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Hepatic Metastases from Soft-Tissue Sarcoma

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Objective
Hepatic metastases from soft-tissue sarcoma are evaluated to define treatment and its limitations.

Methods
From 981 adult patients with diagnoses of soft-tissue sarcoma, 65 patients with hepatic metastases were studied.

Results
An intra-abdominal primary site was present in 61 of 65 patients, with 85% high-grade leiomyosarcoma. Hepatic resection was performed in 14 patients (22%). All patients have had recurrences after hepatic resection—11 of 14 in the liver—with a median survival of 30 months. Chemotherapy resulted in partial response in three patients and no complete responses. Survival is not influenced by grade, type, primary site, disease-free interval, chemotherapy, or hepatic resection.

Conclusions
The uncommon response to conventional chemotherapy does not support its use in the treatment of hepatic metastases from soft-tissue sarcoma. Extent of disease limits the application and success of hepatic resection for soft-tissue sarcoma, and anything less than complete resection is not indicated.

Metastases to the liver form a common pattern of recurrence from visceral and retroperitoneal sarcomas. It is a distinctly uncommon site of spread from extremity and trunk sarcomas. Multiple, bilobar hepatic metastases from soft-tissue sarcoma are the common presentation within the liver, often in association with local recurrence. The Memorial Sloan-Kettering Cancer Center experience with hepatic metastases from 1982 to 1987 is reviewed. Incidence and survival as influenced by grade, histology, primary site, and treatment are evaluated.

MATERIAL AND METHODS

From July 1982 to July 1987, 981 adult patients were admitted to Memorial Sloan-Kettering Cancer Center with a diagnosis of soft-tissue sarcoma. A prospective sarcoma database, maintained by the department of surgery, identified 65 patients with hepatic metastases. These patients form the basis of this report. All records, films, and histology were reviewed, and accurate follow-up was assured. Sixty patients were observed for follow-

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Table 1. HEPATIC METASTASES FROM SOFT-TISSUE SARCOMA: DISTRIBUTION BY HISTOLOGIC TYPE AND GRADE

Histologic Type	No. of Patients (%)	No. of High Grade (%)	No. of Low Grade (%)
Leiomyosarcoma	55 (85%)	48 (87%)	7 (13%)
Angiosarcoma	5 (8%)	5 (100%)	0 (0%)
Rhabdomyosarcoma	3 (5%)	3 (100%)	0 (0%)
Liposarcoma	1 (1%)	1 (100%)	0 (0%)
Malignant fibrous histiocytoma	1 (1%)	1 (100%)	0 (0%)

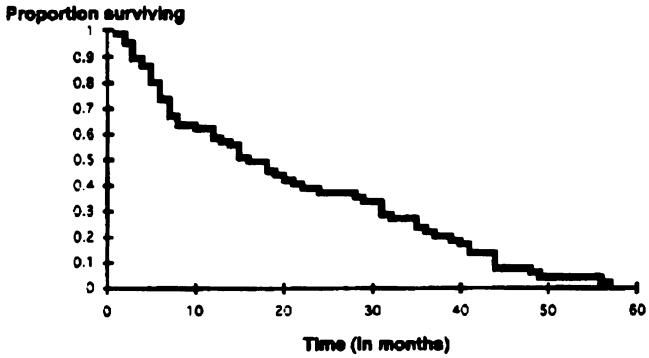

Figure 1. Overall survival from diagnosis of metastasis.

up until death, and the remaining five were unable to be observed for follow-up after a mean of 8 months, when each was alive with extensive, unresectable, and unresponsive disease. The histopathology of the primary tumor was confirmed in all cases. Pathologic or radiologic criteria were used for confirmation of the hepatic metastases. Patients with primary hepatic sarcoma and patients with direct invasion of the liver from a contiguous intraabdominal primary tumor are excluded from this review. Kaplan-Meier survival curves were developed, and prognostic variables were assessed with log-rank test.

RESULTS

Hepatic metastases have been identified in 65 of 981 (7%) adult patients admitted to Memorial Sloan-Kettering Cancer Center from 1982 to 1987 with soft-tissue sarcoma. Pathologic confirmation of the hepatic metastasis was made in 43 patients, and radiologic evidence only identified the site in the remaining 21 cases. The mean age at diagnosis was 52 years (range 21–73 years). There were 39 men and 26 women. The histology of the sarcoma was high grade in 58 patients (89%) and low grade in 7 (11%). The histologic type was leiomyosarcoma in 55 of 65 patients (85%) (Table 1). Patients with angiosarcoma included in this review had previously established extrahepatic primary sites.

Thirteen patients (20%) had metastases to the liver on initial presentation. The primary soft-tissue sarcoma had been completely resected in 27 patients, whereas 20 were inoperable for primary disease and 18 were explored but not resected. The median time from primary diagnosis to development of hepatic metastases was 12 months in the remaining individuals (Fig. 1). A disease-free interval of more than 60 months was observed in 20% of cases. Metastasis to the liver was a component of the first recurrence in 86% of patients.

An intra-abdominal primary site was present in 61 of 65 patients (94%) (Table 2). The primary site was visceral in 35 patients and retroperitoneal in 24. Hepatic metastases were seen in only 3 of 637 patients (0.5%) with extremity or trunk primary sites, compared with prevalence rates of 16% and 62% for retroperitoneal and visceral primary tumors.

Of 981 patients with soft-tissue sarcoma, 324 (33%) have developed distant metastases in 376 sites. The lung was a site of metastases in 212 patients (56%), and the liver was a site of metastases in 65 patients (17%); other sites of metastases (bone, lymph nodes, soft tissue, viscera, bone marrow, and brain) were discovered in 99 patients (26%) (Table 3). The primary site influences this pattern of metastasis. The proportion of lung:liver as a site of distant spread from an extremity primary is 75:1. The spread to liver in those with extremity primaries never was the sole or first site of metastasis. This is in

Table 2. HEPATIC METASTASES FROM SOFT TISSUE: INCIDENCE BY PRIMARY SITE

Primary Site	No. of Patients	No. of Hepatic Metastases (%)
Extremity/trunk	637	3 (0.5%)
Trunk	124	0 (0%)
Lower extremity	384	3 (0%)
Upper extremity	100	0 (0%)
Buttock	29	0 (0%)
Abdomen	272	61 (22%)
Retroperitoneum	149	24 (16%)
Viscera	56	35 (62%)
Gynecologic	47	1 (2%)
Genitourinary	20	1 (5%)
Other	72	1 (1%)
Breast	6	0 (0%)
Head and Neck	51	0 (0%)
Thoracic	15	1 (7%)
Total	981	65 (7%)

Table 3. HEPATIC METASTASES FROM SOFT-TISSUE SARCOMA: SITE OF DISTANT METASTASES IN 981 PATIENTS WITH SOFT-TISSUE SARCOMA

Site of Distant Metastases	No. of Patients (%)
Lung	212 (21%)
Liver	65 (6%)
Bone	22 (2%)
Other*	77 (8%)
Total	345 (35%) (376 sites)

* Soft tissue, retroperitoneum, bone marrow, lymph nodes, viscera, brain.

Table 5. HEPATIC METASTASES FROM SOFT-TISSUE SARCOMA: RESPONSE TO INITIAL COURSE OF CHEMOTHERAPY

Agent	No. of Patients	No. of Partial Response	No. of Complete Response
Doxorubicin hydrochloride (Adriamycin, Adria Laboratories, Columbus, OH)*	34	2 (6%)	0
Other (conventional)	4	0	0
Other (experimental)	14	1	0
Total	52	3 (6%)	0

* Adriamycin alone or in combination.

contrast to retroperitoneal primary tumors, where 38% of metastases developed in the lung and 62% developed in the liver (1:1.5), and to visceral sarcomas, where 7% of metastases developed in the lung whereas 88% developed in the liver (1:10) (Table 4). Hepatic metastases were not observed in the 310 patients with trunk, upper extremity, buttock, head and neck, or breast primary tumors.

The extent of hepatic involvement was determined at exploratory laparotomy or by computerized tomography. Seven patients had solitary hepatic metastases, 10 had multiple, unilobar metastases, and 48 had multiple and bilobar metastases. When used, angiography identified these lesions as hypervascular. Two of 65 patients had spontaneous rupture of metastatic leiomyosarcoma.

Fifty-two of 65 patients (80%) received chemotherapy at the time of diagnosis of hepatic metastases (Table 5). Doxorubicin hydrochloride (Adriamycin, Adria Laboratories, Columbus, OH) was used alone or in combination in 34 patients (65%) in this group. A partial response to chemotherapy was documented in three patients (6%), and no complete responses were observed. There were no responses identified in 32 patients receiving a second, salvage course of chemotherapy. By univariate analysis, there was no improvement in survival in patients receiving chemotherapy (Fig. 2).

Each patient was considered for hepatic resection, and 28 (43%) were judged by radiologic evaluation of extent of disease to be inoperable. Twenty-three patients (35%) were unable to be resected at operation. The findings that precluded operation or resection in these 51 patients were additional distant sites of metastases (6 patients), extrahepatic, intra-abdominal disease (10 patients), bilobar, multiple hepatic metastases (30 patients), and size and location of metastasis in the liver (5 patients). The mean disease-free interval from diagnosis to hepatic metastasis was 30 months for patients who underwent hepatic resection and 11 months for those who did not.

Hepatic resection for metastatic soft-tissue sarcoma

Table 4. HEPATIC METASTASES FROM SOFT-TISSUE SARCOMA: DISTRIBUTION OF METASTASES BY PRIMARY SITE OF TUMOR

Primary Site	Percent of Lung Metastases	Percent of Liver Metastases	Percent of Other Metastases
Abdomen	39	43	17
Retroperitoneum	38	62	3
Visceral	7	88	7
Gynecologic	64	3	22
Genitourinary	44	11	56
Extremity/trunk	75	1	14
Extremity	78	2	20
Trunk/buttock	64	0	36

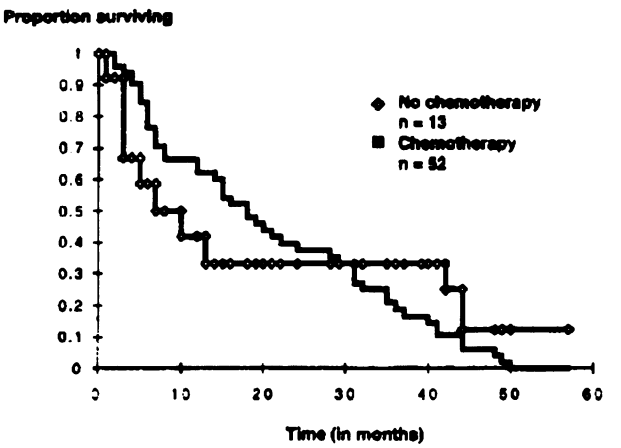

Figure 2. Survival by chemotherapy.

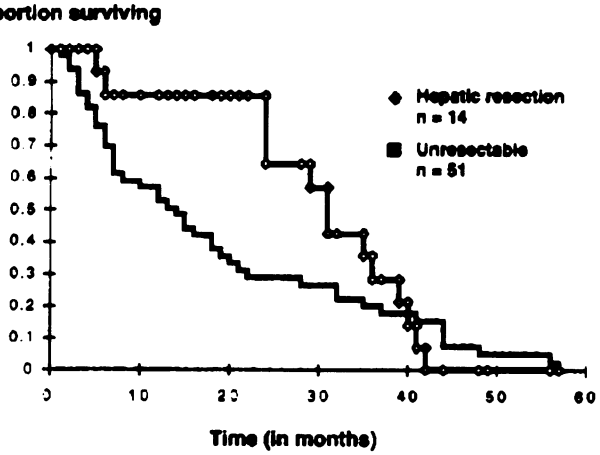

Figure 3. Survival by resectability.

was performed in 14 patients (22%). Ten of 14 had primary visceral leiomyosarcoma. Three patients underwent wedge resection, ten patients underwent lobar or segmental resection, and one patient had an incomplete resection. There were histologically free margins of resection in 13 patients. There was no 30-day operative mortality. All patients have had recurrences after hepatic resection. The site of recurrence was the liver in 11 patients, the primary site in 2, and the lung in 1. Although median survival in the resected group is 30 months compared with 12 months in the group that did not undergo resection, there is no significant difference in survival by univariate analysis (Fig. 3). There are no 5-year survivors after hepatic resection.

The median survival from time of diagnosis of hepatic metastases is 12 months. By univariate analysis, this is not influenced by histologic grade, histologic type, primary site, disease-free interval, chemotherapy, or hepatic resection.

DISCUSSION

Unlike sarcoma metastases to the lung,[1] the natural history and treatment of hepatic metastases from soft-tissue sarcoma has not been well described. An evaluation of risk factors for their development shows the importance of three features—histologic grade, histologic type, and primary site.

Histologic grade of soft-tissue sarcoma strongly predicts outcome,[2] with 5-year survival differences of 20% *versus* 80% when multiple unfavorable factors are present. High-grade histology is observed in 66% of patients. In this series, 89% of patients with hepatic metastases had a high-grade primary tumor, comparable to the observation for pulmonary metastases. The most prevalent histologic type was leiomyosarcoma (85%). Retroperitoneal leiomyosarcomas metastasized to the liver in 16 of 24 patients, thereby identifying a subset of patients with soft-tissue sarcoma who must be observed carefully for spread to the liver. There was only 1 patient of the 55 with retroperitoneal liposarcomas who developed liver metastases. Angiosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma also were observed to infrequently spread to the liver. Histologic type, histologic grade, and disease-free survival did not predict survival once hepatic metastases were observed.

Intra-abdominal primary site influences development of hepatic metastases. The overall incidence of hepatic metastases from soft-tissue sarcoma is 7%. The likelihood of developing a hepatic metastasis from an extremity primary site is 1%[1,3] compared with retroperitoneal (14%),[4–6] visceral (52%)[7–10] and uterine (7%) sites.[11,12] The relative incidence of lung:liver metastases is remarkably different for each of these primaries, ranging from 75:1 for extremity sites to 1:10 for visceral sites. Pulmonary and hepatic metastases occur in equivalent proportion for retroperitoneal sarcomas. Appropriate follow-up of patients with retroperitoneal or visceral soft-tissue sarcoma would include periodic radiologic evaluation of the liver at a frequency comparable to pulmonary assessment.

Hepatic metastases are readily identified by computed tomography scan. When evaluated by angiography, they typically are hypervascular. Most are multiple (89%) and bilobar (74%). Twenty percent were discovered at time of diagnosis. Fifty percent of patients who developed hepatic metastases did so within the first year from diagnosis of sarcoma; this is the period of most intense evaluation of the liver for patients with intra-abdominal leiomyosarcomas.

Chemotherapy does not have a substantial impact on hepatic metastases from soft-tissue sarcoma. Doxorubicin hydrochloride is associated with a 35% response rate in treatment of metastatic soft-tissue sarcoma. Leiomyosarcoma is reported to have an 18% response rate to doxorubicin hydrochloride and as high as 44% to doxorubicin hydrochloride and dacarbazine in combination.[13] Response of leiomyosarcoma hepatic metastases cannot be determined from the literature. In this series, 2 of 34 patients with leiomyosarcoma metastatic to the liver were observed to have a partial response to doxorubicin hydrochloride-containing regimens. There were no complete responses observed. This had no impact on survival. Several multidrug salvage and experimental protocols were similarly ineffective.

With the addition of this series, there are 48 patients reported in the literature as having hepatic resection for metastatic soft-tissue sarcoma[14–26] (Table 6). In this series, 57% of patients had intraoperative assessment of extent of hepatic disease. Of these, 38% had an hepatic re-

Table 6. HEPATIC METASTASES FROM SOFT-TISSUE SARCOMA: SURVIVAL AFTER HEPATIC RESECTION—POOLED DATA

Series (Year)	No. of Patients	No. of 5-Year Survivors
Brasfield[14] (1973)	3	1
Foster[15] (1977)	11	2
Fortner[16] (1978)	3	0
Morrow[17] (1982)	2	1
Thompson[18] (1983)	2	0
Iwatsuki[19] (1983)	2	0
Pommier[20] (1987)	3	N/A
Hemming[21] (1993)	3	N/A
Others[22-26] (1980–1993)	5	1
Current series	14	0
Total	48	5 (11%)

section, with no 30-day operative mortality. Unresectability was predominantly caused by bilobar, multiple metastases. Retroperitoneal sarcomas have a 75% rate of local recurrence. This had an impact on resectability of hepatic metastases and must be evaluated intraoperatively before consideration of hepatic resection. Ten of the 14 patients who had undergone resection had a visceral leiomyosarcoma; thus, this group is most likely to benefit from consideration of hepatic resection.

Resection of colorectal hepatic metastases is well described and readily accepted.[27,28] The primary difference observed in outcome after resection of colorectal *versus* sarcoma liver metastases is the infrequent 5-year survival typified in this series. Although the median survival from time of resection of hepatic metastases is similar for colorectal and sarcoma primary tumors (30 months), the 5-year survival is not. A 25% to 37% 5-year survival can be anticipated after hepatic resection of colorectal metastases. In the collected series, 5 of 48 patients (11%) were alive at 5 years. There are no 5-year survivors among the 14 patients resected in this series. The pattern of recurrence after hepatic resection of soft-tissue sarcoma metastases is liver alone (79%), liver and other site (0%), and other site only (21%). This is compared with colorectal liver metastases resection, in which the liver is a component of recurrence in 66% of patients and is the sole site in 33%.[29] Before contemplating hepatic resection, these patients must have a thorough evaluation for extrahepatic disease along with preoperative and intraoperative sensitivity to the possibility of multiple, bilobar spread. With the high frequency of post-resection failure in the liver and the absence of effective chemotherapy, resection should not be contemplated unless clear margins can be assured. Frequent multicentricity and bilobar involvement will continue to make major resection uncommon.

The median survival after diagnosis of hepatic metastases is 12 months. The natural history of untreated hepatic metastases from soft-tissue sarcoma most closely approximates a group of patients with multiple colorectal carcinoma metastases.[30-32] Five-year survival is uncommon after hepatic metastasis from soft-tissue sarcoma.

CONCLUSION

Hepatic metastases occur in 7% of patients with soft-tissue sarcoma—most commonly from visceral of retroperitoneal leiomyosarcoma. The 12-month median survival from diagnosis of hepatic metastases is not affected by histologic grade, histologic type, primary site, or disease-free interval. The uncommon response to conventional chemotherapy does not support its use and invites the consideration of nonstandard regimens. Extent of hepatic and extrahepatic disease limits the application and success of surgical resection of the liver for metastatic soft-tissue sarcoma, and anything less than complete resection is not indicated.

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