Risk Factors for Early Death due to Recurrence After Liver Resection for Hepatocellular Carcinoma: Results of a Multicenter Study

JEAN MARC REGIMBEAU, MD,1 EDDIE K. ABDALLA, MD,2 JEAN NICOLAS VAUTHEY, MD,2 GREGORY Y. LAUWERS, MD,3 FRANÇOIS DURAND, MD,1 DAVID M. NAGORNEY, MD,4 IWAO IKAI, MD,5 YOSHIO YAMAOKA, MD,5 AND JACQUES BELGHITI, MD1*

1Hôpital Beaujon, Paris, France
2The University of Texas M.D. Anderson Cancer Center, Houston, Texas
3Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts
4Mayo Clinic, Rochester, Minnesota
5Kyoto University Graduate School of Medicine, Kyoto, Japan

Background and Objectives: Recurrence after partial liver resection for hepatocellular carcinoma (HCC) is a major cause of death from this disease. To identify risk factors for early death from recurrence after liver resection for HCC.

Methods: All 547 patients in this study had greater than 1 year of follow-up after complete resection of HCC (1980–1999) at one of the four hepatobiliary centers in Japan, France, and the United States. Patients who died of recurrence <1 year post-resection and all of those alive at least 1 year were compared. Survival and clinico-pathological factors associated with death from recurrence within 1 year of resection were analyzed.

Results: Overall postoperative mortality rate was 5%. In the first postoperative year, 123 (22%) patients died. Of these, 53 (43%) died of recurrence, 30 (24%) of postoperative complications, and 40 (33%) of liver failure/hemorrhage. On multivariate analysis, tumor size greater than 5 cm \( P < 0.02; \) odds ratio, 3.0), multiple tumors \( P < 0.01; \) odds ratio, 3.3), and greater than 5 mitoses per 10 high-power fields \( P < 0.03; \) odds ratio, 3) were associated with increased risk of early death due to recurrence.

Conclusions: These findings enable identification of patients with HCC who are at high risk for early death due to recurrence following potentially curative resection who might be candidates for adjuvant therapy trials.


Key Words: hepatocellular carcinoma; liver resection; Child–Pugh class; hepatitis; fibrosis; cirrhosis

INTRODUCTION

Liver resection is the only curative treatment for hepatocellular carcinoma (HCC). Over the past 2 decades, death in the early postoperative period has been a major pitfall of this procedure [1]. However, identification of preoperative risk factors for postoperative liver failure in patients with cirrhosis [2–4] and improvements in surgical technique [5–7] have made partial liver resection safer and have prompted re-evaluation of overall and disease-free survival rates after resectional therapy for HCC.

Although patterns of recurrence after potentially curative resection for HCC have been documented in detail in several studies, only a few reports have

This study was carried out by the International Cooperative Study Group on Hepatocellular Carcinoma at various centers mentioned in the affiliations.

*Correspondence to: Dr. Jacques Belghiti, MD, Service de Chirurgie, Hôpital Beaujon 100, Boulevard du Général Leclerc, 92 118 Clichy Cedex, France. Fax number: (33)1.40.87.09 26.
E-mail: j.bel@bjn.ap-hop-paris.fr
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examined early recurrence (i.e., within the first year). Previously reported risk factors for early recurrence reflect tumor characteristics—such as high preoperative alpha-fetoprotein level, intrahepatic metastasis [8], large tumor size [9], presence of venous invasion [10,11], tumor rupture [11]—and liver function characteristics, such as high serum alanine transferase level [12]. To our knowledge, the risk factors for death due to recurrence within the first year after liver resection for HCC have not been studied. Because as many as 28% of patients can survive 3 years without treatment [13], it can be argued that the value of resection is questionable for some patients who are at high risk of death due to recurrence less than 1 year after resection. The need for better patient selection criteria for resection is apparent.

The aim of this study was to identify risk factors for early death (≤1 year) due to recurrence after partial liver resection for HCC using a multi-institutional database of liver resections performed at four hepatobiliary centers.

MATERIALS AND METHODS

Patient Selection

A multi-institutional database was developed from the prospective databases at The University of Texas M. D. Anderson Cancer Center (Houston, Texas), Mayo Clinic (Rochester, Minnesota), Kyoto University Graduate School of Medicine (Kyoto, Japan), and Hôpital Beaujon (Paris, France). All patients underwent partial hepatic resection for HCC with curative intent between 1980 and 1999. Complete histopathologic review of the slides and clinical reports was performed on site by three of the authors (J.N.V., D.M.N., and G.Y.L.). Mortality rate during the postoperative period, which includes all deaths within 31 days after surgery, was 5% (30/591). Overall 5- and 10-year survival rates for the entire cohort were 39 and 17%, respectively. The median follow-up time for the entire cohort was 33 ± 31 months (range, 0–206 months).

After exclusion of 28 patients who died of unknown causes and 16 patients with follow-up of less than 1 year, 547 patients were included in this study. Patients were divided into two groups: those who died of recurrence within 1 year after liver resection and those who survived at least 1 year after liver resection, whatever their status at last follow-up (dead with or without recurrence, alive with or without recurrence).

Death due to recurrence of HCC was strictly defined when evidence of recurrence was documented and no other cause of death was found after analysis of the clinical data. Recurrence was confirmed according to the usual practices for clinical research at each institution. Criteria for diagnosis of recurrence included a rising serum alpha-fetoprotein concentration compared with the post-resection baseline level, and imaging or postmortem evidence of intrahepatic or extrahepatic recurrence as the proximate cause of death. Radiological criteria for the diagnosis of HCC were as follows: (a) one or more hypoechoic, hyperechoic, or mixed nodules on ultrasonography in association with one or more hypervascular nodules with enhancement in the arterial phase on computed tomography (CT) and/or (b) one or more hypervascular nodules on magnetic resonance imaging (MRI) with gadolinium infusion. When findings on CT scan or MRI were inconclusive or discordant, hepatic angiography with infusion of iodized oil (Lipiodol, Ultra-Fluide, Laboratoires Guerbet, Aulnay-sous-Bois, France) was performed. Biopsy was not required to define recurrence.

Criteria Analyzed

Deaths due to recurrence of HCC were plotted as a function of time after resection. The following criteria were studied in all patients: (a) age, sex, and ethnic origin; (b) Child–Pugh class, based on a scoring scheme described elsewhere [1,14]; (c) serum alpha-fetoprotein level; (d) hepatitis B serology (serologic presence of any hepatitis B antigen or antibody; data concerning hepatitis C status were available for only a minority of patients); (e) tumor characteristics, including number of tumors (single or multiple), intrahepatic distribution of tumor(s) (unilobar or bilobar), tumor size (based on the largest dimension of the tumor specimen), histopathologic type (microtrabecular or macrotrabecular, acinar, diffuse), tumor grade (according to the scheme outlined by Edmondson and Steiner [15] and based on the area of highest grade), degree of necrosis, presence or absence of a peritumoral fibrous capsule (and capsular invasion), number of mitoses per 10 high-power fields (less than or more than 5—with the cutoff value of 5 representing the median value), nuclear polymorphism (graded as mild, moderate, or marked), minor vascular invasion (defined as either gross or histological involvement of the lobar or segmental branches of the portal or hepatic vein), and major vascular invasion (defined as gross invasion of the right or left main branches of the portal or hepatic vein) [16]; (f) type of resection (hepatic lobectomy and greater versus less than a formal lobectomy—i.e., wedge resection or segmentectomy); (g) surgical margin (defined as the closest margin on paraffin section and classified as less than 10 vs. 10 mm or greater); and (h) characteristics of the host liver: hepatitis activity grade (0–5 and 6–12 vs. 13–18) and extent of fibrosis/cirrhosis (fibrosis stage: 0–2 [mild], 3–4 [moderate], or 5–6 [severe/cirrhosis]) based on the modified grading and staging scheme for chronic hepatitis proposed by Ishak et al. [17].
Statistical Analysis

Quantitative data were expressed as means ± SD. Groups were compared by univariate analysis using the chi-square test or Student's t-test as appropriate, and by multivariate analysis using logistic regression analysis with backward and forward step selection (performed on significant variables in univariate analysis).

RESULTS

Causes of Death Within 1 Year

One hundred twenty-three (22%) patients died in the first year after surgery. Of these, 53 (43%) died of recurrence, 40 (33%) of liver failure/hemorrhage, and 30 (24%) of postoperative complications. No patient who died of a postoperative complication was found to have recurrence. Figure 1 reveals that deaths from recurrence or liver failure/hemorrhage occurred throughout the first year post-resection.

Of the patients who died of recurrence within 1 year after resection, 42 were men and 11 women, and the mean age was 59 ± 15 years (range, 18–82 years). The control group of patients who survived greater than 1 year included 282 men and 142 women, and the mean age was 59 ± 13 years (range, 15–96 years). The mean follow-up interval of these patients was 55 ± 32 months (range, 12–206 months).

Analysis of the entire cohort of 547 patients demonstrated that most deaths from recurrence occur within the first year after potentially curative resection (Fig. 2). Finally, precise pattern of recurrence data were available for 29 of the 53 patients who died of recurrence: 4/29 recurred at a distant site only while 25 recurred in the liver (23 in the liver only, 2 in the liver and at a distant site).

Factors Predictive of Early Death due to Disease Recurrence

Of the 21 variables assessed in the univariate analysis, only 6 were associated with a significantly higher risk of death within the first year after liver resection: tumor size greater than 5 cm (76 vs. 42%, \( P = 0.004 \)), multiple tumors (51 vs. 30%, \( P = 0.03 \)), presence of minor vascular invasion (68 vs. 42%, \( P = 0.005 \)) or major vascular invasion (30 vs. 13%, \( P = 0.01 \)), more than 5 mitoses per 10 high-power fields (80 vs. 46%, \( P = 0.02 \)), and hepatitis grade less than 5 (85 vs. 58%, \( P = 0.04 \)) though every data point was not available for analysis in every patient (Table I).

In multivariate analysis, only tumor size greater than 5 cm (\( P = 0.03 \)), multiple tumors (\( P = 0.01 \)), and more than 5 mitoses per 10 high-power fields (\( P = 0.03 \)) remained associated with a significantly higher risk of death within the first year after liver resection (Table II).

Eighteen (38%) of the 47 patients with all 3 risk factors died in the first year after liver resection (sensitivity, 35%; specificity, 93%; positive predictive value, 38%; negative predictive value, 96%). Two (2%) of the 88 patients with none of the risk factors died within first year. The sensitivity, specificity, positive predictive value, and negative predictive value for these predictive criteria are summarized in Table III.

DISCUSSION

Early recurrence after liver resection is one of the most important factors that impact the prognosis and quality of life of patients with HCC. Results of this multicenter study indicate that despite improvements in patient selection and operative technique, at least 10% of the patients who undergo radical surgery for HCC die of recurrence within the first year after resection. Recurrent disease was the leading cause of death during the first year after complete primary tumor resection. Only factors reflecting tumor behavior—tumor size greater than 5 cm (76 vs. 42%), multiple tumors (51 vs. 30%), and presence of more than 5 mitoses per 10 high-power fields (80 vs. 46%)—predicted increased risk of early death due to recurrence.
Several series have indicated that the underlying liver disease has a more important role in predicting long-term survival after hepatic resection than tumor characteristics [1,18,19]. There are two possible explanations for the adverse effect of existing fibrosis or cirrhosis on long-term survival. First, patients with advanced fibrosis or cirrhosis are more likely to develop recurrence of the primary HCC and subsequently die of the disease. Second, fibrosis and cirrhosis may represent a field of cancerization associated with development of a new metachronous HCC after resection [20–22]. In the series presented here, no factor reflecting the nature of the nontumorous host liver was a reliable predictor of early death.

### TABLE I. Univariate Analysis of Possible Predictive Factors of Early Death due to Recurrence Following Resection of HCC

<table>
<thead>
<tr>
<th>% Of patients or (mean ± SD)</th>
<th>Death ≤1 year due to recurrence</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, % male</td>
<td>79</td>
<td>67</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (59 ± 15)</td>
<td>(59 ± 13)</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Country of origin, France/United States/Japan</td>
<td>21/30/49</td>
<td>31/41/28</td>
<td>n.s.</td>
</tr>
<tr>
<td>Childs classification&lt;sup&gt;a&lt;/sup&gt;, A/B/C</td>
<td>57/43/0</td>
<td>70/30/0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum alpha-fetoprotein (ng/ml)</td>
<td>19,710 ± 54,084</td>
<td>4,258 ± 24,607</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hepatitis B serology positive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>34</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Tumor characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size, mm</td>
<td>(81 ± 39)</td>
<td>(60 ± 42)</td>
<td>0.004</td>
</tr>
<tr>
<td>Tumor number, single/multiple</td>
<td>49/51</td>
<td>70/30</td>
<td>0.03</td>
</tr>
<tr>
<td>Tumor location, uni/bilobar</td>
<td>83/17</td>
<td>91/10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Histopathologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro/macrotubular</td>
<td>20/30</td>
<td>22/24</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acinar/diffuse</td>
<td>22/28</td>
<td>13/41</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Tumor grade&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well/moderately differentiated</td>
<td>—/29</td>
<td>9/55</td>
<td>n.s.</td>
</tr>
<tr>
<td>Poorly/undifferentiated</td>
<td>71/—</td>
<td>32/4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Degree of necrosis, 0%/&lt;50%/≥50%/100%</td>
<td>33/52/8/7</td>
<td>46/38/9/7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fibrous capsule present</td>
<td>60</td>
<td>40</td>
<td>n.s.</td>
</tr>
<tr>
<td>Microvascular invasion present</td>
<td>68</td>
<td>42</td>
<td>0.005</td>
</tr>
<tr>
<td>Macrovascular invasion present</td>
<td>30</td>
<td>13</td>
<td>0.01</td>
</tr>
<tr>
<td>Nuclear polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate/marked</td>
<td>2/39/59</td>
<td>14/43/43</td>
<td>n.s.</td>
</tr>
<tr>
<td>&gt;5 Mitoses per 10 high-power fields</td>
<td>80</td>
<td>46</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Nontumorous liver characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis grade&lt;sup&gt;a&lt;/sup&gt;, 0–12/13–18</td>
<td>85/15</td>
<td>58/42</td>
<td>0.04</td>
</tr>
<tr>
<td>Fibrosis grade&lt;sup&gt;a&lt;/sup&gt;, 0–2 (mild)/3–4 (moderate)/5–6 (severe)</td>
<td>44/17/39</td>
<td>30/21/49</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Surgical factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic lobectomy or greater</td>
<td>40</td>
<td>56</td>
<td>n.s.</td>
</tr>
<tr>
<td>Wedge resection or segmentectomy</td>
<td>60</td>
<td>44</td>
<td>n.s.</td>
</tr>
<tr>
<td>Margin&lt;sup&gt;a&lt;/sup&gt;, &lt;10 mm/≥10 mm</td>
<td>61/39</td>
<td>52/48</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

SD, standard deviation; n.s., not statistically significant.

Patients who died within the first year after liver resection because of postoperative complications (n = 30) or liver failure/hemorrhage (n = 40) were excluded from the analysis.

<sup>a</sup>Every data point evaluated in this table was available for 98–100% of patients except preoperative Childs Classification (available in 70% of early recurrence group and 77% of control group), AFP (77 and 84%, respectively), fibrous capsule (96 and 94%), hepatitis and fibrosis grade (85–92% in each group), and margin size (79 and 83%).

### TABLE II. Logistic Regression Analysis of Significant Predictive Factors of Early Death due to Recurrence Following Resection for HCC From Univariate Analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Wald chi square</th>
<th>Odds ratio</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 5 mitoses per 10 high-power fields</td>
<td>4.3</td>
<td>3.0</td>
<td>0.52</td>
<td>0.037</td>
</tr>
<tr>
<td>Tumor size greater than 5 cm</td>
<td>4.7</td>
<td>3.0</td>
<td>0.51</td>
<td>0.030</td>
</tr>
<tr>
<td>Multiple tumors</td>
<td>5.6</td>
<td>3.3</td>
<td>0.50</td>
<td>0.018</td>
</tr>
</tbody>
</table>
greater than 5 cm is a recognized limitation to orthotopic liver transplantation [24,25]. In the series of Bismuth et al. [24], 3-year disease-free survival rate was 60% in patients with tumor size less than 3 cm versus only 28% in patients with tumor size greater than 5 cm (P < 0.05). One of the mechanisms favoring the association of early recurrence and death with larger tumor size may be a de facto incomplete resection in spite of apparent margin-negative resection. Indeed, Yoshida et al. [26] and Lai et al. [27] have reported that in the case of large tumors, a margin of 10 mm from the cut surface of HCC in the fresh resected specimen is inadequate to achieve cure. Lai et al. have also shown that when the tumor size is 4 cm or greater, microsatellites may be found more than 90 mm from the dominant nodule [27]. Consistent with these pathological results, studies have shown an improvement in survival rate when the width of the surgical margin is greater than 1 cm [28,29]. However, multivariate analyses in larger series have failed to show that wider resection margins overcome traditional risk factors for recurrence and shorter survival, such as the presence of venous invasion or satellite lesions [30]. A higher incidence of intrahepatic metastasis and portal venous invasion with tumors larger than 5 cm [20,31] underscores the prognostic significance of large tumor size.

Recent studies suggest that vascular invasion is a strong predictor of outcome in patients with HCC after resection [10,11,32] or orthotopic liver transplantation [33] (number of mitoses was not considered in these series). Although vascular invasion was a significant predictor of early death by recurrence in this series, its confidence interval failed to reach statistical significance on multivariate analysis, likely because of confounding by high levels of cell proliferation and sample size limitations. Careful analysis of these and literature-based data, which report degree of cell proliferation and survival, are revealing. Prior reports suggest that tumor size and number of nodules are factors linked with recurrence but not with death due to recurrence after resection, and these studies have not examined the risk for death in the first year after resection [29,30]. Tumor biologic factors related to the growth and invasiveness of HCC may be more relevant indicators of death due to recurrence after resection. Indeed, we found that the proliferative activity as measured by increased mitotic activity was a risk factor for early death due to recurrence [30]. The level of proliferating cell nuclear antigen, the expression of which is related to DNA synthesis and cell replication, has been reported to be associated with a higher incidence of venous invasion and direct liver invasion, which in turn may play an important role in survival [34,35]. Similarly, Soini et al. [36] have shown that HCC with a high proliferation index, and a low degree of apoptosis and necrosis is associated with shortened survival. In aggregate, these results suggest that the degree of cell proliferation should be added to the classic pathological prognostic factors for HCC. Although the present study is retrospective, and therefore every data point is not available for every patient, multivariate analysis confirms the importance of multiple tumors, tumor size, and presence of mitotic activity as statistically significant prognostic factors (Tables II and III).

The identification of significant prognostic factors for early death due to recurrence may not only improve patient selection for resection of HCC but also enable better selection of patients for postoperative adjuvant therapy. Systemic chemotherapy and hormonal therapy have failed to improve disease-free or overall survival rates in HCC [11,37]. However, several other adjuvant approaches have shown promise, including postoperative transarterial chemoembolization [11,38], intra-arterial iodine-131-labelled Lipiodol infused during transarterial chemoembolization [39], or adoptive immunotherapy [40].

**CONCLUSIONS**

We propose that the patients with a high risk of recurrence within the first year after primary tumor resection for HCC—i.e., the patients with tumors larger than 5 cm,
multiple tumors, or more than 5 mitoses per 10 high-power fields, and particularly those with 2 or 3 of these risk factors—should be enrolled in adjuvant therapy trials. Future studies are necessary to integrate tumor biology into the current treatment algorithm to enable optimal selection of patients for surgical and adjuvant therapies.

REFERENCES


