Role of Liver Resection for Hepatocellular Carcinoma with Vascular Invasion: Emerging Evidence from Western Countries

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Abstract

Patients with advanced hepatocellular carcinoma (HCC) with macrovascular invasion, that is, tumor thrombosis in the portal vein or hepatic vein, are generally considered not eligible for liver resection in Western countries, and only systemic therapy is recommended. However, there is a subgroup of patients who can survive long after surgical treatment despite having a very advanced stage of the disease. Some Asian surgical centers and a few Western surgical centers have been using surgery to treat BCLC stage C HCC as long as it is operable, and those centers have reported acceptable outcomes. In this issue of \textit{Liver Cancer}, Govalan et al. report on the superiority of surgical resection over other treatments for patients with vascular invasion based on data from the National Cancer Database. This is a first report analyzing a large set of contemporary US cohort data, and its findings may catch the attention of many hepatologists in Western countries who are hesitant about sending eligible patients to surgeons. In this era of advanced systemic therapy using molecular targeted agents and immuno-checkpoint inhibitors, a combination of promising systemic therapy and surgery may be a future path to improve survival for patients with this very advanced disease.

Patients with advanced hepatocellular carcinoma (HCC) with macrovascular invasion, that is, tumor thrombosis in the portal vein (portal venous tumor thrombus) or hepatic vein (hepatic venous tumor thrombus), have been reported to have a poor prognosis [1, 2]. Portal venous tumor thrombus can cause intrahepatic metastasis and increased portal pressure, leading to esophagogastric variceal hemorrhage. Hepatic venous tumor thrombus can cause intrapulmonary dissemination, pulmonary embolism, or even sudden death [3].
Patients with vascular invasion are generally considered not eligible for liver resection in Western countries, and only systemic therapy is recommended in the BCLC guidelines endorsed by the AASLD and EASL [4]. However, there is a subgroup of patients who can survive long after surgical treatment despite having a very advanced stage of the disease. Some Asian surgical centers and a few Western surgical centers have been using surgery to treat BCLC stage C HCC as long as it is operable, and those centers have reported acceptable outcomes [5, 6]. There has been a consensus among liver surgeons in Asia on the use of liver resection for macrovascular invasion. Several studies, including those analyzing Japanese national data, have reported a better OS or DFS with liver resection than other nonsurgical treatments in this situation [7, 8]. Randomized controlled trials may not be feasible in this situation because of tumor heterogeneity, how relatively rare that situation is, and the difficulty in obtaining informed consent for randomization. Precise analysis of a large-scale cohort data using an appropriate statistical methodology, which includes propensity score matching (PSM), may be the next best option.

In this issue of Liver Cancer, Govalan et al. [9] report on the superiority of surgical resection over other treatments for patients with vascular invasion based on data from the National Cancer Database (NCDB). Surgical resection was associated with improved survival compared to systemic therapy (adjusted hazard ratio: 0.496, 95% confidence interval: 0.426–0.578), with a median survival of 21.4 months for the former versus 8.1 months for the latter. Superiority of surgical resection was observed in PSM and inverse probability of treatment weighting adjusted analysis. We have to be cognizant of several limitations inherent in using the NCDB, including the unavailability of data on the extent of vascular invasion or the Child-Pugh classification, which are key prognostic variables for HCC. However, the study by Govalan et al. [9] analyzed a large set of contemporary US cohort data for the first time, and their finding may catch the attention of many hepatologists in Western countries who are hesitant about sending eligible patients to surgeons. Table 1 summarizes recent studies that used PSM to compare the long-term outcomes of liver resection and nonsurgical treatment of HCC with vascular invasion.

In this era of advanced systemic therapy using molecular targeted agents and immuno-check point inhibitors, a study recently reported on a very potent drug combination that can prolong survival for patients with vascular invasion [10]. A combination of promising systemic therapy and surgery may be a future path to improve survival for patients with this very advanced disease. A few studies on neoadjuvant systemic therapy before liver resection are underway or are being planned [11]. Current guidelines might be modified depending on the outcome of clinical trials of those approaches.

### Table 1. Comparison of MST as a result of liver resection and nonsurgical treatment of HCC with vascular invasion

<table>
<thead>
<tr>
<th>Lead author [ref.]</th>
<th>Inclusion criteria</th>
<th>Liver resection patients, n</th>
<th>MST, mo</th>
<th>Nonsurgical treatment patients, n</th>
<th>MST, mo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torzilli [6]</td>
<td>BCLC-C</td>
<td>274</td>
<td>36*</td>
<td>–</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kokudo [7]</td>
<td>PVTT</td>
<td>2,093</td>
<td>34.4</td>
<td>4,381</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After PSM</td>
<td>1,058</td>
<td>29.4</td>
<td>1,058</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kokudo [8]</td>
<td>HVTT</td>
<td>540</td>
<td>53.6</td>
<td>481</td>
<td>19.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After PSM</td>
<td>223</td>
<td>41.0</td>
<td>223</td>
<td>21.7</td>
<td>0.023</td>
</tr>
<tr>
<td>Govalan [9]</td>
<td>Vascular invasion</td>
<td>325</td>
<td>21.4</td>
<td>4,268</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After PSM</td>
<td>132</td>
<td>19*</td>
<td>132</td>
<td>11*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MST, median survival time; PVTT, portal venous tumor thrombus; HVTT, hepatic venous tumor thrombus; PSM, propensity score matching. * Approximate value obtained from survival curves.

### Conflict of Interest Statement

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N. Kokudo, T. Kokudo, and K. Hasegawa conceived, wrote, and approved the final manuscript.

References