Postoperative Outcomes in Patients With Hepatocellular Carcinomas Resected With Exposure of the Tumor Surface

Clinical Role of the No-Margin Resection

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Hypothesis: We hypothesized that no-margin resections for hepatocellular carcinoma do not negatively affect patient outcomes.

Design: Inception cohort study.

Setting: Department of surgery at a university hospital.

Patients: From January 1992 to December 2005 at our institute, 465 consecutive patients with a preoperative diagnosis of hepatocellular carcinoma with curative potential were evaluated.

Intervention: Liver resection performed with or without surgical margins.

Main Outcome Measures: Overall survival and no-recurrence survival.

Results: Of the 465 patients, 62 underwent resections with exposure of the tumor surface at the cut stump (the cut surface of the remnant liver) with no surgical margins (exposure group), because the tumor adhered to the major hepatic vascular structures. The remaining 365 patients underwent resections without exposure of the tumor surface (nonexposure group). There were no significant differences between the 2 groups regarding the recurrence and overall survival rates. There were also no significant differences between the 2 groups with respect to the recurrence rate at the cut stump or the number and the location of intrahepatic recurrences, despite the less favorable clinical histories in the exposure group.

Conclusions: Limited resection with no margin seems to be the best procedure for patients with tumors close to the major hepatic vessels and with hepatic functions that do not permit wide-margin resections.

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Resection margin has been widely examined for its effect on the postoperative outcome of patients with hepatocellular carcinoma (HCC), but its significance remains controversial. A few studies have shown that a resection margin smaller than 1 cm was an adverse prognostic factor for long-term survival, but others have found no correlation between the width of the resection margin and long-term outcome. These seemingly conflicting results have resulted in a discrepancy among hepatic surgeons on the definition of curative resection for HCC.

See Invited Critique at end of article

In general, it is thought that both surgical curability and postoperative hepatic functional preservation are crucial for the successful treatment of patients with HCCs. Especially in patients with cirrhosis, smaller surgical margins would better prevent postoperative complications, including liver failure, though there is a concern of recurrence in the remnant liver, including the cut stump (the cut surface of the remnant liver). For patients with cirrhosis, the balance between surgical curability and preservation in function of the remnant liver is of great importance.

Liver resection for a central tumor is often anatomically restricted by the hilar structures, including the main portal branches as well as the main trunks of the hepatic veins. For such centrally located tumors that are close to the major intrahepatic vessels, resections are difficult to perform with adequate surgical margins. To avoid postoperative liver failure for patients with cirrhosis, hepatic surgeons often have no choice but to carefully dissect and resect the tumor away from vascular structures (exposing the tumor surface) to remove tumor tissue adhering to or compressing the large vascular structures.
Although many reports have recently indicated that there is no correlation between surgical margins and postoperative outcome,\(^\text{17-19}\) most hepatic surgeons believe that an adequate margin should be at least 5 mm or wider for HCC resections. In addition, there is no worldwide consensus or clear evidence that a 0-mm margin for curative resection is feasible for HCC associated with cirrhosis.\(^\text{20}\)

To evaluate the clinical utility of a 0-mm margin resection for HCC, we analyzed the outcomes of patients whose tumors were peeled from the major hepatic vessels and removed (exposing the tumor surface) and the outcomes of patients whose tumors were resected without exposing the tumor surface at the cut stump.

**METHODS**

**PATIENTS**

To assess the validity for no-margin resections for HCC, we used a database from Kansai Medical University, the data of which were prospectively collected from January 1, 1992, to December 31, 2005. We enrolled all consecutive patients with a preoperative diagnosis of HCC who were admitted to our department as candidates for surgical resections with curative intent (**Figure 1**). By December 31, 2005, a total of 465 patients had undergone surgical treatment for their HCCs. Of these 465 patients, a total of 38 cases were excluded: 2 cases of open laparotomy were excluded because of advanced unresectable tumors; 11 patients who underwent ablation therapy by laparotomy alone were excluded because they had advanced unresectable tumors; 20 cases with tumors were excluded postoperatively, because the tumors were histologically proven to be lesions other than HCCs (ie, preoperatively misdiagnosed); and 1 patient case was excluded because its resection margin status was unknown. Four patients withdrew from follow-up just after discharge.

The remaining 427 patients were observed either until death or until the last follow-up date for the living patients. The resection method and the length of the resection margin of these patients were recorded immediately after operation. Because the tumors adhered to and compressed the major hepatic vascular structures, the tumors in 62 of these 427 patients were peeled from the vascular structures and removed, thus exposing the tumor surface at the cut stump (exposure group). These 62 patients underwent an operation with a macroscopic 0-mm resection margin. The remaining 365 patients underwent conventional resections with no macroscopic exposure of the tumor surface at the cut stump (nonexposure group) (**Figure 1**).

Twenty cases were preoperatively misdiagnosed in this study. However, if these patients were enrolled for survival analysis, they would elevate the apparent survival, as postoperative histopathological examination revealed that 14 of these misdiagnosed patients had benign tumors. To avoid this potential bias, cases of preoperative misdiagnosis were excluded. In contrast, operative or hospital cases of death and even macroscopically noncurative cases were included. For example, we included patients whose main tumors were removed and whose remaining satellite nodules were treated with ablation therapy.

**FOLLOW-UP**

Perioperative clinical factors, such as patient characteristics, preoperative liver function data, operative factors, and tumor characteristics, were compared in the exposure and nonexposure groups. Patients’ cirrhotic statuses were histopathologically determined in the noncancerous liver tissues, according to the New Inuyama Classification.\(^\text{21}\) The staging system we used followed General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan,\(^\text{22}\) which is commonly used in Japan. The overall survival, defined as the interval between the date of operation and the date of death or last follow-up information for the living patients, was also evaluated. By the time of analysis, the latest enrolled patient had been followed up for at least 2 months. The most common cause of death was cancer; all other causes of death, such as liver failure and variceal bleeding, were included. The recurrence rate was also evaluated and was defined as the interval between the date of operation and the date that a diagnosis of recurrence was confirmed by sonography, computed tomography, magnetic resonance imaging, or hepatic angiography. The no-recurrence rate was calculated after censoring the patients who had not shown a recurrence at the time of death.

All patients were given follow-up examinations with routine liver biochemical tests. Every 3 months, biochemical tests were performed at the central hospital laboratory. Liver ultrasonography was also performed every 3 months. In addition, computed tomography and/or magnetic resonance imaging were performed every 6 months. Finally, an angiographic examination was performed after admission when a recurrence was suspected. Once an intrahepatic recurrence was confirmed, patients in both groups generally received transarterial chemoembolization. The largest recurrent tumor was found at the cut stump.

**OPERATIVE PROCEDURE**

After laparotomy, the tumor location and its relationship to the Glisson sheath and hepatic veins were determined by intraoperative ultrasonography following liver exposition. Liver tissue was coagulated by repeated insertion of a monopolar microwave tissue coagulator needle electrode along the intended resection line that was 1 to 2 cm away from the tumor, as previously described by Ryu et al.\(^\text{23}\) The liver tissue coagulated with the microwave tissue coagulator was dissected with forceps without using the Pringle procedure. When exposed blood vessels were encountered,
they were ligated with sutures. Each tumor was resected as previously mentioned, even if more than 2 liver tumors were detected and liver function was well preserved. In patients with relatively severe functional liver damage, the main tumor was resected and, simultaneously, the other remaining tumors underwent ablation therapy using the microwave tissue coagulator.

**STATISTICAL ANALYSIS**

To evaluate the homogeneity of the exposure vs nonexposure groups with respect to clinical background factors and to compare differences between the 2 groups with respect to operation-related factors and the modality of primary recurrence, data were analyzed using the \( \chi^2 \) test or Mann-Whitney test. The no-recurrence curves and the overall survival curves were plotted using the Kaplan-Meier method; log-rank tests were also performed. A \( P \) value < .05 was considered statistically significant.

**RESULTS**

Typical images of patients in the exposure group are shown in Figure 2. Preoperative computed tomography scans and an echogram indicate that the major hepatic vascular structures were compressed by the deep
tumors. These compressions were relieved after the tumors were peeled from the vascular structures and removed. The removed specimen showed that the tumor was resected just along the tumor surface and the surrounding liver tissue was not resected at all.

**Table 1** presents similar clinical histories among patients in the 2 groups. However, age, albumin levels, alkaline phosphatase levels, operation method (anatomical resection or limited resection), and tumor diameters were significantly different between the 2 groups. All of the differences, except for the operation method, had a harmful effect on outcome in the exposure group.

**Table 2** indicates the results of operation-related factors. Of the 6 factors estimated in the study, total blood loss, amount of blood transfusion, and operation duration were significantly greater in the exposure group than in the nonexposure group. In contrast, there were no significant differences between the 2 groups in incidence of postoperative complications, the rate of hospital death, and the length of the postoperative hospital stay.

**Table 3** presents the outcome of modality of primary recurrence by the end of the follow-up period. There were no significant differences in recurrence at the cut stump or the number and location of intrahepatic recurrences between the 2 groups. In contrast, the extrahepatic recurrence rate was significantly lower in the exposure group than in the nonexposure group.

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**Table 1. Clinical History of Patients**

<table>
<thead>
<tr>
<th>Clinical characterisric</th>
<th>Exposure Group (n = 62)</th>
<th>Nonexposure Group (n = 365)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range), y</td>
<td>69 (64-74)</td>
<td>65 (59-71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>48/14</td>
<td>291/74</td>
<td>.68</td>
</tr>
<tr>
<td>Histological cirrhosis, yes/no</td>
<td>23/33c</td>
<td>149/210c</td>
<td>.95</td>
</tr>
<tr>
<td>Child-Turcott classification, A/B/C</td>
<td>34/26/2</td>
<td>250/105/6</td>
<td>.1</td>
</tr>
<tr>
<td>Alcohol intake, yes/no</td>
<td>22/40</td>
<td>157/202c</td>
<td>.23</td>
</tr>
<tr>
<td>Esophageal varices, yes/no</td>
<td>12/40</td>
<td>90/219c</td>
<td>.37</td>
</tr>
<tr>
<td>Hepatitis viral infection, type B/type C/none</td>
<td>5/48/9</td>
<td>67/259/39</td>
<td>.12</td>
</tr>
<tr>
<td>Preoperative TACE, yes/no</td>
<td>40/22</td>
<td>191/167c</td>
<td>.10</td>
</tr>
<tr>
<td>Previous or concurrent malignancy, yes/no</td>
<td>8/54</td>
<td>47/318</td>
<td>.1</td>
</tr>
<tr>
<td>Treatment for recurrence, yes/no</td>
<td>33/4</td>
<td>200/27</td>
<td>.85</td>
</tr>
<tr>
<td>Cause of death, recurrence/nonrecurrence</td>
<td>15/6</td>
<td>134/23</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Preoperative liver function data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exposure Group</th>
<th>Nonexposure Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin level, median (interquartile range), g/L</td>
<td>36 (33-39)</td>
<td>37 (34.5-39.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Total bilirubin level, median (interquartile range), mg/dL</td>
<td>0.8 (0.65-0.95)</td>
<td>0.8 (0.55-1.05)</td>
<td>.38</td>
</tr>
<tr>
<td>Cholinesterase level, median (interquartile range), U/L</td>
<td>100 (77.5-121.5)</td>
<td>102 (78-126)</td>
<td>.58</td>
</tr>
<tr>
<td>Aspartate transaminase level, median (interquartile range), U/L</td>
<td>48 (27.5-67.5)</td>
<td>48 (24-71)</td>
<td>.4</td>
</tr>
<tr>
<td>Alanine transaminase level, median (interquartile range), U/L</td>
<td>48 (24-71)</td>
<td>45 (25.5-64.5)</td>
<td>.73</td>
</tr>
<tr>
<td>Alkaline phosphatase level, median (interquartile range), U/L</td>
<td>311 (243-379)</td>
<td>267 (190-344)</td>
<td>.02</td>
</tr>
<tr>
<td>γ-Glutamyltransferase level, median (interquartile range), U/L</td>
<td>68 (29.5-106.5)</td>
<td>64 (31.5-96.5)</td>
<td>.65</td>
</tr>
<tr>
<td>Platelet count, median (interquartile range), ×10⁹/L</td>
<td>131 (88.5-164)</td>
<td>129 (82.4-176)</td>
<td>.33</td>
</tr>
<tr>
<td>Prothrombin time, median (interquartile range), %</td>
<td>87 (77-97)</td>
<td>88 (80-96)</td>
<td>.44</td>
</tr>
<tr>
<td>Antithrombin III, median (interquartile range), %</td>
<td>84 (72-96)</td>
<td>83 (71-95)</td>
<td>.82</td>
</tr>
<tr>
<td>Hepaplastin test, median (interquartile range), %</td>
<td>79 (66-92)</td>
<td>78 (66-90)</td>
<td>.49</td>
</tr>
<tr>
<td>ICG retention rate at 15 min, median (interquartile range), %</td>
<td>18.6 (13.4-23.8)</td>
<td>16.7 (10-23.4)</td>
<td>.4</td>
</tr>
</tbody>
</table>

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**Abbreviations:** GSA, galactosyl human serum albumin; ICG, indocyanine green; PIVKA-II, protein induced by vitamin K absence or antagonist II; TACE, transarterial chemoembolization.

a Values are number of patients, unless otherwise indicated.

b P value < .05 was significant.

c The sum of the subgroups was not equal to the total number of patients, as the data of some patients were unknown.

Tumor stage was defined according to General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan.®
In the exposure group, tumor capsules of 2 patients were fractured when the tumors were peeled from vascular structures during operation. However, these 2 patients had no local recurrences at the cut stump until death.

By December 31, 2005, 37 (59.7%) patients in the exposure group had recurrence of HCCs, while 227 (62.2%) in the nonexposure group had recurrences. Five years after operation, the no-recurrence rates of the exposure group and the nonexposure group were 19.1% and 23.5%, respectively. There was no significant difference between the 2 groups in the no-recurrence rate (Figure 3). By the end of the follow-up period, 21 (33.9%) patients had died in the exposure group, whereas 157 (43.0%) had died in the nonexposure group. Five years after the operation, the overall survival rates of the exposure group and the nonexposure group were 55.7% and 55.8%, respectively. There was also no significant difference between the 2 groups in overall survival. The follow-up period for the living patients ranged from 2 to 112 months (median, 29 months) in the exposure group and from 2 to 158 months (median, 33 months) in the nonexposure group.

### Table 2. Operation-Related Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Exposure Group (n = 62)</th>
<th>Nonexposure Group (n = 365)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood loss, &lt;1000–100 mL</td>
<td>16/46</td>
<td>199/164&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood transfusion, yes/no</td>
<td>38/24</td>
<td>163/202</td>
<td>.02</td>
</tr>
<tr>
<td>Operation duration, &lt;240–240 min</td>
<td>12/50</td>
<td>151/212&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative complications, yes/no</td>
<td>19/43</td>
<td>83/282</td>
<td>.18</td>
</tr>
<tr>
<td>Hospital death, yes/no</td>
<td>3/59</td>
<td>12/353</td>
<td>.54</td>
</tr>
<tr>
<td>Postoperative hospital stay, &lt;20–20 days</td>
<td>33/28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>188/174&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.75</td>
</tr>
</tbody>
</table>

<sup>a</sup> P value < .05 was significant.

<sup>b</sup> The sum of the subgroups was not equal to the total number of the patients, as the data of some patients were unknown.

### Table 3. Modality of Primary Recurrence

<table>
<thead>
<tr>
<th>Modality of Recurrence</th>
<th>Exposure Group (n = 62)</th>
<th>Nonexposure Group (n = 365)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence, yes/no</td>
<td>37/25</td>
<td>227/138</td>
<td>.71</td>
</tr>
<tr>
<td>Intrahepatic recurrence, yes/no</td>
<td>37/25</td>
<td>213/152</td>
<td>.85</td>
</tr>
<tr>
<td>No. of intrahepatic recurrences, 1/≤2</td>
<td>18/19</td>
<td>97/116</td>
<td>.73</td>
</tr>
<tr>
<td>Location of intrahepatic recurrence, ipsilateral/contralateral/bilateral lobe</td>
<td>10/9/14&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>65/63/57&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>.42</td>
</tr>
<tr>
<td>Recurrence at the cut stump, yes/no</td>
<td>5/31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15/187&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.2</td>
</tr>
<tr>
<td>Extrahepatic recurrence, yes/no</td>
<td>1/36</td>
<td>38/189</td>
<td>.03</td>
</tr>
</tbody>
</table>

<sup>a</sup> P value < .05 was significant.

<sup>b</sup> The 1 patient in whom the locations of intrahepatic recurrence were unknown was excluded.

<sup>c</sup> The 3 patients whose primary hepatic lesions existed in bilateral lobes were excluded.

<sup>d</sup> The 11 patients in whom the locations of intrahepatic recurrence were unknown were excluded.

<sup>e</sup> The 17 patients whose primary hepatic lesions existed in bilateral lobes were excluded.

In the exposure group, tumor capsules of 2 patients were fractured when the tumors were peeled from vascular structures during operation. However, these 2 patients had no local recurrences at the cut stump until death.

By December 31, 2005, 37 (59.7%) patients in the exposure group had recurrence of HCCs, while 227 (62.2%) in the nonexposure group had recurrences. Five years after operation, the no-recurrence rates of the exposure group and the nonexposure group were 19.1% and 23.5%, respectively. There was no significant difference between the 2 groups in the no-recurrence rate (Figure 3). By the end of the follow-up period, 21 (33.9%) patients had died in the exposure group, whereas 157 (43.0%) had died in the nonexposure group. Five years after the operation, the overall survival rates of the exposure group and the nonexposure group were 55.7% and 55.8%, respectively. There was also no significant difference between the 2 groups in overall survival. The follow-up period for the living patients ranged from 2 to 112 months (median, 29 months) in the exposure group and from 2 to 158 months (median, 33 months) in the nonexposure group.

### COMMENT

With liver resection for HCC, the main concern of a narrow or positive resection margin is postoperative recurrence (in particular, recurrence in the liver remnant). Using a wide resection margin to ensure histological clearance is a general principle of surgical oncology, but its significance for HCC resections has remained controversial despite extensive studies.1-19 There is no consensus regarding the definition of adequate surgical margins for curative operations for HCCs associated with cirrhosis.20 Hepatic surgeons often encounter tumors that are centrally located and close to large vascular structures. In patients with severely impaired liver function or with tumors close to these large vascular structures, an adequate surgical margin may not be feasible. Determining an optimal resection margin for HCC has remained a dilemma for surgeons, because the balance between the postoperative hepatic reserve and surgical curability will greatly influence outcome in patients with cirrhosis.9-11,14,17,18 We conducted a study to assess whether resection without a surgical margin would have an impact on cancer recurrence or survival rates in patients with HCCs, focusing on tumor recurrence in the liver remnant.

In the exposure group, operative blood loss was considerably greater than in the nonexposure group, inevitably increasing the necessity of a blood transfusion. This difference is caused by inherent difficulty (without using the Pringle procedure) in resecting tumors that are centrally located and close to large vascular structures. Therefore, the average duration of operation was also signifi-
cantly longer in the exposure group for the same reason. However, the incidence of postoperative complications, hospital death rate, and postoperative hospital stay was not different between the 2 groups. Furthermore, our data showed that the overall survival and no-recurrence rates in the exposure group were similar to those in the nonexposure group. In addition, there was no difference in the recurrence patterns between the 2 groups, including cut-stump recurrence, despite the less favorable clinical histories in the exposure group compared with those in the nonexposure group. The surgical margin seems to have no relationship with this recurrent pattern in the remnant liver. Our results also showed that the extrahepatic recurrence rate is significantly lower in the exposure group. The cause of this difference in the extrahepatic recurrence rate is uncertain. It might be a statistical anomaly. However, this result implies that the no-margin resection does not promote distant metastases.

Although tumor clearance at the resection margin may be helpful in preventing local recurrence, given that most intrahepatic recurrences arise from either portal venous dissemination\(^7,16\) or multicentric carcinogenesis,\(^2,7,28\) it is understandable that a wide resection margin may not have a significant impact on the risk of HCC recurrence. In patients with limited functional liver reserve undergoing resection for their HCCs, preservation of liver parenchyma may be a more important consideration than a wide resection margin. An extensive resection of a nontumorous liver is often necessary to secure a surgical margin, especially when the tumor is close to a major vessel. However, our findings suggest that nontumorous liver parenchyma need not be sacrificed for the sake of securing a surgical margin. Furthermore, with the high incidence of recurrence in the liver remnant, a resection of HCC cannot be considered curative in a strict sense, irrespective of the resection margin. In this context, it might be said that liver resection is a palliative treatment for HCC patients with cirrhosis.

Sakon et al\(^21\) recently reported that the intrahepatic recurrences resulted mostly from multicentric carcinogenesis or from cancer cells that already existed within the systemic circulation at the time of hepatectomy. Our results show that there were several multiple primary intrahepatic recurrences in the bilateral lobes, probably suggesting a multicentric hepatocarcinogenesis or intrahepatic recurrence via systemic circulation. This might be explained by the dominance of hepatitis C viral infections in our study population. Because it might be difficult, theoretically, to prevent multicentric carcinogenesis or intrahepatic metastasis via systemic circulation, even if wide-margin resection is accomplished, we believe that liver resection with no margin, according to tumor size and location, could achieve a good outcome for HCC patients with cirrhosis.

It was hypothesized that the increased hepatocyte regeneration after wide-margin resection might enhance hepatocarcinogenesis in the liver remnant,\(^5,25,29\) because as more hepatic parenchyma is resected, more hepatocyte proliferation is required with increased replication of the hepatocytes. Therefore, it was suggested that the volume of the resected liver parenchyma should be minimal.

The angioarchitecture of the fibrous capsule of HCC is known to differ from that of the primary tumor; the blood supply of the fibrous capsule arises from both the artery and the portal vein.\(^11,30,31\) If the fibrous capsule formation results from one of the host defense responses against the tumor, the true surgical margin might only be the width of the tumor capsule itself. Not needing a margin in an HCC resection may account for the reason why local ablation therapy—such as ethanol injection, microwave coagulation, cryosurgery, and radiofrequency ablation—is also effective for treatment of HCC.\(^20,22-26\)

Although surgical resection represents the best hope for long-term survival in patients with HCC, only approximately 30% or less of these patients are appropriate for operative resection because of either the extent of their disease or cirrhosis-related liver dysfunction.\(^2,27\) One of the reasons for this lower resection rate is that the large amount of sacrificed nontumorous liver restricts the surgical indication for patients with HCC, especially for those with cirrhosis, to avoid postoperative liver failure.\(^15,18,20,38,39\) If surgeons consider the no-margin resection as a surgical option, patients with HCC who were previously deemed to have an unresectable form of the disease might be good candidates for curative resections, resulting in a higher resection rate.
In conclusion, the inability to secure a resection margin should not be regarded as a contraindication for the resection of HCC. In patients with limited liver functional reserve and with tumors that are centrally located and close to large hepatic vascular structures, the preservation of vascular structures adjacent to the tumors should take priority and a no-margin resection for HCC should be recommended.

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REFERENCES