Management of Giant Hemangioma of the Liver: Resection versus Observation

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BACKGROUND: Management of patients with giant hemangiomas of the liver encounters persistent controversy. Although recent case series suggest a low complication rate with nonoperative management, the classic paradigm of preventive operative resection remains.

STUDY DESIGN: A retrospective cohort study was conducted of 492 patients with giant hepatic hemangioma (≥4 cm in size) diagnosed between 1985 and 2005 at Mayo Clinic Rochester. Long-term outcomes were assessed by patient survey, with a follow-up of 11 ± 6.4 years.

RESULTS: Of 492 patients, 289 responded to the survey. In the nonoperative group (n = 233), 20% had persistent or new onset of hemangioma-associated symptoms, including potentially life-threatening complications in 2%. In the operative group (n = 56), perioperative complications occurred in 14%, including potentially life-threatening complications in 7%. None of the operative patients had persistent or new onset of hemangioma-associated symptoms after resection of the dominant hemangioma. In group comparison, the rate of adverse events was similar (20% versus 14%; p = 0.45) with an overall low risk for potentially life-threatening complications (2% versus 7%; p = 0.07). Size of hemangiomas was not associated with adverse events in either group. Subjective health status and quality of life at follow-up were similar in both groups (p > 0.54).

CONCLUSIONS: Clinical observation of patients with giant hemangioma of the liver has a similar rate of complications compared with operative management, but might prevent the need for invasive interventions in some patients. Clinical observation is preferred in most patients and operative treatment should be reserved for patients with severe symptoms or disease-associated complications. (J Am Coll Surg 2010;211:724–730. © 2010 by the American College of Surgeons)

Hemangioma is the most common neoplasm of the liver, affecting 3% to 20% of the general population. Most hepatic hemangiomas are small (<1 cm in diameter), stable, and are usually managed expectantly in the absence of symptoms or complications. Management of patients with giant hemangiomas of the liver (ie, ≥4 cm in size), however, has been controversial. Life-threatening complications associated with hemangiomas have been reported but their true incidence is poorly documented.

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Although several recent case series suggest a low complication rate with nonoperative management of giant hepatic hemangiomas, the natural disease course of giant hemangiomas is insufficiently determined. A classic paradigm advocating preventive treatment of giant hemangiomas by enucleation, resection, or hepatic artery embolization/ligation in the absence of clear evidence of the natural history persists in the medical community. At the same time, indications for therapeutic intervention for persistent symptoms or complications with enucleation, resection, and, in selected patients, liver transplantation or hepatic artery occlusion, are poorly defined.

This large retrospective single-institutional cohort study evaluated the rate of hemangioma-associated complications in patients with giant hemangioma of the liver after clinical observation and after operative treatment, with the goal of identifying an optimal treatment algorithm.
METHODS

All adult patients (18 years or older) who gave research authorization and who received a diagnosis of hepatic hemangioma during a medical evaluation between January 1, 1985 and December 31, 2005 at Mayo Clinic Rochester documented in the Medical Index database were evaluated. After review of the clinical charts, the study group was limited to patients with hemangioma of the liver >4 cm in largest diameter diagnosed at our institution through abdominal CT, MRI, or ultrasonography. Incidence of death and presumed cause of death of patients meeting eligibility criteria were identified through Mayo Clinic records and Social Security Death Index. Alive patients meeting the eligibility criteria received a survey by mail. Initial nonresponders received a second mailing. If still nonresponding, patients were contacted by phone. Written consent was obtained from responders for the purpose of this study. Survey responders were assigned to either a nonoperative or operative group according to the following criteria: patients who underwent an operative intervention (excluding endovascular procedures) with hemangioma as the primary indication within 6 months after first diagnosis at Mayo Clinic Rochester were assigned to the operative group; patients who did not undergo hepatic operative intervention or underwent hepatic resection for symptoms or complications attributed to hemangiomas after an observation period ≥6 months after the initial diagnosis at Mayo Clinic were assigned to the nonoperative group; and patients who underwent liver resection for hemangioma-unrelated reasons with the hemangioma contained in the operative specimen were included in the nonoperative group but censored at time of liver resection. Duration of follow-up was defined as the time interval between diagnosis at Mayo Clinic Rochester and response to survey (nonoperative group) and the time interval between operation and response to survey (operative group). Perioperative morbidity and mortality included complications or death during the hospital stay or within 30 days of operation. Perioperative morbidity was categorized according to Clavien classification. Medical comorbid conditions were assessed by Charlson score. The last follow-up radiographic cross-sectional study was reviewed if conducted at our institution and performed ≥6 months after initial diagnosis or operative treatment. The study was approved by the Mayo Clinic Rochester Institutional Review Board.

Descriptive statistics were reported as percentage or mean ± SD, unless specified otherwise. Two-sample t-test, chi-square test (or Fisher’s exact test), and log-rank test were used to compare outcomes between the operative and nonoperative groups as appropriate. Cumulative probability was estimated using Kaplan-Meier estimates. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using SAS version 9.0 computer software (SAS Institute).

RESULTS

During the study period, there were 2,865 adult patients who gave research authorization and who were evaluated at Mayo Clinic Rochester with a documented diagnosis of hemangioma of the liver. After review of the radiographic reports, 492 patients were identified with a giant hemangioma of the liver (>4 cm in greatest diameter). Of the 492 patients, 42 were identified as deceased at the time of the survey. Causes of death in the 42 deceased patients were unrelated to the hepatic hemangioma in 32 patients and unknown in 10 patients. Of the 450 patients alive at the time the survey, 289 (64%) responded to the survey, with a mean follow-up of 11.6 years (median 10 years, range 1.5 to 24 years), and were included in the study group. Nonresponders were not assessed. Of the 161 nonresponders, 155 did not return the survey, 4 elected not to participate in the survey, and 2 were unable to be contacted.

There were 211 women and 78 men in our study group. The mean age at diagnosis of the 289 patients was 51 ± 11 years (range 22 to 80 years). The initial radiographic study providing the diagnosis of hemangioma included CT scan (61%), ultrasonography (28%), and MRI (11%). The mean size of the greatest diameter of the largest hemangioma was 8.4 ± 4.6 cm (median 7.0 cm, range 4.1 to 30.0 cm; Fig. 1). Nearly half of the patients (47%) had more than 1 hemangioma (range 1 to 20 hemangiomas per patient; Fig. 2) and 8% of patients had more than 1 giant hemangioma per liver (range 1 to 3 giant hemangiomas per patient). The average medical comorbidity index in this group measured by Charlson score was 0.5 ± 1.2. Of the 289 patients,
233 (81%) were categorized into the nonoperative group and 56 (19%) into the operative group based on our selection criteria.

**Nonoperative group (n = 233)**

Of the 233 patients treated by clinical observation, 26 (11%) had symptoms attributed to the hemangioma at diagnosis. Additionally, in 20 patients (9%) who were asymptomatic at diagnosis, symptoms or complications developed during follow-up at a median of 3.9 years (range 7 months to 18.2 years) after diagnosis (Fig. 3). Among the 46 patients (20%) who had persistent or new-onset symptoms, symptoms resolved during the follow-up period in at least 18 patients. Types of symptoms or complications encountered are listed in Table 1. Neither size nor number of giant hemangiomas (p = 0.15 and p = 0.08, respectively) were associated with occurrence of new onset of symptoms or complications. Even for 42 patients with extremely large hemangiomas >10 cm in size, the frequency of new onset of symptoms and complications was not significantly greater than for the patients with hemangiomas ≤10 cm in size (14% versus 7%; p = 0.22). Symptoms required hospitalization during follow-up in 17 patients (7%). Intervention for these symptoms was necessary in 14 patients (6%; Table 2) and included hepatic resection or enucleation in 11 patients, hepatic artery embolization in 2 patients, and liver transplantation in 1 patient with hemangiomatosis. Nine of the 14 procedures were performed at our institution. Perioperative morbidity and mortality in these 9 patients was 33% and 0%, respectively, with major complications (Clavien grade III to V) in 1 patient.

Of the 233 patients in the nonoperative group, 8 reportedly suffered major abdominal trauma, eg, motor vehicle collision, during follow-up. One of the 8 patients had a hepatic injury, but none reportedly injured or ruptured a hemangioma. Subjective health status and quality of life in the nonoperative group was good to excellent for most patients at follow-up (Table 3). Only 2 patients (1%) were unable to work full- or part-time due to symptoms attributed to hemangiomas. Follow-up radiographic studies were available in 91 patients (39%), performed at a mean of 5.1 ± 4.4 years after initial diagnosis. The follow-up radiographic study included CT scan (60%), ultrasonography (31%), and MRI (9%). The modality of follow-up imaging differed from the initial imaging modality in 40% of patients. On these 91 follow-up studies, mean size of the largest hemangioma did not change significantly (initial imaging 7.4 ± 3.3 cm versus follow-up imaging 7.6 ± 3.5 cm; p = 0.32). Only 14% of patients had an increase in size >1 cm during follow-up. Interestingly, 18% of these patients had a new hemangioma identified on follow-up imaging.

**Operative group (n = 56)**

Indications for operation in the 56 patients in our operative group were chronic abdominal pain (52%), considerable increase in size (14%), pain in combination with gastrointestinal symptoms (11%), gastrointestinal symptoms alone (9%), chronic fever (4%), obstructive jaundice (2%), hemorrhage (2%), patient anxiety (2%), and unknown (2%). Thirty-four patients underwent partial hepatectomy (including 1 laparoscopic resection) and 22 patients underwent hepatic enucleation (including 1 patient with synchronous radiofrequency ablation of a small hemangioma). There was a significant trend toward enucleation in recent years (1985 to 1998: 27% of operations versus 1999 to 2006: 58% of operations; p = 0.03). Multiple hemangiomas were removed in 23% of patients. Microscopic negative margins were achieved in all but 1 patient (2%).
all perioperative morbidity was 14% (partial hepatectomy 18% versus enucleation 9%; p = 0.45). Complications were minor (Clavien grade I and II) in 4 patients and major (Clavien grade III to V) in 4 patients. Perioperative mortality was 0%. Neither hemangioma size nor number of hemangiomas removed was significantly associated with perioperative morbidity (p = 0.40 and p = 0.97, respectively). In fact, even resection of extremely large hemangiomas (>10 cm) had a perioperative morbidity rate of only 19% (n = 26). Mean length of hospital stay was 6 ± 3 days.

During follow-up, none of the 56 patients had persistence or recurrence of preoperative symptoms; and new symptoms attributed to hemangiomas developed in none (Fig. 3, Table 1). Based on responses in patient surveys, subjective health status at follow-up was rated good or better in 93%; with a quality of life rated as good or better in 93% (Table 3). After resection or enucleation of the hemangioma, all patients were able to work full- or part-time. Follow-up radiographic studies, available in 16 patients, showed residual hemangioma in 1 patient who had microscopic positive margins initially. Three patients developed new hemangiomas at a different site within the liver.

**Comparison of adverse outcomes by groups**

The rate of adverse events during the study period was compared between groups. For the nonoperative group, adverse events included new or persistent symptoms or complications attributed to hemangiomas and any intervention for hemangiomas during the follow-up period. For the operative group, adverse events included perioperative morbidity and adverse events, as described in the nonoperative group occurring after operation. There was no statistically significant difference in the overall rate of adverse events between groups (nonoperative 20% versus operative 14%; p = 0.45; Table 2). Although the operative group had an initial greater adverse event rate due to perioperative complications, there was no apparent statistical difference in cumulative probability of new adverse events between the groups (p = 0.30, log-rank). The cumulative probability at 5 years (nonoperative 5.6% [95% CI 2.3–8.7] versus

### Table 1. Frequency of Symptoms and Complications Associated with Hemangiomas in 289 Survey Responders at Time of Diagnosis, Persistent since Time of Diagnosis or Operation, and New Onset during Follow-Up

<table>
<thead>
<tr>
<th>Symptoms and complications*</th>
<th>Nonoperative group (n = 233)</th>
<th>Operative group (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At diagnosis</td>
<td>Persistent</td>
</tr>
<tr>
<td>Chronic abdominal pain</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Early satiety</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Chronic nausea or vomiting</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Jaundice</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chronic fever</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemobilia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemangioma-associated heart failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic hemorrhage or rupture</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis of hemangioma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Kasabach-Merritt syndrome</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total patients with symptoms or complications</td>
<td>26</td>
<td>11</td>
</tr>
</tbody>
</table>

*More than 1 symptom or complication per patient possible.

### Table 2. Comparison of Adverse Outcomes during Follow-Up between Nonoperative and Operative Group

<table>
<thead>
<tr>
<th>Type of adverse events*</th>
<th>Nonoperative group (n = 233)</th>
<th>Operative group (n = 56)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Perioperative morbidity</td>
<td>—</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Persistence of symptoms or complications</td>
<td>26</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>New onset of symptoms or complications</td>
<td>20</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Need for intervention or reoperation</td>
<td>14</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Total patients with adverse event</td>
<td>46</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

*More than 1 type of adverse outcomes per patient possible.
operative 14.3% [95% CI 4.6–23.0]), at 10 years (nonoperative 9.2% [95% CI 4.7–13.5] versus operative 14.3% [95% CI 4.6–23.0]), and at 20 years (nonoperative 17.3% [95% CI 7.9–25.7] versus operative 14.3% [95% CI 4.6–23.0]) showed that 95% confidence intervals were overlapping, suggesting no significant differences at these points in the follow-up (Fig. 3). Potentially life-threatening complications (hepatic hemorrhage/rupture, hemobilia, Kasabach-Merritt syndrome, or hemangioma-associated heart failure) were uncommon. Such complications in the nonoperative group (2%) were offset by occurrence of major complications (Clavien grade III to IV) in the operative group (7%; p = 0.07). Subjective health status and quality of life were not significantly different between groups (p = 0.54 and p = 0.57, respectively; Table 3).

**Evaluation of study’s internal validity**

The study’s internal validity was analyzed by comparing selected clinical variables in survey responder versus nonresponders and in the nonoperative versus operative group. Results are listed in Tables 4 and 5.

**DISCUSSION**

The findings of this study demonstrate that nonoperative management of giant hemangioma of the liver is safe in most patients. We have shown that the long-term risk of adverse events associated with nonoperative management is similar to the short-term risk of operative morbidity associated with operative management; with an overall low rate of potentially life-threatening complications. In addition, any potential occurrence of non–life-threatening adverse events during clinical observation will likely resolve without invasive measures. Although, hepatic resection or enucleation of hemangiomas can be performed with low morbidity, operative intervention should only be recommended for patients with symptoms sufficiently severe enough to affect lifestyle and to justify operative risk.

Hemangiomas of the liver occur more commonly in women and during middle age (mean age at diagnosis 50 years). Cross-sectional imaging usually provides an accurate diagnosis.1 Because the diagnosis is usually made at an age with an average life expectancy of 30 or more years, it has to be prudent that any form of nonoperative management is not only safe in the short-term, but also provides a low failure rate in the long-term. Our study showed that the risk for new complications, such as compression of surrounding structures, arteriovenous shunting, and rupture or symptoms of pain, nausea, and early satiety occurred in about 9% of the 233 patients managed with observation during an 11 ± 6.4 year follow-up. This rate is greater than that observed by others, who showed that 0% to 5% of patients with giant hepatic hemangioma develop symptoms under nonoperative management.4,6 However, these reports differ from ours in size of study cohort (n = 17 to 62) and duration of follow-up (1.8 to 4.9 years).4,6 Similar to other studies, we were unable to identify clear risk factors for the occurrence of adverse events with clinical observation.

Consequently, we believe that prophylactic operative in-
tervention, with rare exception, cannot be recommended, even in patients with extremely large hepatic hemangiomas. The risk for potentially life-threatening events of only 2% in the nonoperative group compared with a 7% risk of major morbidity in the operative group suggests that prophylactic operative intervention is not broadly applicable. Patients with access to medical care and who are aware of the natural history of hemangiomas of the liver should be initially managed nonoperatively. Operative intervention for giant hepatic hemangiomas, preferably by enucleation, should be reserved for patients who fail nonoperative management. Prophylactic resection independent of size has no role, with the rare exception of patients with uncompensated anxiety related to the hemangioma, some select patients without access to medical care, or rarely when a definitive diagnosis cannot be made and malignancy cannot be excluded by other means. We and others demonstrated that even extremely large hemangiomas (>10 cm) are not necessarily associated with an increased rate of complications. Size alone should not be the indication for hepatic resection. Even if the hemangioma would grow and subsequent symptoms or complications would develop, hepatic resection or enucleation can still be performed with similar morbidity in experienced hands.

A misperception exists that enucleation or resection of giant hemangiomas is "risky and bloody" and that hemangiomas recur after excision. Our study and others were able to demonstrate that operations for hemangiomas can be performed safely. Several series reported a morbidity rate of 10% to 27% with low blood loss and a mortality of 0% to 2% after enucleation or resection of hepatic hemangiomas compared with 14% and 0% observed in this study, respectively. Recurrence has been reported in <5%. Most likely, reputed recurrence represents progression of incompletely resected hemangioma. Enucleation of hepatic hemangiomas is preferred over partial hepatectomy due to parenchymal sparing with potentially lower morbidity and similar rates of recurrence. Enucleation is feasible because of the well-circumscribed capsule of hemangiomas and discrete interface with the adjacent hepatic parenchyma. In addition, hepatic hemangiomas displace and splay bile ducts and vessels, and for the most part have few feeding arteries. Most hemangiomas, therefore, can be enucleated; 38% to 79% at other institutions and 59% in this study. Whether the outcomes of laparoscopic enucleation of hemangiomas will be similar to open techniques is unknown. One caveat about enucleation of hemangiomas warrants comment. We have found that resection of the small attenuated hepatic parenchyma peripheral to the enucleation site reduces the risk of necrotic hepatic remnants and bile leaks for very large hemangiomas.

Although this study represents one of the largest reported series while providing sufficient duration of follow-up, our findings have limitations. First, response to surveys was limited, which affected sample size in the operative group. The potential bias due to nonresponse of the survey did not appear substantial because of a response rate of 64% and, despite statistical differences, there were no clinically significant differences in disease features between survey responders and nonresponders. Second, typical for an observational study, there is a potential bias in treatment selection. Although there was a trend toward operative treatment in larger hemangiomas, size did not appear to have an influence on adverse outcomes in our patient population. Regardless, patients in the operative group had a greater rate of symptoms at diagnosis than patients in the nonoperative group, providing a potential for selection bias. Third, the specificity of symptoms attributed to hemangiomas is often difficult to determine. The survey asked patients to include only symptoms that they related to the hemangioma. Clearly the possibility exists that some symptoms perceived as associated with hemangioma were related to other pathology. Even for an experienced clinician this determination can be difficult. Finally, referral bias does not appear to be the case because 17% of the 2,865 patients with hepatic hemangiomas assessed in this study had giant hemangiomas. This is about the same rate seen at other institutions. It is therefore our opinion that the results of this study can be applied to the majority of the United States population.

Author Contributions
Study conception and design: Schnelldorfer, Harmsen
Acquisition of data: Schnelldorfer, Ware, Smoot
Analysis and interpretation of data: Schnelldorfer, Schleck, Harmsen, Nagorney
Drafting of manuscript: Schnelldorfer, Nagorney
Critical revision: Schnelldorfer, Ware, Smoot, Schleck, Harmsen, Nagorney

REFERENCES