequency ablation would today be potential candidates for preoperative portal vein embolization followed by extended hepatectomy.

The option of staged resection is also considered at our center. In patients with bilobar liver metastases, even with involvement of the left lateral bisegment, we consider staged resection with portal vein embolization. Usually, the first resection involves clearance of the left lateral bisegment. A week later, the patient gets portal vein embolization extended to segment IV followed by second-stage extended right hepatectomy.

Regarding the comparison between radiofrequency ablation and chemoembolization or infusion for some of these patients, how did we select the patients for one treatment or another? You well know that surgeons, unfortunately, are often prisoners of their referrals and the choice is not in our hands. Having said that, we try to discuss most of our patients with our colleagues, and usually the choice of radiofrequency was made based on the fact that the patient had small and diffusely distributed metastases. We have, during this period, also performed chemoembolization or infusion. In fact, right now we have a protocol of arterial infusion. This is done in most in-

stances in patients with dominant disease, large tumors, who are not candidates for resection or radiofrequency ablation.

Regarding the question of preoperative treatment with Gleevec, how long should you treat the patients with Gleevec prior to surgery remains to be evaluated further. We have an in-house institutional protocol for resectable patients which calls for a very short course of Gleevec followed by surgery within 1 week of treatment. We are looking at tumor genotype and response. Patients are then treated with Gleevec if there is biologic response to Gleevec as demonstrated by PET [positron emission tomography] scan. We try not to have patients off protocol. I think it is very important to include these patients in protocols. There is currently no meaningful data to support Gleevec treatment off protocol in patients without disease.

How soon do you start Gleevec after surgery? Gleevec has a very large therapeutic index, and treatment can be started as soon as the patient recovers from surgery and the liver function tests are returning to within normal limits.

Laurens R. Pickard, MD, Houston, Tex: I just wanted to ask about toxicity with Gleevec. Is there any morbidity or mortality from Gleevec?

Dr Vauthey: Toxicity is uncommon (5%). In rare instances, there is fluid retention, gastrointestinal dysfunction with diarrhea, and very rarely, neutropenia. Surgeons should be aware of the fact that patients may bleed also from GIST any place along the GI tract as a result of treatment from Gleevec. So, at the beginning of treatment with Gleevec, it may be advisable to resect patients who have primary involvement of the gut prior to treatment.

Richard C. Thirlby, MD, Seattle, Wash: Could you update for us the role of c-kit assays in predicting response to Gleevec? That is, what percent of c-kit-positive tumors

respond to Gleevec, and do c-kit-negative tumors ever respond?

Dr Vauthey: Ninety percent of gastrointestinal stromal tumors have a gain-of-function mutation of tyrosine kinase called c-kit, and this mutation can be identified with immunohistochemistry and predicts response to Gleevec, but 10% of GISTs have other mutations. Before 2001 and the c-kit immunostaining, the diagnosis of gastrointestinal stromal tumor was made based on electron microscopy and other immunohistochemical stains. I am not aware of c-kit mutations in other types of sarcomas.

Mitchell C. Posner, MD, Chicago: The obvious question that is raised by your study is not Gleevec vs no Gleevec in patients with GIST or hepatic resection vs RFA, but in the era of Gleevec, what additional value is there in treating patients with hepatic resection? And, is there a way to dissect out, in this era where we are treating almost all patients with Gleevec, what additional benefit we get with resection vs treating patients medically until they develop progression?

Dr Vauthey: You are quite right, and because of the excellent tumor control (70%-90%) and minimal toxicity, many of our medical colleagues would advocate salvage surgery at the time of progression on Gleevec. Resection, however, is the mainstay of treatment and should remain the mainstay of treatment if resectable because complete pathologic response with Gleevec occurs in less than 5% of patients, mutations develop while on treatment, and progression while on Gleevec is usually noted after 2 years of treatment. Resection for sarcoma metastases should remain the mainstay of treatment also based on its pre-Gleevec era track record showing long-term survival (actual 5-year survivors) after hepatic resection of gastrointestinal stromal tumors and leiomyosarcoma (*Ann Surg.* 2001;234:540-547).

Announcement

On the new Calendar of Events site, available at <http://pubs.ama-assn.org/cgi/calendarcontent> and linked off the home page of the *Archives of Surgery*, individuals can now submit meetings to be listed. Just go to <http://pubs.ama-assn.org/cgi/cal-submit/> (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.