Long-term Survival After Surgery for Primary Hepatic Sarcoma in Adults

Hanno Matthaei, MD; Andreas Krieg, MD; Moritz Schmelzle, MD; Edwin Boelke, MD; Christopher Poremba, MD; Xavier Rogiers, MD; Wolfram Trudo Knoefel, MD; Matthias Peiper, MD

Hypothesis: Patients with primary hepatic sarcomas benefit from resection, with possible long-term cure.

Design: Retrospective and prospective cohort study.

Setting: University hospitals of Hamburg-Eppendorf and Düsseldorf, Germany.

Patients: Between 1985 and 2006, 22 patients (8 men and 14 women; median age at initial diagnosis, 54 years [range, 19-80 years]) were surgically treated for primary hepatic sarcomas.

Intervention: Tumor resection with curative intent ranging from nonanatomical resection to liver transplant.

Main Outcome Measures: Effects on overall survival were analyzed using the log-rank test.

Results: The majority of tumors were more than 5 cm (n=19), with a median tumor size of 7 cm (range, 4-14 cm); of intermediate differentiation (G2; n=15); and classified as leiomyosarcoma (n=7). Ten patients received a hemihepatectomy. In 4 patients, a bisegmentectomy was performed and in 2 patients, a segmentectomy, while 4 patients received a nonanatomical resection. Liver transplant was performed in 2 patients. In 18 patients, complete tumor resection (R0) was achieved. Perioperative mortality was 0%. Median follow-up was 88 months (range, 6-246 months). Local recurrence occurred in 6 patients. Distant metastases were diagnosed in 10 patients, predominantly in the lung (n=6). The 5-year survival after surgery was 65%, with 41% of the patients living more than 10 years without disease. Patients with angiosarcoma had a poor prognosis (P = .03).

Conclusions: Although primary hepatic sarcoma is a rare malignant tumor, no standard treatment is established. A long-term survival is possible after complete tumor resection in a preselected population with early-stage disease.


SARCOMAS ARE RARE MALIGNANT tumors arising from mesenchymal cells exhibiting heterogeneous histological patterns. In the liver, these tumors represent only 0.1% to 2% of primary hepatic cancer.1,2 In most patients, causative factors remain unclear. Primary symptoms are nonspecific. In spite of precise preoperative imaging, it remains difficult to find the correct diagnosis.

Chemotherapy may stabilize the disease, whereas primary hepatic sarcomas seem to be resistant to radiation therapy.8,9 Only a few studies about surgical treatment of primary hepatic soft tissue sarcomas have been published and treatment is not yet standardized. The aim of this report was to analyze our experience with this rare malignancy.

See Invited Critique at end of article

METHODS

Data of all patients with a soft tissue sarcoma were prospectively entered into a computerized database during hospitalization. Follow-up was recorded for each patient thereafter. Institutional review board approval was obtained for this study and each participant gave written informed consent.

Between October 1985 and October 2006, 22 consecutive patients with primary hepatic sarcoma received surgical treatment with curative intent. Of those, 21 patients had their initial operation at our departments, whereas 1 patient was initially treated at another hospital.

We collected and evaluated data of those patients with respect to patient history, charac-
Table. Population Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Histology</th>
<th>Tumor Size, cm</th>
<th>Grade</th>
<th>Initial Operation, R Status</th>
<th>Relapse</th>
<th>Follow-up, mo</th>
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<tbody>
<tr>
<td>1/F/75</td>
<td>HAP</td>
<td>7</td>
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<td>DOD, 35</td>
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<td>DOD, 30</td>
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<td>4/F/36</td>
<td>MFH</td>
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<td>Segmentectomy and partial</td>
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<td>6/F/19</td>
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<td>G2</td>
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<td>Lung, DOD, 73</td>
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<td>7/F/64</td>
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<td>G1</td>
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<td>G3</td>
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<td>Lung, DOD, 20</td>
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<td>G2</td>
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<td>Local, lung</td>
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<tr>
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<td>G3</td>
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<td>4</td>
<td>G2</td>
<td>Atypical liver resection, R0</td>
<td>NED, 145</td>
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Abbreviations: AWD, alive with disease; DOD, date of death; HAP, hepatic sarcoma; HAS, hepatic angiosarcoma; HE, hemangiopericytoma; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; NED, no evidence of disease; RMS, rhabdomyosarcoma; US, undifferentiated sarcoma.

RESULTS

The characteristics of our population are shown in the Table. The median age of our patients was 54 years (range, 19-80 years). There were 14 female and 8 male patients.

Most patients presented with unspecific symptoms. Three patients had pressure sensations or pain in the right epigastrium. In 2 patients, a recent weight loss was assessed. Hepatomegaly could be diagnosed on palpation or imaging in 2 patients, while no patient presented with jaundice. In the majority of patients (n=15), the hepatic lesions were incidental findings during routine medical examinations. Only 1 patient (71-year-old man) with a primary hepatic angiosarcoma had a known thorotransfusion, a potential risk factor for hepatic sarcoma.

The median diagnostic interval (time between first symptoms and diagnosis of primary liver sarcoma) was 2 months (range, 0-72 months). A 19-year-old woman had been treated for recurrent abdominal cramps since the age of 14 years. Her complaints were continually misdiagnosed as a common gastritis. Eventually, ultrasonography of the epigastrium revealed a large tumor near the portal hilum and she was eventually referred to our hospital for surgical treatment.

Liver function tests were performed in 5 patients, resulting in 4 pathological functions. Common serum tumor markers (a-fetoprotein, carcinoembryonic antigen, and cancer antigen 19-9) proved to be negative.

\*R status was defined according to the staging system of the International Union Against Cancer. See “Methods” section for further explanation.

CLINICAL PRESENTATION

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The following candidate variables were compared by the log-rank test: age at primary surgery, tumor grade, and histology. P < .05 was considered statistically significant. Statistical evaluation was performed using SPSS software (SPSS Inc, Chicago, Illinois).

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preoperatively as well as postoperatively in the entire group. Only 1 patient (80-year-old woman) with a perforated angiosarcoma had an elevated serum level of cancer antigen 12-5 (ovarian cancer tumor marker), in spite of unsuspicous female pelvic organs. Viral hepatitis serology results were negative in all patients.

At initial clinical presentation, imaging (ultrasonography, spiral computed tomographic scan, or magnetic resonance) revealed 21 sarcomas to be solitary with intrahepatic location. The earlier-mentioned 19-year-old woman presented with a multifocal leiomyosarcoma.

At the time of initial staging, 19 tumors were more than 5 cm and 3 tumors, 5 cm or less in maximum diameter. The median tumor size was 7 cm (range, 4-14 cm).

**SURGERY**

The technique of resection for primary hepatic sarcomas did not differ from surgery for any other hepatic malignancy. In 21 patients, primary surgery was performed at our departments. Most of these patients received a hemihepatectomy (n=10). Of those, 3 were performed as an extended hemihepatectomy. In 4 patients, a bisegmentectomy was carried out and twice a segmentectomy was required to resect the lesion to achieve tumor-free margins. Three times a nonanatomical resection was performed. Initial orthotopic liver transplant was performed in 2 patients. One patient was referred to our department for recurrent tumor after undergoing an enucleation (R1) for his hepatic sarcoma. We performed a resection with curative intention, which thereafter was confirmed as R0 by histological examination.

R0 resection (at least 1 cm) was confirmed in 18 patients. Microscopically positive margins (R1 resection) were found in 4 patients. No patient had macroscopic residual tumor (R2 resection).

The postoperative mortality was 0%. Two patients required reoperation for bile leakage. In 1 patient, a postoperative abscess was successfully treated by placing an interventional drain.

**HISTOLOGY**

Leiomyosarcoma (n=7) was the most frequent histological subtype, followed by rhabdomyosarcoma and angiosarcoma (n=5 each). While in 15 patients the tumors were moderately (G2) and in 6 patients poorly (G3) differentiated, 1 sarcoma was classified as well differentiated (G1).

**ADJUVANT TREATMENT**

The adjuvant regimen in oncological surgery is changing continuously. Therefore, the adjuvant setting also varied in our patient cohort. It was always determined by our weekly interdisciplinary tumor board. No preoperative (neoadjuvant) therapy or postoperative radiotherapy was applied.

Eight patients with poorly differentiated tumors received postoperative chemotherapy with doxorubicin hydrochloride, cyclophosphamide, etoposide phosphate, and/or ifosfamide after interdisciplinary consultation. Mostly, indication for chemotherapy was based on the diagnosis of poorly differentiated tumors and distant metastases. Three patients underwent chemotherapy for a recurrent tumor relapse. No patient was included in a prospective randomized trial for adjuvant therapy strategies.

**LOCAL RECURRENT AND METASTASES**

Within the follow-up period, a local recurrence after our resection was diagnosed in 6 patients (27%) after a median interval of 13 months (range, 4-47 months). Most of the distant tumor manifestations (n=7) were diagnosed within 2 years after initial surgery, 4 of them within the first postoperative year. The lung was affected in 6 patients and proved to be the most common site of metastatic spread, followed by hepatic metastases (n=4). Primary sarcomas of patients with distant metastases had been assigned the following histological subtypes: 4 leiomyosarcomas, 3 angiosarcomas, 1 rhabdomyosarcoma, 1 hemangioendothelioma, and 1 malignant peripheral nerve sheath tumor; all of them proved to be moderately differentiated (G2). An ideal resection quality (R0 resection) could not prevent metastatic spread in 6 patients. Four patients relapsed after R1 resection.

**SURVIVAL**

The median follow-up was 88 months (range, 6-246 months). By the time of last data actualization, 12 patients (55%) were still alive without evidence of disease, with a median postoperative survival time of 153 months (range, 16-246 months) after their initial operation.

Nine patients died, with a median postoperative survival time of 34 months (range, 10-73 months). The most frequent cause of death was tumor cachexia (n=5). Further reasons were hepatic decompensation, gastrointestinal hemorrhage, or tumor rupture. One patient’s death 21 months after tumor extirpation could not be attributed to the initial disease.

Calculations from the Kaplan-Meier plot with the probabilities of survival 2, 3, and 5 years after primary surgical treatment were 85.2%, 70.2%, and 65.2%, respectively, for the entire cohort (Figure 1). For the 18 patients who underwent R0 resection, the 5-year disease-specific survival was 77%. All patients in whom an R1 resection was performed (n=4) died within 36 months. Eleven patients (50%) survived longer than 5 years and 9 of them (41%) were still alive without any proof of tumor relapse 10 years after their initial operation.

Statistical significance with respect to factors affecting survival could be assessed for tumor histology (angiosar-
Soft tissue sarcomas are rare malignant tumors originating from mesenchymal cells. In adults, a majority (>95%) of all primary hepatic tumors are carcinomas. However, sarcomas represent only 0.1% to 2% of the latter.1,2 Mostly located on the extremities or trunk, the liver is—apart from metastatic disease—a rather rare location for this entity.

Children have these tumors much more often. Carriaga and Henson1 found 23% of all primary pediatric tumors of the liver to be of mesenchymal origin. Sarcomas represent merely 2% of primary hepatic cancer. The median age of our population was 54 years, corresponding to age distributions in the literature.

Unlike hepatocellular carcinomas, which are highly associated with chronic hepatitis, alcohol abuse, or cirrhosis, causative parameters for hepatic sarcomas remain unclear in most patients. Only a few risk factors, such as neurofibromatosis,13 hemochromatosis,14 and ingestion of oral contraceptive agents,15 have been discussed in the past. Arsenic, vinyl chloride, and thorotrast16,17 have been related to the incidence of hepatic angiosarcomas. In our study, 1 patient with primary hepatic angiosarcoma had a thorotrastosis of the prostate gland, whereas oncogenesis in the other patients remained unclear. Consistent with the literature showing that most patients present with nonspecific symptoms, such as abdominal discomfort or pain, weight reduction, or chills,4-6,18,19 our patients had comparable complaints. Common tumor markers (such as α-fetoprotein, carcinoembryonic antigen, cancer antigen 19-9) are not elevated in patients with sarcoma.

Because of their various histological compositions, including areas of necrosis and hemorrhage, sarcomas present inconsistently in computed tomographic scan as well as in magnetic resonance and ultrasonography. In spite of constantly improving imaging techniques, it is still a challenge to differentiate sarcomas from other liver diseases like hepatic cysts, hemangiomas, or metastases.20

Therefore, the diagnosis of a hepatic sarcoma always depends on a histopathological analysis. Percutaneous biopsy of hepatic tumors is still debatable. Malignancy cannot be excluded on the basis of tumor-negative biopsy specimens, as there is never a guarantee for a representative probe. Samples taken from necrotic areas or perifocal parenchyma may lead to false-negative results. On the other hand, liver puncture may cause severe bleeding and bile duct injuries and is thought to be responsible for metastatic spread.21 Therefore, we believe that an open biopsy is associated with fewer complications. In addition, explorative laparotomy with intraoperative ultrasonography contributes to an exact staging of the disease. Using fast-frozen sections, a differentiation between a benign and malignant lesion is, according to our experience, always possible, so that surgical resection strategy is determined by malignancy rather than its histological subtype.

Most sarcomas have one distinct histological pattern. However, tumors with 2 or more histological phenotypes have been described.22 Distributions of histological subtypes vary in the literature and correspond to the respective patient population. Angiosarcoma, for example, is found 3 times more often in male than in female patients.23 Unlike in our study, where most patients had a leiomyosarcoma, the most frequent subtype of liver sarcoma in adults is angiosarcoma.24 In childhood, rhabdomyosarcoma is the predominant subtype.25 In patients with hepatic leiomyosarcoma or gastrointestinal stromal tumor, a primary tumor of the gastrointestinal tract should be excluded.

The rareness of primary hepatic sarcomas averts a broader understanding of this disease. So far, only a few reports about primary hepatic sarcoma with low case numbers have been described in the literature, making it understandable that no standard therapy exists. Therefore, therapy of every single case requires a strict interdisciplinary foundation of an experienced tumor board.

There is no doubt that a complete resection of the primary tumor (R0 status) is the leading component in curative therapy for patients with primary sarcoma of the liver.4-6,18,19 Liver surgery has improved and new tech-

Figure 1. Kaplan-Meier diagram showing estimates of survival after initial hepatic surgery.

Figure 2. Tumor histology was a significant prognostic parameter in our population (angiosarcoma vs all other histologies, P =.03).
niques of resection and a wider understanding of the perioperative treatment are constantly reducing the perioperative morbidity and mortality. Today, wherever feasible, a malignant tumor of the liver should be resected. Hospitals with high-volume liver resections seem to have better results regarding patient outcome compared with lower-volume hospitals.26,27

In our study, the extent of initial surgery varied. Because of their multifocal growth, we prefer resections with respect to anatomical boundaries. One patient received an enucleation for his primary tumor, resulting in an R1 situation. He was referred to our department for definitive surgery. Today this technique is obsolete because it results in an increased risk for local relapse.

Liver transplant for primary soft tissue sarcomas has not fulfilled its expectations. Rapid tumor relapse leads to a poor outcome.7 Our experience confirms this observation: 1 patient, a 19-year-old woman, who underwent this procedure developed diffuse pulmonary metastasization. Nevertheless, this young woman survived 73 months.

A supportive role of neoadjuvant/adjuvant radiation or chemotherapy is not confirmed in primary hepatic sarcomas. In some patients, adjuvant chemotherapy seems to slow the course of disease. However, hepatic sarcomas seem to be radioresistant. Also, the adverse effects for the neighboring organs would be too severe for high radiation dosages.8,9

The role of radiofrequency ablation for primary sarcoma of the liver is yet not determined. Though it could be found that long-term survival for liver metastases of soft tissue sarcoma is possible, best results are still gained by surgical resection.28 In addition, for patients with unresectable primary soft tissue sarcoma, therapeutic strategies may include cryotherapy or intra-arterial chemotherapy, though this was not performed in our study cohort.

The survival in most patients with primary sarcoma of the liver is poor. Patients with inoperable disease die within a short period after initial diagnosis because of local tumor progression or early metastatic spread. However, as in our population, a long-term survival for more than 10 years after curative surgery (R0 resection) is possible.29 Our patients presented with localized resectable disease and with acceptable preoperative physical conditions. In this preselected population, we achieved overall favorable courses of disease. The 5-year disease-specific survival of more than 65% in our cohort is comparable with a recent analysis from the Memorial Sloan-Kettering Cancer Center by Weitz et al,29 who presented a series of 16 patients who underwent resection surgery for hepatic soft tissue sarcomas and had a survival rate of 64%, though they included only patients with R0 resection for this analysis. In accordance with this study, none of our patients survived longer than 3 years after incomplete tumor resection. Therefore, both studies demonstrate clearly that complete surgical resection seems to be the only potentially curative treatment.

Patients with hepatic angiosarcoma are known for having a fatal outcome.24,29,30 This aggressive tumor tends to spread at an early stage. Even after potentially curative resection, most patients die within months. In our study, patients with angiosarcoma had a poor outcome, too. Long-term tumor-free survival of more than 8 years was only achieved in 1 patient. In spite of early local and distant relapse, we believe that resection surgery should nevertheless be aimed at patients with primary hepatic angiosarcoma to prevent tumor rupture followed by severe abdominal bleeding. Surgery is apparently the only curative treatment, whereas chemotherapy in this sarcoma subtype bears only little benefit so far. It can be administered after surgery or as a palliative treatment option in cases of an unresectable lesion. Novel molecular therapies (eg, vascular endothelial growth factor antagonist) may be a treatment alternative to improve outcome in the future.

**CONCLUSIONS**

There is no standard treatment in patients with primary hepatic sarcomas. Only a few reports are found in the literature. Our study demonstrates that long-term postoperative survival is possible in a preselected subset of patients with localized, low-stage disease and in suitable preoperative physical condition. Early diagnosis is an important factor and improvements in imaging techniques will hopefully help to distinguish resectable from nonresectable tumors in the future. In particular, ultrasonography of the abdomen applied routinely should detect hepatic tumors at an earlier stage. In addition to surgery, new adjuvant strategies applied in clinical studies (eg, tyrosine kinase inhibitors) may help to improve the prognosis of this rare disease.

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**REFERENCES**
As we enter the 21st century, there is no question that liver resections will be done more frequently, more safely, and by more surgeons than ever before. New techniques for resection are being introduced, so that blood loss and complications are at an all-time low. The accepted mortality for liver resection used to be around 5%, but now the large centers are doing major resections with mortalities of less than 2%. These conditions lead surgeons to be more liberal as to patient selection for hepatic resection. This study about primary hepatic sarcomas is an example of a clear indication for liver resection as a treatment for a condition in which many once thought was incurable.

Primary hepatic sarcomas are very rare tumors, so there are no real experts on this pathology. Matthaei et al were able to collect 22 patients in 20 years who underwent a resection as treatment for primary hepatic sarcoma. A recent study in 2007 from Memorial Sloan-Kettering Cancer Center, one of the largest cancer centers in the United States, reviewed the same pathology seen at their institution over a period of 24 years and only had 16 patients who underwent resection. This is indeed a rare tumor.

The main value of reports on very rare tumors is to compile data to lead to more empirical factors on how to treat such patients. Matthaei et al show us in their report that patients with primary hepatic sarcoma should have a resection, because this gives a decent chance for survival. Both this study and the Memorial Sloan-Kettering Cancer Center study had 5-year survival rates of more than 60% for patients with R0 resections, that is, resections with pathologically negative margins. The Matthaei et al report actually had a 77% 5-year survival rate for their 18 patients who had R0 resections. The clear take-home message is that liver resections for solitary hepatic angiosarcoma: findings at CT and MR imaging. Radiology. 2002;222(3):667-673.


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