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REVIEW

Liver transplantation and conventional surgery for advanced hepatocellular carcinoma

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Summary

This study intended to discuss the roles of hepatic resection (HR) and liver transplantation (LT) in patients with advanced hepatocellular carcinoma (HCC) through our experience and literature review. For large HCC > 10 cm, HR is regarded as the treatment of choice when hepatic function is preserved. Considering frequent extrahepatic recurrence and acceptable outcome after curative HR, LT has not been recommended. For multiple HCCs, HR has been attempted in different preferences worldwide. HR can offer acceptable survival outcome for patients with small oligo-nodular HCCs and well-preserved liver function. Recurrence pattern lowers the applicability of salvage LT, thus primary LT is suggested. For HCC patients with major portal vein tumor thrombus, HR with thrombus removal can be performed, in contrast LT is contraindicated. For HCC with bile duct tumor thrombus, aggressive en bloc resection can lead to prolongation of survival. There is no consensus on transplantability of HCC with bile duct tumor thrombus, but complete resection may provide survival gain after LT. In conclusion, HR and LT have complementary roles, thus they should be associated to rather than being opposed. Multi-modality treatment strategy especially, for patients with advanced HCC, provides new fields of investigation for diverse indications of HR and LT.

Introduction

Hepatocellular carcinoma (HCC) is often associated with chronic liver disease and more than 80% of HCCs occur in cirrhotic livers. Various treatment modalities for HCC have been performed after considering tumor extent and hepatic functional reserve, but only hepatic resection (HR) and liver transplantation (LT) can meet the conditions of curative treatment. LT offers a chance of cure for HCC and the underlying liver cirrhosis simultaneously, but the availability of liver grafts and adverse oncological effects from inevitable immunosuppression become the critical limitation of LT. In practice, HR and LT have been often considered simultaneously since they have reciprocally associated therapeutic roles.

Several important selection criteria of LT for HCC were proposed, in which the balance of risk and benefit is the main topic of concern. Recently, a number of major LT centers in Western countries have focused on expanded criteria regarding the tumor diameter (more than 5 cm) and the Milan criteria (defined as presence of one tumor ≤ 5 cm or three tumors less than 3 cm) [1–4]. Some major centers, mainly those performing living-donor LT in East Asia, even have accepted to transplant patients presenting a higher number (5 or more) of HCC nodules (Table 1) [5–8]. The Asan criteria consist of three components as tumor diameter ≤ 5 cm, tumor number ≤ 6 and absence of gross vascular invasion.

The value of HR in the treatment of HCC is usually focused on operative risk and curability. Many publications have discussed the transplantability of HCC, but LT for patients with advanced tumors exceeding clearly most selection criteria had been discussed only occasionally [1–8]. Due to the shortage of available organs, the value of

Table 1. Selection criteria of living-donor liver transplantation for hepatocellular carcinoma in East Asia.

Institution	Selection criteria	Primary diagnosis	Number of patients	Overall patient survival rate within criteria	Overall patient survival rate exceeding criteria
Asan Medical Center, Korea [5]	Diameter ≤ 5 cm; Number of lesions ≤ 6; No gross vascular invasion	HBV: 93%, HCV: 7%	221	1-year: 94.3%, 3-year: 87.5%, 5-year: 81.6%	1-year: 71.9%, 3-year: 37.2%, 5-year: 20.7%
Kyoto University, Japan [6]	Diameter ≤ 5 cm; Number of lesions ≤ 10; PIVKA-II ≤ 400 mAU/mL	HBV: 34%, HCV: 53%	125	5-year: 86.7%	5-year: 34.4%
Tokyo University, Japan [7]	Diameter ≤ 5 cm; Number of lesion ≤ 5	HCV: 62%	78	Recurrence-free 3-yr: 94%	Recurrence-free 3-yr: 50%

HBV, hepatitis B virus; HCV, hepatitis C virus; PIVKA-II, prothrombin induced by vitamin K absence II.

both HR and LT in the treatment of HCC needs continuously to be discussed. We studied the place of HR as well as of LT in patients presenting advanced HCC based on our own extensive experience at Asan Medical Center and literature review.

Surgery for large HCC greater than 10 cm

A considerable proportion of the patients present with advanced large HCC lesions at the time of initial diagnosis. For patients with HCC larger than 10 cm in diameter, transarterial chemoembolization has an overall 5-year survival rate (5-YSR) of less than 10%, whereas HR showed overall 5-YSRs ranging from 16.7% to 38.5%, which are not surpassed by any other currently available treatment [9–16]. HR is regarded as the treatment of choice for these large HCCs when hepatic function is acceptably preserved. Hepatic parenchymal transection using an anterior approach has often been performed to avoid intravascular tumor spilling or to overcome the impossibility of conventional mobilization of the tumor-bearing right lobe (Table 2) [17]. However, tumor recurrence in these cases is very common after HR, the risk factors being major vascular invasion and resection margin less than 1 cm [16]. Therefore the overall patient survival period is determined by the sum of the survival outcomes from primary HR and additional recurrence treatment. In our series of 100 patients undergoing HR for HCC greater than 10 cm, overall and disease-free 5-YSRs were 31% and 20%, respectively. A noticeable feature in the observed recurrences was the high incidence of extrahepatic metastasis at the detection time of initial recurrence (34%) [16]. Considering this extrahepatic recurrence and the acceptable favorable outcome after curative HR and active treatment of tumor recurrence, LT should not be recommended for patients presenting a unusually large HCC greater than 10 cm. According to the survival-predicting diagram from a multi-center trial [18], LT in patients having a single 10 cm-sized HCC with or without microvascular invasion showed 5-YSRs of 30–35% and 55–60%, respectively. These survival outcomes appear to be much better than expected. However, the case number

Tumor extent	Technical knacks
Large HCC ≥ 10 cm	Extraglissonian encircling of hilar glissonian pedicles
	Parenchymal transection with anterior approach and hanging-over maneuver
Multiple HCC	Frequent right portal vein embolization
	En bloc resection for adjacent tumors
	Separate non-anatomical resection for small lesions
HCC with major Portal vein invasion	Tumor thrombectomy with or without vein resection
	Anatomical resection including the whole portal vein beds
	Frequent preoperative transarterial chemoembolization
HCC with hepatic vein invasion	Total vascular exclusion
	Retrohepatic vena cava replacement
	Major hepatic vein resection and interposition graft
	Autotransplantation after ex-situ resection
HCC with bile duct tumor thrombus	En bloc bile duct resection
	Complete thrombectomy with common bile duct exploration
	Frequent preoperative transarterial chemoembolization

Table 2. Technical knacks to facilitate curative resection of advanced hepatocellular carcinoma currently used at the Asan Medical Center.

of LT for such unusually large-sized HCCs might not be large enough to obtain convincing statistical results, thus its predicting power should be verified by using other large-volume series.

Surgery for multiple HCCs

There are two distinct types of multiple HCCs: the multicentric pattern and intrahepatic metastases. The multiple tumors from intrahepatic metastasis are usually defined as tumors clearly originating and growing from portal vein tumor thrombus, tumors surrounding a large main tumor with multiple satellite nodules, or small solitary tumor near the main tumor that is histologically similar or less differentiated than the main tumor. Multiple tumors not met the above-mentioned definition can be regarded as multi-centric tumors. Satellite nodules detected in the resected liver specimens and single HCC of multi-nodular confluent type are not considered as multiple HCCs because they can be submitted to en bloc resection. Surgery for patients with multiple HCCs is still a matter of debate [17,19]. In Western countries, HR is usually indicated for single HCC because HR for multiple tumors carries a high recurrence risk and has an unfavorable survival outcome [20]. In contrast, HR for multiple tumors has been attempted in up to 20–30% of all surgeries for HCC in East Asia [17,21–24]. The prognosis of HR for HCC with multiple occurrences is usually better than that for intrahepatic HCC metastasis, thus HCC with synchronous or metachronous multiple occurrences represents an indication for surgical resection. To eradicate all of the tumors which are distributed in one or both lobes, various types of hepatectomies eventually combined with other local ablation therapies have been used in practice (Table 2). A favorable survival rate was reported after HR in Child-Pugh class A patients presenting two or three tumors and HR was also advantageous in comparison to ablative therapies with regard to prevention of tumor recurrence in patients with no more than three HCCs [25,26]. These results reported from East Asian countries suggest that HR can offer an acceptable survival in patients with small oligo-nodular HCCs and well-preserved liver function. However, it is clear that recurrence is very common even after curative resection of multiple HCCs. In our series of 101 patients undergoing HR for multiple HCCs, overall and disease-free 5-YSRs were 39.4% and 15.2%, respectively. The recurrence rate after HR for two HCC lesions was comparable to that for single HCC, but tumor number of 3 or more resulted in a higher recurrence rate. The features of recurrence showed again high incidences of extrahepatic metastasis and vascular invasion, which of course reduces the applicability of salvage LT. As a result, poorer outcome would be anticipated after salvage or bridge LT comparing to primary LT [27,28]. Thus, if the tumor extent of three or more lesions meets the eligibility criteria for LT, it may be beneficial to perform primary LT in the absence of general contraindications.

Surgery for HCC with major portal vein tumor thrombus

The incidence of main portal vein tumor thrombus formation ranged from 5.3% to 15.4% in patients undergoing HR, from 11.3% to 38.0% in patients receiving non-surgical treatment, and from 32.0% to 62.2% in autopsy cases [29]. The median survival period in untreated patients with HCC and main portal vein tumor thrombus was only 9.7 weeks [30]. Patients with major portal vein invasion usually show a very high recurrence rate after HR, but a small number of patients with definite risks survived more than 5 years after resection. An en bloc resection consisting of hemihepatectomy with segmental resection of the main portal vein and tumor thrombectomy has been used for HCC with portal vein tumor thrombus extending into the main portal trunk (Table 2) [31,32]. In our series of 44 patients undergoing HR for HCC with major portal vein tumor thrombus, overall and disease-free 5-YSRs were 31% and 10%, respectively. As major vascular invasion is unequivocally regarded as a risk factor for recurrence after LT, LT should not be performed [1–8].

Surgery for HCC with bile duct tumor thrombus

Jaundice can be caused in HCC patients due to bile duct obstruction by tumor thrombus; this condition is present in 1% to 12% of HCC patients. The biological features of bile duct tumor thrombus are very similar to those of portal vein tumor thrombus. The classification proposed by Ueda has been used to define the extent of bile duct tumor thrombus [33]. Vigorous preoperative management including biliary drainage, transarterial chemoembolization and/or portal vein embolization had preceded surgical treatment. The prognosis was poor in those patients having palliative tube drainage. Aggressive HR led to prolongation of survival. As choledochotomy performed in order to remove the tumor thrombus has been reported to cause tumor seeding, en bloc resection without choledochotomy must be advocated (Table 2) [34]. However, contradictory results have been reported showing no significant difference between HR with choledochotomy and en bloc bile duct resection [35,36]. In our series of 1697 resections for HCC, HCC with bile duct thrombus involving the second-order branch or more centrally was diagnosed in 27 patients (1.6%). Their overall and disease-free 5-YSRs were 27.6% and 21.6%,

Tumor extent	Resection	Liver transplantation	Transplantability
Large HCC ≥ 10 cm	5-YSR 20%	5-YSR < 10%	No
Multiple HCC ≥ 3*	5-YSR < 20%	5-YSR > 50%	Yes
HCC with macrovascular invasion	5-YSR 31%	5-YSR < 20%	No
HCC with bile duct tumor thrombus	5-YSR 21.6%	5-YSR < 50%	Yes

*Within the Asan criteria.

Table 3. Suggestions for surgical treatments of advanced hepatocellular carcinoma based on the institutional experience at the Asan Medical Center.

respectively. Patients with Ueda type 3 involving the hepatic hilum showed better survival after HR with bile duct resection than HR with choledochotomy, thereby favoring concurrent bile duct resection. Patients who had curative resection showed a favorable outcome of 70.6% of overall 5-YSR, comparable to non-icteric HCC patients. There is today no consensus about the transplantability of HCC with bile duct tumor thrombus, but tumors permitting en bloc resection of the extrahepatic bile duct may present an indication for LT as a survival gain may be expected.

Conclusions

HR is the treatment of choice for HCC, but its long-term result is impaired by tumor recurrence and progressive worsening of liver function. Even in patients with small HCC and preserved liver function, long-term outcome after HR is definitely inferior to LT [37]. It is generally accepted that there is 10% loss of patients per year due to progressive liver failure or tumor recurrence after HR of a small tumor in Child class A patients. The expansion of indication criteria of LT for HCC resulted in a worsened outcome of LT. However, patients with HCC meeting some eligibility criteria ensure a statistically proven favorable survival outcome after LT [18]. Patients clearly exceeding these criteria, as described in this paper, have a substantially lower survival benefit due to higher incidence of HCC recurrence after LT. Since deceased-donor LT represents an effective contribution of the society, liver graft allocation must take in account possible organ wastage due to futile LT. In contrast, for living-donor LT, each liver graft has to be considered as a private gift to a beloved one presenting with a liver disease. Recipient survival rate should be improved by the exclusion of high-risk patients from living-donor LT because of the dedication of living donors [5]. Patients with advanced HCC with large tumor size and major vascular invasion should be excluded from LT. Instead, multi-modality treatment strategies including surgical resection would be beneficial to improve patient survival outcomes. Our suggestions for surgical treatments of advanced HCC are summarized at Table 3.

After HR, applicability of LT can be considered in three different settings [38]. Firstly, HR can be used as a primary treatment modality followed by LT as a salvage therapy for patients who would develop later recurrence and/or hepatic failure. Secondly, HR can be used as an initial treatment to select patients who might have prognostic benefit from LT according to the tumor pathology and biology as a natural selection modality. Thirdly, HR can be used as a bridge therapy for patients who have been already listed for LT. As HR and LT have complementary roles, they should be associated to rather than being opposed to each other. The use of different strategies on HR and LT depends on the availability of liver graft and the waiting time in different centers and allocation organizations as well as on the center-specific experience both in the field of HR and, deceased- and/or living-donor, LT. This multi-modality treatment strategy, especially for patients with advanced HCC, provides a new field of investigation in order to further refine the respective indications for HR and LT.

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