Spontaneous Rupture of Hepatocellular Carcinoma

A Systematic Review

Eric C. H. Lai, MB, ChB, MRCSEd; W. Y. Lau, MD, FRCS, FRACS(Hons)

Objectives: To review the management of spontaneous ruptured hepatocellular carcinoma in the acute phase, the definitive treatment after hemostasis, and the prognosis.

Data Sources: A MEDLINE search was undertaken to identify articles in English from 1970 to 2004 using the key words “hepatocellular carcinoma,” “spontaneous rupture,” “therapeutic embolization,” and “laparoscopy.” Additional articles were identified by a manual search of the references from the key articles.

Study Selection: There were no exclusion criteria for published information on the topics.

Data Extraction: All studies that contained material applicable to the topic were considered.

Data Synthesis: In the acute phase, transarterial embolization for hemostasis has a high success rate (53%-100%). It has a lower 30-day mortality rate than open surgical methods (0%-37% vs 28%-75%). For the definitive treatment, staged liver resection has a higher resection rate (21%-56% vs 13%-31%) and a lower in-hospital mortality rate (0%-9% vs 17%-100%) than 1-stage emergency liver resection. Staged liver resection has a good survival rate (1-year survival, 54.2%-100%; 3-year survival, 21.2%-48%; 5-year survival, 15%-21.2%).

Conclusions: Transarterial embolization is effective in controlling bleeding from ruptured hepatocellular carcinoma in the acute phase. The serum bilirubin level, shock on hospital admission, and prerupture disease state are important prognostic factors to predict survival in the acute phase. For definitive treatment, staged liver resection after attaining hemostasis is better than 1-stage emergency liver resection. Laparoscopy and laparoscopic ultrasonography may decrease unnecessary exploratory laparotomy, thus increasing the resection rate of previously ruptured hepatocellular carcinoma. Prolonged survival can be achieved in select patients with definitive treatment. It is still uncertain whether the long-term outcome of liver resection is the same for hepatocellular carcinoma with and without rupture when patients with the same tumor stage and liver functional state are compared.

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Methods

A MEDLINE search was undertaken to identify articles in English from 1970 to 2004 using the key words “hepatocellular carcinoma,” “spontaneous rupture,” “therapeutic embolization,” and “laparoscopy.” Additional articles were identified by a manual search of the references from the key articles. All studies, even case reports, that contained materials related to the topic were considered. This review covered about 1500 patients with spontaneous ruptured HCC.

Results

Mechanism

The mechanism of spontaneous rupture is still not exactly known. Hypotheses include rapid growth of the tumor and necrosis, rupture by splitting the overlying nontumorous liver parenchyma or erosion of a vessel, increased intratumor pressure with the occlusion of he-

Author Affiliations:
Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong.
patic veins by tumor thrombi or invasion,\(^5,6,8\) and coagulopathy.\(^8\) Recently, Zhu et al\(^{29,30}\) postulated that spontaneous rupture of HCC may be related to vascular dysfunction. The vascular dysfunction results from degeneration of elastin and degradation of type IV collagen, rendering the blood vessels stiff and weak and causing them to split easily when the vascular load increases from hypertension or minor trauma. Large and peripherally located tumors are more prone to rupture.\(^5,17,27,31\)

**MANAGEMENT OF RUPTURED HCC IN THE ACUTE PHASE**

The primary aim of management is to attain hemostasis and to preserve as much functioning liver parenchyma as possible. From the 1960s to the 1980s, the open surgical method was the mainstay of treatment for hemo-

### Table 1. Results of Open Surgical Hemostasis for Ruptured Hepatocellular Carcinoma in the Acute Phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Size of Tumor, cm, Mean (Range)</th>
<th>Type of Method</th>
<th>Success Rate, %</th>
<th>Rebleed Rate, %</th>
<th>Liver Failure Rate, %</th>
<th>In-Hospital Mortality Rate, %</th>
<th>7-Day Mortality Rate, %</th>
<th>30-Day Mortality Rate, %</th>
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<tr>
<td>Chearanai et al,,</td>
<td>37</td>
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<td>NA</td>
<td>NA</td>
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<tr>
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<td></td>
<td></td>
<td>electrocauterization (n = 1); HR (n = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chen et al,,</td>
<td>27</td>
<td>NA</td>
<td>Packing, suturing, and electrocauterization</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td>1988</td>
<td></td>
<td>(n = 7);</td>
<td>(n = 7); HR (n = 6); HR (n = 14)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lai et al,,</td>
<td>56</td>
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<td>Plication (n = 2); CHAL (n = 39); SHAL (n = 8);</td>
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<td>28.5</td>
<td>75</td>
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</tr>
<tr>
<td>1989</td>
<td></td>
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<td>HR (n = 7)</td>
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</tr>
<tr>
<td>Cherqui et al,</td>
<td>5</td>
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<td>HAL (n = 1); HR (n = 4)</td>
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<td>1993</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Xu and Yan,</td>
<td>19</td>
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<td>Packing (n = 7); HAL (n = 9); HR (n = 2);</td>
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<td>Leung et al,</td>
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<td>Packing (n = 14); plication (n = 12); HAL (n = 9);</td>
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<td>NA</td>
<td>NA</td>
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</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td>HR (n = 12); alcohol injection (n = 6)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Liu et al,</td>
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<td>NA</td>
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<tr>
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<td>HR/debridement (n = 2); packing (n = 8)</td>
<td></td>
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</table>

**Abbreviations:** CHAL, common hepatic artery ligation; HAL, hepatic artery ligation; HR, hepatic resection; NA, not available; SHAL, selective hepatic artery ligation.

Conservative Treatment

Conservative treatment for ruptured HCC includes correction of coagulopathy, close monitoring, and urgent medical imaging to confirm the diagnosis after initial resuscitation. It is most commonly used in patients in a moribund state and with inoperable tumor.\(^5,10,14,37\) It is therefore not surprising that conservative treatment had poor results in some studies.\(^8,12,26\) Chearanai et al\(^8\) reported a 100% mortality for 16 patients who received conservative treatment. Miyamoto et al\(^12\) reported a 3-month survival rate of 10% and a mean survival of 19.2 days for 14 patients who received conservative treatment.

On the other hand, conservative treatment has been used in some centers on stable patients who have no signs of continuous bleeding.\(^16,18,19,30\) In patients who show signs of continuous bleeding but with good liver function, a hemostatic procedure is carried out. The hemostatic procedure can either be an open surgical approach or TAE.
Xu and Yan\textsuperscript{6} used conservative treatment in this way, and the 1-week and 1-month mortality rates were 26.5% and 48.5%, respectively. These results were comparable with those obtained with emergent open surgery, HAL, and TAE. Unfortunately, in the Xu and Yan study, there was a lack of information on the patients’ background and liver function status. Leung et al.\textsuperscript{18} reported a retrospective study on 112 patients with ruptured HCC. In this study, the outcome of patients treated by a conservative approach was compared with an aggresive approach. In the conservative approach, conservative treatment was used initially with all the patients. A hemostatic procedure was used only when the patients showed signs of continuous bleeding. In the aggressive approach, a hemostatic procedure was used unless the patient’s condition was moribund. The differences between the aggressive and the conservative approaches in the overall in-hospital mortality rate (62% vs 51%) and the median survival time (7 days vs 12 days) were not significant. They concluded that the conservative approach gave similar results to the aggressive approach. However, the conservative approach had the advantage of a lower intervention rate; thus, it was more cost-effective. In the subgroup analysis in which patients with terminal disease were excluded, the in-hospital mortality rate and survival for the conservative approach were significantly better than for the aggressive approach.

\textbf{Perihepatic Packing}

Packing of a bleeding tumor achieves hemostasis by the tamponade effect. It is effective especially for oozing tumors situated near the diaphragm. There was a lack of data on the additional effects of topical hemostatic agents to be combined with perihepatic packing for ruptured HCC. Ong and Taw\textsuperscript{6} suggested that the pack should only be left in situ for 24 to 48 hours if the pack was left longer, infection would invariably take place. To our knowledge, there was no well-planned study to find out how long the perihepatic packing should be left in situ for ruptured HCC in the literature. Most of the clinical evidence was derived from perihepatic packing for liver trauma. The rate of intra-abdominal abscess and sepsis following packing within 72 hours was 23% to 32\textsuperscript{39,40}. If the pack was left in place longer than 72 hours, the infection rate would significantly increase.\textsuperscript{31,42} Thus, the packs should be removed within 72 hours after perihepatic packing. The role of prophylactic antibiotics for perihepatic packing is unclear. Removal of packs also carries the risk of rebleeding.\textsuperscript{6,45} Perihepatic packing is a good procedure in hemodynamically unstable patients who require a quick damage-control laparotomy for further resuscitation and stabilization the patient.

\textbf{Suture Plication}

Suture plication is only applicable when the bleeding site is small and easily accessible. Its use is limited by the friable tumor tissue.\textsuperscript{33} Miyamoto et al.\textsuperscript{7} described 30 patients who underwent packing and/or suture plication. The 3-month survival rate was 26.9%, and the mean survival was 81.5 days.

\textbf{Absolute Alcohol Injection}

Sunderland et al.\textsuperscript{44} reported successful hemostasis in 8 of 9 patients with ruptured HCC using laparotomy and absolute alcohol injection. Bleeding was controlled by a combination of factors including an increase in tissue tension, fixation of tissue, and thrombosis of blood vessels. However, there have been no further studies to validate the results.

\textbf{Hepatic Artery Ligation}

The liver has a dual blood supply from the hepatic artery and the portal vein. In the normal liver, the portal vein supplies 70% of the total hepatic perfusion, and the hepatic artery supplies the rest. However, HCC derives its blood supply almost exclusively from the hepatic artery. In ruptured HCC, HAL has a hemostatic success rate of 68% to 100\textsuperscript{6,8,10}. It also reduces blood flow to the tumor and results in tumor regression. However, the effect is only temporary because the arterial collateral circulations from any of the nearby arteries develop rapidly to supply the tumor from 1 to 4 weeks.\textsuperscript{9} Hepatic artery ligation can either be selective or common. Selective HAL is preferable to common HAL because it results in a lower risk of postoperative liver failure. In addition, the preservation of the contralateral arterial supply allows the possibility of future definitive liver resection or TACE. The use of HAL is limited by its high in-hospital mortality rate of 50% to 77\textsuperscript{5,9,10}.
Transarterial Embolization

The role of TAE in the management of ruptured HCC has increased rapidly in the last 20 years. It has been shown to be highly effective in achieving immediate hemostasis, even in patients with massive hemoperitoneum. With the use of angiographic techniques, the location of tumor, the active bleeding site, and the patency of the portal vein can be assessed. The agents used for embolization are sterile absorbable gelatin sponge (Gelfoam), stainless steel coils, or polyvinyl alcohol sponge (Ivalon). The choice of the embolization agents depends on the size of the artery being embolized. Stainless steel coils and Ivalon particles can produce permanent occlusion of the hepatic artery, while Gelfoam can only produce temporary occlusion. Gelfoam has the advantage of re-cannalization of the embolized artery and provides an opportunity of further TACE. Transarterial embolization is generally considered a contraindication in patients with complete occlusion of the main portal vein by tumor thrombus because of the high risk of hepatic infarction. However, partial occlusion of the portal vein should not be regarded as an absolute contraindication to TAE. Corr et al reported successful TAE without complications in 3 patients with partial portal vein occlusion. The advantage of TAE over surgery is that hemostasis can be achieved better by occluding the feeding vessels more distally and a major surgery can be avoided in a poor-risk patient. Transarterial embolization for hemostasis has a high success rate of 53% to 100% (Table 2). It has a lower 30-day mortality rate (0%-37%) than open surgical hemostasis. The tumor recurrence rate after TAE, which has an extremely poor prognosis, is 0% to 35%. The most common complication of TAE is postembolization syndrome (26%-85%), which consists of fever, abdominal pain, nausea, and liver enzyme elevation. The syndrome usually resolves within 1 to 2 weeks. The major life-threatening complication is liver failure (11.8%-33.3%), which is the most common cause of death after TAE. The selection criteria for TAE in ruptured HCC are not well studied. In the presence of continuous bleeding from the ruptured HCC, TAE should be used for hemostasis in patients with reasonable liver function but without complete portal vein thrombosis. Four retrospective studies showed that TAE was rarely effective in prolonging survival in patients with a serum bilirubin level higher than 2.92 mg/dL (50 µmol/L). It is unclear whether routine TAE will benefit patients with stable hemodynamic parameters in the prevention of tumor rupture and survival.

DEFINITIVE TREATMENT OF RUPTURED HCC

One-Stage Emergency Liver Resection vs Staged Liver Resection

Liver resection provides the only hope of cure for patients with ruptured HCC. Emergency liver resection has been advocated to achieve both hemostasis and to provide a definitive treatment in a single operation. Ong and Taw suggest that a delay in liver resection after initial hemostasis might compromise the resection rate. Their rationale is that ruptured HCC is due to the sudden obstruction of the outflow of blood from the tumor growth. Once HCC invades the venous drainage system, the spread of the tumor will be very rapid. The resection rate during emergency is between 12.5% to 31%. One-stage emergency liver resection carries an inhospital mortality of 16.5% to 100% (Table 3). Emergency liver resection is associated with a poor outcome because the tumor stage and the liver functional reserve are unclear. Furthermore, the presence of hemorrhagic shock renders the liver function poorer than usual. The presence of coagulopathy in a patient with compromised liver function further increases the surgical risk.

Nowadays, most authors advocate staged liver resection as the preferred definitive treatment after the patients and the liver have recovered from the rupture episode. In the medical literature, there is no study, to our knowledge, on the optimal time to carry out staged liver resection. The time ranged from 10 to 126 days. After adequate workup, staged liver resection has a resection rate of 21% to 56%, which is comparable with the resection rate of nonruptured HCC. When compared with 1-stage emergency liver resection, staged liver resection has a much lower in-hospital mortality rate (0%-9%) and a better survival rate (1-year survival rate, 54.2%-100%; 3-year survival rate, 21.2%-48%; 5-year survival rate, 15%-
21.2% (Table 4). One-stage emergency liver resection should be reserved for patients with a small and easily accessible tumor and a noncirrhotic liver.

### Role of Laparoscopy and Laparoscopic USG in the Definitive Treatment of Ruptured HCC

Laparoscopy and laparoscopic USG have been found to be useful in staging hepatobiliary malignancy. With their use, unnecessary laparotomy can be avoided with the detection of peritoneal secondary tumors, liver secondary tumors, or major vessel invasion. Patients with unresectable tumors can benefit from a shorter hospital stay, a lower operative morbidity, and an earlier intervention with another procedure, such as local ablative therapy, internal radiation, TACE, or chemotherapy. A small proportion of patients with unresectable HCC can benefit from salvage surgery after tumor downstaging with these treatments. In patients with a previous ruptured HCC, the tumor stage can be more advanced than in those without rupture. The tumor may progress during the recovery phase from the acute bleed-

### Table 3. Results of 1-Stage Emergency Liver Resection for Definitive Treatment of Ruptured Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Resection Rate, %</th>
<th>Size of Tumor, cm</th>
<th>Operation</th>
<th>In-Hospital Mortality Rate, %</th>
<th>Recurrence Rate, %</th>
<th>1-Year Survival Rate, %</th>
<th>3-Year Survival Rate, %</th>
<th>5-Year Survival Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ong and Taw, 1972</td>
<td>13</td>
<td>31</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>38.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Lai et al, 1989</td>
<td>7</td>
<td>12.5</td>
<td>NA</td>
<td>NA</td>
<td>R hemihepatectomy (n = 2); L hemihepatectomy (n = 2); L lateral segmentectomy (n = 3)</td>
<td>71.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cherqui et al, 1993</td>
<td>4</td>
<td>NA</td>
<td>Mean, 6.5 (range, 4-10)</td>
<td>Wedge resection (n = 2); segmentectomy (n = 1); extended R hepatectomy (n = 1)</td>
<td>25</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>Yoshida et al, 1999</td>
<td>3</td>
<td>16.7</td>
<td>NA</td>
<td>NA</td>
<td>Segmentectomy (n = 1); wedge resection (n = 5)</td>
<td>100</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
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<td>Chiappa et al, 1999</td>
<td>6</td>
<td>NA</td>
<td>Mean, 4.2 (range, 3-8)</td>
<td>Segmentectomy (n = 3); bisegmentectomy (n = 2); R hemihepatectomy (n = 1)</td>
<td>16.5</td>
<td>33.3</td>
<td>NA</td>
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<td>33.3</td>
</tr>
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<td>Vergara et al, 2000</td>
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<td>Mean, 8.75 (range, 4-15)</td>
<td>NA</td>
<td>NA</td>
<td>87.5</td>
<td>NA</td>
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Abbreviation: NA, not available.

### Table 4. Results of Staged Liver Resection for Definitive Treatment of Ruptured Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Resection Rate, %</th>
<th>Size of Tumor, cm</th>
<th>Type of Treatment in First Stage</th>
<th>Interval Between 2 Stages, d</th>
<th>Second Stage Liver Resection—Major Resection, %</th>
<th>In-Hospital Mortality Rate, %</th>
<th>Recurrence Rate, %</th>
<th>1-Year Survival Rate, %</th>
<th>3-Year Survival Rate, %</th>
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<td>Inoue et al, 1992</td>
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<td>NA</td>
<td>Mean, 5</td>
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<td>NA</td>
<td>100</td>
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<td>7</td>
<td>43.8</td>
<td>Median, 9</td>
<td>TAE (n = 7)</td>
<td>12-78; Median, 30</td>
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<td>16-126; Mean, 74</td>
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<td>70</td>
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<td>77</td>
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<td>Liu et al, 2001</td>
<td>33</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>70</td>
<td>9</td>
<td>45.5</td>
<td>25.7 mo</td>
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<tr>
<td>Takebayashi et al, 2002</td>
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<td>50</td>
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<td>0</td>
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<td>36 mo</td>
<td>100</td>
<td>40</td>
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<td>7.1</td>
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<td>NA</td>
<td>54.2</td>
<td>35</td>
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<td>38.5</td>
<td>Mean, 9.6</td>
<td>Conservative (n = 2); TAE (n = 3)</td>
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<td>NA</td>
<td>80</td>
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<td>Mizuno et al, 2004</td>
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<td>Mean, 5.5</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>69.3 (33)*</td>
<td>21.2 (0)*</td>
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Abbreviations: NA, not available; TAE, transarterial embolization.

*Disease-free survival rate.
Table 5. Results of Liver Resection for Ruptured HCC (Staged) and Nonruptured HCC

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Median Survival, mo</th>
<th>1-Year Survival Rate, %</th>
<th>3-Year Survival Rate, %</th>
<th>5-Year Survival Rate, %</th>
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<tr>
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<td>Yeh et al.20 2002</td>
<td>60</td>
<td>54.2</td>
<td>35.0</td>
<td>21.2 (13.4)*</td>
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<tr>
<td>Mizuno et al57 2004</td>
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<td>69.3 (33)*</td>
<td>21.2 (0)*</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Median Survival, mo</th>
<th>1-Year Survival Rate, %</th>
<th>3-Year Survival Rate, %</th>
<th>5-Year Survival Rate, %</th>
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<tbody>
<tr>
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</table>

Abbreviations: HCC, hepatocellular carcinoma, NA, not available.
* Disease-free survival rate.

RADIOFREQUENCY ABLATION

Radiofrequency ablation is increasingly used in patients with small nonruptured HCC confined to the liver, especially when the tumors are unresectable because of poor general condition of the patient or because of compromised liver function. However, the role of radiofrequency ablation in the management of spontaneous ruptured HCC is still unknown. The data on this treatment for ruptured HCC are very limited in the medical literature.75

PROGNOSIS AND SURVIVAL

Ruptured HCC is associated with a high in-hospital mortality rate of 23% to 75%.6,14-19 The serum bilirubin level, shock on hospital admission, and prerupture disease state are important prognostic factors.59,22-25,46 Evidence from retrospective studies showed that a serum total bilirubin level higher than 2.92 mg/dL (50 µmol/L) was a critical level in predicting the outcome. In the series of patients treated with TAE reported by Ngan et al,24 none of the patients with serum total bilirubin levels higher than 2.92 mg/dL (50 µmol/L) survived longer than 9 weeks (median survival of 1 week), while patients with a serum total bilirubin level of 2.92 mg/dL (50 µmol/L) or lower survived 15 weeks. In the series of patients treated with TAE reported by Leung et al,23 the mean survival of patients with a serum total bilirubin level higher than 2.92 mg/dL (50 µmol/L) was only 34 days while that of patients with a serum total bilirubin level lower than 2.92 mg/dL (50 µmol/L) was 165 days.

After curative liver resection for patients with previous ruptured HCC, the 1-year survival rate was 50% to 100%, the 3-year survival rate was 21% to 50%, and the 5-year survival rate was 15% to 33%.13,15,19,49-57 In the medical literature, to our knowledge, there are no prospective studies to compare the outcome of surgical treatment of ruptured and nonruptured HCC. The results from retrospective cohort studies are presented in Table 5. Liu et al55 reported that the survival of patients with ruptured HCC was significantly worse than those with nonruptured HCC. However, Yeh et al53 reported that patients with nonruptured HCC had a similar overall survival as those with ruptured HCC but the disease-free survival rate was significantly better. Mizuno et al57 tried to compare the survival rates of patients with ruptured and nonruptured HCC based on the same background factors, such as disease stage and liver function. They found no significant difference in the 2 groups of patients in the overall survival and disease-free survival. Based on the limited data available in the medical literature, it is difficult to draw a definitive conclusion on the long-term outcome after definitive surgical resection in patients with ruptured HCC when compared with patients with nonruptured HCC. One clear message is that prolonged survival is achievable in select patients with ruptured HCC with liver resection.

COMMENT

Transarterial embolization is effective in controlling bleeding for ruptured HCC in the acute phase. The serum bil-
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