Results of Hepatic Resection for Sarcoma Metastatic to Liver

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Objective
To evaluate the outcome of patients with liver metastases from sarcoma who underwent hepatic resection at a single institution and were followed up prospectively.

Summary Background Data
The value of hepatic resection for metastatic sarcoma is unknown.

Methods
There were 331 patients with liver metastases from sarcoma who were admitted to Memorial Hospital from 1982 to 2000, and 56 of them underwent resection of all gross hepatic disease. Patient, tumor, and treatment variables were analyzed to assess outcome.

Results
Of the 56 patients who underwent complete resection, 34 (61%) had gastrointestinal stromal tumors or gastrointestinal leiomyosarcomas. Half of the patients required an hepatic lobectomy or extended lobectomy. There were no perioperative deaths in the completely resected group, although 3 of the 75 patients who underwent exploration (4%) died. The postoperative 1-, 3-, and 5-year actuarial survival rates were 88%, 50%, and 30%, respectively, with a median of 39 months. In contrast, the 5-year survival rate of patients who did not undergo complete resection was 4%. On multivariate analysis, a time interval from the primary tumor to the development of liver metastasis greater than 2 years was a significant predictor of survival after hepatectomy.

Conclusions
Complete resection of liver metastases from sarcoma in selected patients is associated with prolonged survival. Hepatectomy should be considered when complete gross resection is possible, especially when the time to the development of liver metastasis exceeds 2 years.
the liver were excluded. There were 56 patients who underwent complete resection of all gross liver disease. In general, patients were selected based on adequate overall health, estimated safety of the procedure, control of the primary tumor, absence of extrahepatic disease, and distribution of intrahepatic metastases.

Data were collected and entered prospectively into the sarcoma database of the Department of Surgery. Patient demographics, tumor characteristics, treatment, recurrence, and survival data were recorded. The diagnoses of all primary tumors and hepatic metastases were confirmed by members of the Department of Pathology at MSKCC. The largest dimension of the largest metastasis was recorded as tumor size. A synchronous (as opposed to metachronous) presentation was defined as a time interval between the primary tumor and liver metastasis of 6 months or less.

Statistical analyses were performed with SPSS statistical software (Chicago, IL). Statistical significance was defined as \( P < .05 \). Actuarial survival was calculated by the Kaplan-Meier method. Univariate analysis was performed with the log-rank test. Multivariate analysis was performed using a forward conditional Cox proportional hazards model.

**RESULTS**

**Entire Population**

**Patient Characteristics**

The clinicopathologic variables of the entire population (\( N = 331 \)) with sarcoma metastatic to liver are shown in Table 1. There were 184 (56%) women and 147 (44%) men. The median age at diagnosis of the primary sarcoma was 53 years (range 15–91). The median age for men and women separately was also 53 years. The distribution of race was...
270 (82%) white, 31 (9%) black, 11 (3%) Hispanic, 6 (2%) other, and 13 (4%) not recorded. There were 284 (86%) patients who presented with metachronous liver disease; 47 (14%) had synchronous liver metastases.

**Tumor Characteristics**

There were 131 (40%) patients with gastrointestinal stromal tumor (GIST) or intestinal leiomyosarcoma. GIST and gastrointestinal leiomyosarcoma are grouped together for the purpose of analysis because before about 1993, GISTS were thought to be, and thus recorded as, leiomyosarcomas. There were 84 (24%) patients with extraintestinal leiomyosarcoma. More than two thirds of patients had primary tumors larger than 5 cm. Of the 156 patients with evaluable surgical margins of the primary tumor (many patients had resection of their primary tumor elsewhere), 42 (27%) had positive microscopic margins.

**Treatment**

There were 56 (17%) patients who underwent complete resection of all gross liver disease. Of the 275 patients who did not undergo complete resection, 11 (4%) received hepatic artery embolization, 8 (3%) underwent a noncurative, palliative resection, and the remainder received chemotherapy or supportive care. Palliative resection (leaving residual gross disease) was performed to relieve some patients of pain or hemorrhage.

**Survival**

The median follow-up for the entire population was 25 months (range 1–305) from the resection of the primary tumor. The median follow-up of all surviving patients was 50 months (range 1–305) from the resection of the primary tumor. Currently, 22 (7%) patients are free of disease, 66 (20%) are alive with disease, 240 (72%) are dead of disease, and 3 (1%) are dead of other causes.
Liver resections were categorized into four types, and the largest resection was recorded when multiple liver operations were performed. There were 13 (23%) wedge resections, 15 (27%) segmentectomies, 14 (25%) lobectomies, and 14 (25%) extended resections (greater than half of the liver removed). Negative microscopic surgical margins were attained in 42 (75%) patients. There were 23 (41%) patients known to have had adjuvant chemotherapy at some point in their therapy. Further, embolization was performed at least once in 11 (20%) patients.

Survival

The median follow-up time for patients who had complete resection from the time of resection of the primary was 58 months (range 10–305). The median follow-up from the time of liver resection was 29 months (range 1–91). The median follow-up from hepatectomy for surviving patients was 36 months (range 1–91). There were no perioperative deaths in completely resected patients. However, there were 3 perioperative deaths in the 19 patients who underwent exploration but did not undergo complete resection (11 had no resection and the other 8 had a palliative resection). The 11 patients who underwent only a biopsy at exploration were all explored during the first 10 years of the study. The likelihood of finding unresectable disease at laparotomy has been markedly reduced with the more recent improvements in cross-sectional radiologic imaging and the application of staging laparoscopy. The overall perioperative death rate was therefore 4% (3/75 total patients explored). Of the completely resected patients, 31 (55%) patients have died of disease, 11 (20%) are alive with disease, and 13 (23%) patients remain alive with no evidence of disease (range 2–78 months). One (2%) patient died of other causes.

The impact of treatment on survival is shown in Figure 1. The survival of patients who underwent complete resection was significantly longer than that of patients who did not (P < .0001). Of course, the patients who underwent hepatectomy were highly selected. After complete resection, the disease-specific survival rate at 1, 3, and 5 years was 88%, 50%, and 30%, respectively, and the median survival was 39 months. There have been 10 (18%) actual 5-year survivors, with 14 others still at risk. There are two 5-year survivors who remain disease-free, one of whom had a recurrence after hepatectomy that was resected. In contrast, the 275 patients who did not undergo complete resection had an actuarial disease-specific survival rate from the time of liver metastasis at 1, 3, and 5 years of 50%, 13%, and 4%, respectively, with a median of 12 months. In this group, there have been five (2%) actual 5-year survivors, with another 59 at risk. There are two 5-year survivors who remain disease-free, one of whom had a recurrence after hepatectomy that was resected. In contrast, the 275 patients who did not undergo complete resection had an actuarial disease-specific survival rate from the time of liver metastasis at 1, 3, and 5 years of 50%, 13%, and 4%, respectively, with a median of 12 months. In this group, there have been five (2%) actual 5-year survivors, with another 59 at risk. There was no demonstrable survival benefit to incomplete (gross residual disease) resection: the eight patients survived for a median of only 8 months (range 5–34).
Prognostic Factors

Gender, age, race, tumor distribution (unilateral vs. bilateral), number of metastases, hepatic tumor size, extrahepatic disease, and microscopic margin did not predict survival on univariate analysis (see Table 2). The patients with GIST or intestinal leiomyosarcoma had similar survival to those with other types of sarcoma (Fig. 2). Patients with synchronous (within 6 months of the primary) liver metastases had significantly worse survival ($P < .001$). Whether another recurrence had been resected before hepatectomy did not influence survival. Patients with a time interval between the primary tumor and liver metastasis of greater than 2 years had longer survival, with a median of 61 versus 26 months ($P = .001$ on univariate analysis, Fig. 3). Survival was also predicted by the extent of hepatectomy: those who had a major liver resection ($\geq$ lobe) had a median survival of 59 months, compared with 31 months for those who had lesser resections ($P = .001$). On multivariate analysis, only the time interval to liver metastasis of greater than 2 years was an independent predictor of outcome ($P = .002$, Table 4).

Recurrence

Recurrence after complete hepatic resection has occurred in 47 (84%) patients. Accurate initial recurrence data were available for 39 patients. In this group, the median time to recurrence was 16 months (range 1–44). There were nine patients with multiple sites of first recurrence after liver resection. Overall, the liver was the most common site of

![Figure 1](image1.png)  
**Figure 1.** Effect of treatment on disease-specific survival in the entire population. The 56 patients (upper line) with liver metastases from sarcoma who underwent complete resection of all gross disease had significantly longer survival than the 275 patients (lower line) who underwent other treatment ($P < .0001$).

![Figure 2](image2.png)  
**Figure 2.** Relationship of tumor histology to survival in patients undergoing complete resection. The 34 patients (solid line) with gastrointestinal stromal tumor (GIST) or gastrointestinal leiomyosarcoma (GILMS) had similar survival to the 22 patients (broken line) with other types of sarcoma ($P = .72$).

![Figure 3](image3.png)  
**Figure 3.** Relationship of the timing of liver metastasis to outcome in patients undergoing complete resection. The 32 patients (upper line) who developed liver metastases more than 2 years after the primary tumor had prolonged survival compared with the 24 patients (lower line) with a shorter duration to liver metastasis ($P = .002$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>.42</td>
</tr>
<tr>
<td>Age at hepatectomy &gt; 50 years</td>
<td>.59</td>
</tr>
<tr>
<td>Histology = GIST/intestinal leiomyosarcoma</td>
<td>.72</td>
</tr>
<tr>
<td>Resected recurrences before PHX ≥ 1</td>
<td>.77</td>
</tr>
<tr>
<td>Number of liver tumors &gt; 1</td>
<td>.11</td>
</tr>
<tr>
<td>Liver tumor size &gt; 10 cm</td>
<td>.08</td>
</tr>
<tr>
<td>Extrahepatic disease</td>
<td>.07</td>
</tr>
<tr>
<td>Liver resection ≥ lobectomy</td>
<td>.07</td>
</tr>
<tr>
<td>Positive microscopic liver margin</td>
<td>.22</td>
</tr>
<tr>
<td>Time to liver metastasis &gt; 2 years</td>
<td>.002</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumor; PHX, partial hepatectomy.

Table 4: Multivariate Analysis of Prognostic Factors
tumor recurrence and was involved 56% of the time (Table 5). The other major sites of recurrence were local (including peritoneal recurrences for intraabdominal tumors) and lung. Overall, 23 operations were performed in 18 patients for a subsequent recurrence after liver resection. Five (13%) patients underwent a second hepatectomy for recurrence and one (3%) underwent a total of three liver resections. Another 12 (32%) patients underwent resection of extrahepatic recurrences. At the time of last follow-up, 13 patients were free of disease. The actuarial disease-free survival rates were 88% at 1 year, 45% at 3 years, and 20% at 5 years, with a median of 32 months (Fig. 4).

**DISCUSSION**

The therapeutic options for patients with liver metastases from sarcoma are chemotherapy, ablation, liver transplantation, and partial hepatectomy. Traditionally, chemotherapy has been used for patients with metastatic sarcoma, although chemotherapy generally does not provide a survival benefit in sarcoma.16–18 Methods of ablation such as hepatic artery embolization, radiofrequency ablation, and cryotherapy have been used. Embolization can be effective because these metastases tend to be hypervascular. However, in one study of 14 patients, there was only a single 3-year survivor.19 Overall, ablation should be considered palliative, and more patients are needed to show a survival benefit and to identify the most effective method. Liver transplantation has been performed in a few patients with metastatic sarcoma, with poor results.20,21 On occasion, upper abdominal exenteration and cluster transplantation have been performed.22 Transplantation has been considered for young patients with multifocal, indolent, hepatic metastases without evidence of extrahepatic disease, but it is of unproven value.

There are several reasons to consider partial hepatectomy as a therapy for metastatic sarcoma. The resection of lung metastases from metastatic sarcoma has been shown to improve survival.8 There has been no alternative therapy that is highly effective. During the past two decades, liver surgery has become increasingly safe, thereby liberalizing its indications.9,11 Most major centers now report perioperative death rates of less than 5% in the absence of cirrhosis. The overall perioperative death rate in this series for patients who underwent exploration was 4%. Clearly, some patients with sarcoma metastatic to liver have an indolent course or disease confined to the liver with one or few metastases.

There now appears to be another compelling reason to resect liver metastases in patients with GIST. STI571 is a small molecule being tested in clinical trials that has shown dramatic activity against GIST.23 Most patients with GIST have a somatic mutation in the c-kit protooncogene resulting in constitutive activation of its product, the Kit receptor tyrosine kinase.24 STI571 is a tyrosine kinase inhibitor that blocks Kit and has a large therapeutic index. Preliminary data have shown STI571 to achieve a partial response in more than 50% of patients with metastatic GIST, although there have not been any cures. STI571 may prove useful before hepatectomy to permit resection in patients with initially unresectable disease or after liver resection to prevent tumor recurrence. A Southwest Oncology Group study is evaluating the benefit of the agent in patients with unresectable or metastatic GIST. STI571 may even prevent or delay the development of liver metastases after complete resection of a primary GIST, and this will be studied in a multicenter trial directed by the American College of Surgeons Oncology Group. Debulking of liver metastases, which was ineffective in the eight patients who had incomplete (gross residual disease) tumor resection in this study, may now even be studied in selected patients with GIST who are treated with STI571.

Thus far, the evidence for a survival benefit from hepatic resection of sarcoma liver metastases has been largely anecdotal (Table 6). The initial review by Foster1 on the resection of secondary hepatic malignancies comprised 12 patients with sarcoma, with only a single 5-year survivor. Our initial results were also discouraging.15 Schwartz reviewed the literature and identified 28 patients with sarcoma...
metastases to liver who had undergone resection. Our previous review of published data identified 5 of 48 patients undergoing resection from 1973 to 1993 who survived 5 years. One group reported a patient who survived 12 years after hepatectomy. The largest series reported from a single institution included 18 patients who underwent complete resection of all gross liver disease. The 5-year survival rate for the 15 patients who had negative microscopic margins was 20%, and there were 3 actual 5-year survivors. In the present study, we showed that the 5-year actuarial survival was 30% in 56 patients who underwent liver resection for metastatic sarcoma to the liver. Further, we reported that there have been 10 actual 5-year survivors (with 14 other patients still at risk).

The patients who underwent hepatectomy in this series were highly selected. They were chosen from a cohort of 331 patients with hepatic metastases from sarcoma. The patients undergoing resection tended to have favorable characteristics. Most had one or two liver metastases, lesions that were smaller than 10 cm, and a long disease-free interval. However, there were patients who underwent resection who had multiple or large lesions and a short time to the development of liver metastases. The only predictor of outcome after complete resection of all gross disease on multivariate analysis was time to liver metastasis of greater than 2 years. Time to liver metastasis has been a prognostic marker in colorectal liver metastases and in our analysis of all patients with noncolorectal, nonneuroendocrine liver metastases. The presence of a positive microscopic margin at hepatectomy was not statistically significant, although the study size was small and the liver was the most common site of recurrence after hepatectomy. Most patients had recurrence within 3 years. In most patients, the first recurrence involved the liver. This is likely due to unrecognized microscopic disease in the remnant liver at the time of resection. This mirrors the recurrence pattern of patients who undergo resection of colorectal liver metastases and raises the question of whether postoperative regional chemotherapy should be considered to reduce the rate of intrahepatic recurrence in patients with non-GIST histology. Conversely, hepatic arterial infusion chemotherapy may also prove useful for patients with unresectable disease isolated to the liver if effective agents could be identified. Many patients were able to undergo resection of recurrent disease that developed after hepatic resection, although repeat hepatectomy could be performed in only a minority of patients.

The application of hepatectomy to the treatment of metastatic sarcoma is a result of both the characteristics of the disease and the evolution of surgical techniques for hepatectomy. These data show that hepatic resection can be performed safely and is associated with prolonged survival in a select group of patients with metastatic sarcoma. The development of effective adjuvant or neoadjuvant therapies should further extend the indications for partial hepatectomy in the treatment of liver metastases from sarcoma.

### References


### Table 6. PUBLISHED STUDIES OF COMPLETE HEPATIC RESECTION FOR METASTATIC SARCOMA

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Years</th>
<th>N</th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
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<tbody>
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<td>Foster¹</td>
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<td>Pre-1978</td>
<td>12</td>
<td>58</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Jaques¹⁵</td>
<td>MSKCC</td>
<td>1982–87</td>
<td>14</td>
<td>86</td>
<td>30</td>
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</tr>
<tr>
<td>Elias⁴</td>
<td>Gustave Roussy</td>
<td>1984–96</td>
<td>8</td>
<td>100*</td>
<td>62*</td>
<td>18*</td>
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<tr>
<td>Chen⁴</td>
<td>Johns Hopkins</td>
<td>1984–95</td>
<td>6</td>
<td>100</td>
<td>83</td>
<td>83</td>
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<tr>
<td>Hemming²</td>
<td>Univ. Toronto</td>
<td>1978–98</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>29</td>
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<tr>
<td>Lang²⁵</td>
<td>Essen</td>
<td>1982–96</td>
<td>18</td>
<td>85†</td>
<td>40†</td>
<td>20†</td>
</tr>
<tr>
<td>Present</td>
<td>MSKCC</td>
<td>1982–00</td>
<td>56</td>
<td>88</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>

MSKCC, Memorial Sloan-Kettering Cancer Center.
* Includes 5 other patients who underwent palliative resection.
† For 15 patients who had complete resection of all gross liver disease and had negative microscopic margins.

Discussion

Dr. Christoph Broelsch (Essen, Germany): You are to be congratulated for another excellent presentation and for focusing on something that almost has slipped the minds of the general or liver surgeons because we are all attracted by colorectal metastases. All of a sudden, there is a rare type of sarcoma metastasis in our hands and we achieve some significant and comprehensive results of resecting these lesions, particularly since the treatment of these metastases have been predominantly taken over by adjuvant treatments such as chemotherapy and palliation procedures done by radiologists and others, and even liver transplantation. I agree with you, we should focus more on this entity. Basically, however, we treat a systemic disease similar to colorectal metastases, which appears to affect the liver in a high percentage.

On patient survival, as you pointed out, disease related survival in the group of myelosarcomas is extremely favorable, more than 50% for one year. However, you selected only 17% patients undergo resection. You mentioned several extrapathic criteria such as general conditions, estimated safety of procedure, the control of primary tumor, the absence of extrapathic disease, and also the distribution of intrapathic disease.

My first question relates to the most determinant factor. Is it the control of primary tumor or is it the absence of extrapathic disease at the same time? Several patients undergo several surgical procedures to treat extrahepatic disease. And even with an RI resection margin, overall survival has reached 35% now for five years. The question therefore remains, is it the surgery that provides survival benefit or is it the natural prognosis of the disease that is favorable irrespective of surgery?

One factor you emphasized is the time of onset of liver metastases, which points rather toward a natural factor. However, we too found that in the series published, and you mentioned it, by my associate, Dr. Lang, that in those with RO resected survivors were significantly better compared to an RI resection. This could only be accomplished by several repeat liver resections, and we went to some ex situ or in situ protection procedures.

It is particularly important to emphasize this finding because we are facing competitive approaches by the use of laser therapy, by thermoablation, radio-induced chemotherapy, and it was extremely important to define surgical patients versus ablation or adjuvant patients. I would like to hear your comments on that, how you select these patients for appropriate treatment.

Presenter Dr. Murray F. Brennan (New York, New York): Thank you, Dr. Broelsch. The management of soft tissue sarcoma has been truly a labor of love in my situation. We began in 1982 with a prospective database for everyone admitted to our institution and we have met every week in the last 19 years to review and ensure the integrity of the data. We now have over 5,000 patients entered into that database.

As Dr. Broelsch points out, this is a super selected series. This is a masterpiece of identifying the patients who can and should do well. He made the very important point that it is not the control of the primary in the main that causes demise, they die of liver metastases. They can die of local recurrence, but they predominantly die of liver metastases. We did select people who naturally had a better survival; i.e. those who developed metastases after two years. Conversely there are essentially no other survivors without resection.

We do use other treatments. We have been uniformly disappointed, of course, with systemic chemotherapy, which has not proven of value. We do use embolization, because these tumors, like neuroendocrine tumors, tend to be vascular. And there have been occasions where we have embolized the tumor, waited to ensure that there is not other systemic metastases before proceeding to resection.

Dr. John E. Niederhuber (Madison, Wisconsin): I would also like to congratulate the authors for their excellent and timely report. I believe I have stated before, and probably before this audience, that Dr. Brennan’s creation in 1982 of a prospective sarcoma database at MSKCC has been a very important and significant contribution to the world of cancer surgery. We as surgeons have gained considerable insight into the management of these tumors as a result of his efforts.

The report presented today concerning hepatic resection of sarcoma metastasis to the liver is consistent with our growing confidence in the selection of patients for major liver resection, the greater safety that accompanies such resections today, and most importantly an increasing appreciation that patients may benefit significantly from the resection and ablation of liver metastases from tumors other than colon and rectal cancers.

In the manuscript, which I appreciate having had the chance to review ahead of time, it was stated that if patients have disease outside the liver, this is an important selection criteria that precludes liver resection. I am confused somewhat by this statement and wonder if you really mean this in the strictest of terms. The reason I raise this question is that many of your
patients had resections of metastases outside the liver prior to the development of liver metastases. Also, I believe 18 out of the 56 had resections of other sites after their liver resection.

I am also puzzled by why the resection margin when it is positive isn’t a significant prognostic factor. I know that is what the data shows in your manuscript but I wonder if you would comment further. One would certainly expect a positive margin to impact negatively on prognosis.

Another question I would like to raise is, why is there such a high exploration to resection rate? There were 75 patients explored and only 56 were resected. I wonder what the reasons are for this difference?

I also wonder whether you have looked at your database for any molecular markers that might help in further refining the selection process?

I would also comment that Dr. DeMatteo referred to a statistically significant difference in survival when comparing the palliation group and the resection group. While it is fair to present the results of palliation and the results of resection, these two groups aren’t really comparable and it is not fair to compare statistically.

Certainly this report gives all of us added confidence to continue an aggressive surgical approach with this difficult and often young population of patients. Clearly, as has been stated repeatedly, the key is the appropriate selection of the patient.

Dr. MURRAY F. BRENNAN: Thank you, Dr. Niederhuber, for your comments. Outcome analysis is becoming increasingly important, and databases such as these will surely help that.

Yes, we did resect disease outside the liver, both before when the patient came to liver resection and at the time of liver resection. The positive margin issue I think is purely a number. There were only 14 with positive margins. And as we progressively learned, the determination of positive margin at the time of liver resection has many variables both surgical and pathological.

I think it is very important to emphasize that more recently – and I think this is an indication of the fact that we do have five-year survivors now that we didn’t have when we analyzed the data before – was the safety of the liver resection. Certainly, liver resections done by my senior colleague, Les Blumgart, are far safer than the liver resections I was doing for sarcoma 10 or 15 years ago. And he has brought his colleagues, co-authors Yuman Fong and Dr. Jarnagin in addition to Dr. DeMatteo, to a level far superior than we were practicing 10 years ago.

It is important also to emphasize that there is a drug, for GI stromal tumors – STI-571 is one of the more attractive drugs than we have seen in a very long time – directly attacking a tyrosine kinase. Many of you will be unfamiliar with that drug, but we are hopeful this will form the basis of an adjuvant trial for these tumors run by the American College of Surgeons Oncology Group under the leadership of Sam Wells, and we are hopeful that for the first time we will have a meaningful and certainly effective drug for sarcoma, something we have not had certainly, for GI stromal tumors.

Dr. HAROLD J. WANEBO (Providence, Rhode Island): I would like to compliment Dr. DeMatteo and his co-workers at Memorial Sloan-Kettering for this presentation of the largest series of hepatic resections for metastatic sarcoma. They were able to resect 17% of over 330 patients with identified metastases of sarcoma, and most of these were gastrointestinal stromal tumors or previously described leiomyosarcomas.

Of interest, the only predictive factor was a prolonged free interval period following resection. There was no relationship between survival and the usual predictors for liver resection performed for other metastatic disease, especially in colon cancer where the presence of extrahepatic disease or microscopically involved margins of resection have predictive survival value. My questions to the authors:

The recurrence rate, which was about 84%, was associated with a high failure rate again in the liver as well as a predictable failure rate at the local site of the primary lesion. Would a hepatic artery infusion protocol be of value, as has been demonstrated by your liver resection group, in patients resected for hepatic metastases from colorectal cancer?

A second question refers to the management of the high risk patients with a short free interval period after resection of the primary sarcoma or those who have extrahepatic disease. Would a neoadjuvant protocol be of benefit in these high risk patients and should these patients still be considered resectable?

Dr. MURRAY F. BRENNAN: Obviously, with a tumor that tends to recur only in the liver, it is a natural question to ask, about hepatic infusion. The problem is we have no effective drugs. The only prospect is the drug I mentioned, STI-571, which is a wonderful drug for surgeons. It can be given orally on a once or twice daily basis with minimum toxicity. It would be a great trial for this organization to participate in.

The short disease-free interval. There are certainly occasions when patients have a short disease-free interval where the liver disease is either symptomatic or potentially putting their life at risk where we consider embolization in an effort not to operate on someone who you cannot help. But in those patients who we anticipate can be rendered disease free, I believe in this situation extensive liver resection is justified.

Dr. DONALD L. MORTON (Los Angeles, California): I rise to extemporaneously discuss this paper just to make a few points.

Several decades ago, I presented a paper before this organization on resecting pulmonary metastases of sarcomas. There was a lot of controversy at the time, because logic would suggest that once you have distant metastases, particularly in multiple sites, such patients must have disseminated disease at multiple sites which couldn’t be benefited by surgical resection.

At that time, we found the tumor doubling time, that is the time it took for the tumor to double in volume, was a very important selection factor in determining which patients were likely to benefit from surgical resection and which were not. This correlated roughly, but not completely, with the disease-free interval.

I would suggest that with modern scanning technology, you should be able to go back to these patients’ C–T scans and retrospectively calculate the time it takes for these hepatic metastases to double in volume if you have two or more C–T scans at different time intervals available on each patient. You can then very precisely work out a doubling time that should correlate with the survival following resection. Such information will be helpful in better selection of candidates for resection.

In closing, I would say that many of us have been waiting now for three or four decades for an effective chemotherapeutic agent that would cure people with metastatic cancer. That is what we all dream about. Unfortunately, as a matter of fact, as of now, in 2001, for patients with solid tumors, there are very few solid neoplasms that can be cured by systemic chemotherapy.

I think we as surgeons have given up too soon on the role of surgery in the treatment of metastastic disease. I believe we should again investigate very carefully the role of surgery in the treatment of metastases because modern scanning technology has improved our ability to identify metastatic sites which can be resected with lower morbidity and mortality. In fact, surgery for metastatic disease is less toxic and less costly than many of the newer chemotherapeutic agents for solid neoplasms. Therefore, in my opinion, the initial treatment of choice for most solid tumors with metastatic disease is surgical resection.

Dr. MURRAY F. BRENNAN: Thank you, Dr. Morton. Your contributions to the management of melanoma particularly and metastatic disease from melanoma are well recognized.

It is important to emphasize that we do have meaningful ways to evaluate this. In primary extremity soft tissue sarcoma, the primary site of metastasis is the lung. That occurs in 88% of patients. And we previously reported our results of over 700 patients with lung metastasis.

However, even in those undergoing complete resection in the lung, the three-year survival is 19% with isolated long-term survival. The problem with the GI stromal tumors is that they go to the liver. Seventy percent of the time that is the first and only site.

Your question about doubling time is an important one but it is not as valuable in sarcoma as it is in melanoma. Most sarcoma metastasis to the liver undergo central necrosis. So the ability to determine meaningful doubling time is difficult. Having said that, I have not measured the doubling time to determine it, but I would be concerned that the variation in central necrosis would prevent meaningful interpretation. But I may very well be wrong.