Review

The Recent Development of the Surgical Treatment for Hepatocellular Carcinoma

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Abstract: The optimal treatment for hepatocellular carcinoma (HCC) should be selected based on tumor conditions, liver functional reserve, and performance status. Surgical treatment, such as liver resection and liver transplantation, is the most favorable treatment method; however, its indication criteria differ according to each country's guidelines. In Western countries, liver resection is indicated only for early-stage HCC patients with Barcelona-Clinic Liver Cancer staging classification (BCLC) 0/A. While in Asian countries, liver resection is one of the treatment options for advanced HCC, such as BCLC B/C. Recently, the treatment of HCC is about to enter a drastic transitional period. It started with the widespread use of minimally invasive surgery for HCC, followed by a high rate of hepatitis C virus eradication with the advent of direct acting antivirals and developing a multidisciplinary treatment for highly advanced HCC. As a result, the importance of liver resection for HCC is increasing, and it is time to reconsider the criteria for selecting treatment methods for HCC patients. This article outlines current topics in the surgical treatment of HCC.

Keywords: hepatocellular carcinoma; surgical indication; portal vein tumor thrombus; hepatic vein tumor thrombus; multiple tumors; multidisciplinary treatment; laparoscopic liver resection; HCV; direct acting antivirals; liver transplantation

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1. Introduction

Hepatocellular carcinoma (HCC) accounts for the majority of primary malignancy of the liver. It is the fifth most common cancer and is the second leading cause of cancer-related death worldwide [1]. Liver resection and liver transplantation provide the most favorable outcomes for HCC [2]. However, the indications of liver resection for HCC differ significantly between Asian countries (Japan, Korea, China, Taiwan, etc.) and Western countries (Europe and the United States). In Asian countries, liver resection is recommended even for advanced HCC [3–5]. In contrast, in Western countries, liver resection is indicated only for a limited number of patients with early HCC, and liver transplantation is recommended for others [6,7]. Recently, the treatment of HCC is now at a turning point: the widespread use of minimally invasive surgery with the advancement of laparoscopic surgery, the high eradication rate of hepatitis C virus (HCV) with the advent of direct antiviral agents (DAAs), and the development of multidisciplinary treatment, including surgical treatment, for highly advanced HCC that was previously incurable. In other words, the importance of liver resection in the treatment of HCC is gradually increasing with the development of new therapies and the accumulation of evidence. This article will discuss the current topics of the surgical treatments for HCC by comprehensive search of PubMed, EMBASE, and Cochrane library, taking into account the differences among countries and regions.

2. Surgical Indications for HCC

The indications of liver resection for HCC depends on the liver functional reserve and biological features of the tumor. The first prerequisite is maintained liver function. Many guidelines require Eastern Cooperative Oncology Group performance status 0–1 and Child-pugh A/B as surgical indications [4–6]. Among them, the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC) guidelines state that only patients with PS0, Child-Pugh A, and no ascites are eligible for liver resection [7]. Second, the indications for liver resection, based on tumor progression, are quite different between Asian and West countries. The extent of tumor progression is evaluated by the number and the size of tumors, the extent of vascular invasion, and the presence of extrahepatic metastasis. In Asian countries, in addition to the tumors within the Milan criteria, liver resection is attempted for selected advanced HCC cases outside the Milan criteria as long as the absence of extrahepatic metastasis and technically feasible [3–5]. On the other hand, in Western countries, which follow the Barcelona-Clinic Liver Cancer staging classification (BCLC staging system), have set narrow indications for liver resection [8]. For those with single nodules within 2 cm in size without vascular invasion or extrahepatic metastasis, liver resection is recommended. This is mainly due to the low hurdle for liver transplantation.

3. Surgical Treatment of HCC within Milan Criteria

For patients with HCC less than three in number and less than 3 cm in size or a single tumor less than 5 cm in size (equivalent to BCLC-A), liver resection and radiofrequency ablation (RFA) are recommended with equal weight in Asian countries [3–5]. On the other hand, in Western countries, liver resection is not recommended for patients with two or three tumors. Moreover, in cases with portal hypertension and high bilirubin levels, RFA or liver transplantation is recommended instead of liver resection [6,7]. Certainly, liver transplantation is an ideal treatment that can eliminate unrecognized sites of intrahepatic spread as well as the possibility of de novo HCC arising from the diseased parenchyma. In general, the 10-year recurrence-free survival rate after liver transplantation is around 50–70%, which is extremely good compared to 30–50% for liver resection [2]. Due to severe shortage of liver graft and disease progression while on the waiting list, liver resection and transarterial chemoembolization (TACE) have been used as the second most effective treatment after transplantation. According to the nationwide survey in Japan, the five-year survival rate after liver resection for the HCC patients within the Milan criteria is about 70%. Liver resection may achieve long-term survival comparable to liver transplantation if appropriate treatment against recurrent HCC and resolution of the cause of hepatitis can be performed [9,10]. In addition, recent reports from Western countries suggest the usefulness of liver resection for HCC patients within the Milan criteria for effective utilization of limited liver graft [2]. For increasing resectability with preventing posthepatectomy liver failure due to insufficient future liver remnant (FLR), portal vein embolization was performed as conventional approach [11]. As an alternative approach for FLR augmentation, associating liver partition and portal vein ligation for staged hepatectomy (ALLPS) has been popularized [12]. Most of the evidences focus on ALLPS procedure against colorectal liver metastases [13]. There are still few reports about the safety and efficacy of ALLPS for the treatment of HCC with liver cirrhosis, further studies are warranted [14–16]. On the other hand, RFA is an option for patients who cannot undergo hepatectomy. Currently, a large randomized controlled trial in Japan has shown that there is no significant difference in three-year recurrence-free survival between liver resection and RFA groups, and analysis of long-term prognosis is awaited [17]. HCC has a high recurrence rate even after curative treatment, with intrahepatic recurrence accounting for the majority of cases. The treatment strategy of intrahepatic recurrence is based on the same algorithm as for initial treatment. This means that the choice of treatment depends on the liver functional reserve and the biological features of the recurrent tumor [18,19]. In a comparison of surgical treatment between repeat hepatectomy

and salvage liver transplantation, many reports show that salvage liver transplantation has a good recurrence-free survival rate; however, there is no difference in five-year survival rate between the two groups [20,21]. In view of the current donor shortage, repeat hepatectomy may be a useful option for recurrent HCC.

4. Surgical Treatment of Highly Advanced HCC Outside Milan Criteria

HCCs with vascular invasion are considered as very advanced stage, and liver resection is not recommended in Western countries. In Asian countries, all treatment options, including liver resection, are recommended as treatment options. Still, liver resection is the first consideration if liver function is preserved and technically resectable [3–5]. As for multiple HCCs, tumors outside the Milan criteria are classified as intermediate stage by the BCLC staging system, and TACE is recommended in Western countries; on the other hand, from Asian countries, the effectiveness of liver resection have been reported [22,23]. Systematic review about treatment strategy against intermediate stage HCC reported the effectiveness of liver resection in selected patients [24,25].

4.1. Liver Resection for HCC with Portal Vein Tumor Thrombus

The incidence of Portal vein tumor thrombus (PVTT) has been confirmed in more than 40% of HCCs and have an extremely poor prognosis with a median survival of 2.7–4 months without any treatment [26,27]. In addition, the extent of the disease correlates with prognosis, and the classification of PVTT proposed by the Liver cancer study group of Japan has been widely used worldwide [28,29]. The classification is as follows: Vp0, no tumor thrombus in the portal vein; Vp1, presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein; Vp2, presence of a tumor thrombus in the second-order branches of the portal vein; Vp3, presence of a tumor thrombus in the first-order branches of the portal vein; and Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both) [9]. Systemic therapy is recommended as standard therapy for patients with PVTT in Western countries, but in Asian countries, liver resection is usually attempted regardless of the extent of PVTT [30–32]. In 2016, Kokudo et al. reported the outcomes of 6474 HCC patients with PVTT using Japanese national registry data [28]. Of these patients, 2093 who underwent liver resection (LR) and 4381 who received other treatments (non-LR) were compared. The median survival time (MST) of the LR group was 23.2 months longer than that of the non-LR group (29.6 months vs. 9.7 months) and 12.4 months longer than the non-LR group (28.9 months vs. 16.6 months) in a propensity score-matched cohort. Subgroup analysis based on the degree of PVTT showed that only Vp4 patients did not benefit from resection. Although similar results have been reported from Asian countries, there is an urgent need to develop more appropriate selection criteria and perioperative therapy to control postoperative recurrence [33]. So far, the usefulness of HAIC, radiation therapy, etc., have been reported [34–39].

4.2. Liver Resection for HCC with Hepatic Vein Tumor Thrombus

Unlike HCC with PVTT, HCC with hepatic vein tumor thrombus (HVTT) accounts for only about 5% of all HCC cases [9]. HVTT is categorized as tumor thrombus in a peripheral hepatic vein, including microvascular invasion (pHVTT, Vv1), in a major hepatic vein (mHVTT, Vv2), or in the inferior vena cava (IVCTT, Vv3) according to the Japanese staging system [40]. In 2017, Kokudo et al. reported the outcomes of 1266 HCC patients with HVTT in Japan [41]. The surgical outcome for p/mHVTT was excellent, with a MST of 53.6 months and a five-year survival rate of 44.2%. In a propensity score-matched cohort, the MST of the liver resection group was 19.3 months longer than the non-liver resection group (41 months vs. 21.7 months). On the other hand, PVTT was an independent poor prognostic factor in the p/mHVTT resection group, and the MST of patients with PVTT was 45.4 months shorter than the patients without PVTT (22.6 months vs. 68 months). Similar reports have been reported from Asian countries, and therefore they recommended

that at least HCC patients with intrahepatic HVTT without PVTT could be suitable for liver resection [42–44]. For preventing intrahepatic recurrence, the usefulness of postoperative adjuvant TACE has been reported, and further evaluation with randomized trials are warranted [45].

On the other hand, although IVCTT accounts for only 1% of all HCC cases, the prognosis of HCC patients with IVCTT is extremely poor because of the systemic circulation of the tumor cells and fatal complications such as pulmonary embolism, heart failure, and sudden cardiac death due to occlusion of the tricuspid valve [44]. Clinically, IVCTT is classified into three types according to its anatomic location relative to the heart for surgical guidance: type I, inferior hepatic (TT in the IVC below the diaphragm); type II, superior hepatic (TT in the IVC above the diaphragm, but still outside the RA); and type III, intracardiac (TT entering the RA) [46]. Most IVCTT can be pulled downward along with retracted liver and resected from the abdominal cavity because macroscopic thrombus of HCC is less likely to invade the vascular wall. On the other hand, in the type III IVCTT, if the TT lacks mobility and clamping of RA cannot be safely performed, cardiopulmonary bypass with median sternotomy is often required [47]. In addition, in cases with IVCTT invades the vascular wall, IVC resection and reconstruction along with liver resection has been reported to be safely performed by using an artificial graft. Therefore, surgery should be performed without hesitation [48,49]. The significance of liver resection for the patients with IVCTT should be considered from the perspective of oncology and the prevention of sudden death. In the previous report by Kokudo et al., hepatic resection for IVCTT was performed in 111 patients, with a MST of 17.8 months and a three-year survival rate of 33.1%, which was significantly better than the MST of 10.1 months and a three-year survival rate of 20.1% in the non-resection group (134 patients). However, in the non-resection group, there were few cases with effective systemic therapies such as Sorafenib and Atezolizumab + Bevasizumab. Therefore, careful assessment with further study is needed to evaluate the oncological benefit of liver resection. IVCTT can lead to pulmonary infarction, heart failure, and sudden death due to obstruction of the tricuspid valve. Therefore, even in cases where radical resection is difficult due to the presence of distant metastasis or multiple lesions in both lobes, liver resection and thrombectomy may be useful. Matsukuma et al. reported in a multicenter study that MST did not differ between patients who had resection with curative intent (18.7 months) and those with the residual tumor in the lung only (20.7 months) [47]. Therefore, a comprehensive evaluation of the disease state is necessary to determine the treatment plan.

4.3. Surgical Treatment of Multiple HCC

In addition to tumor size, tumor number is a poor prognostic factor after liver resection of HCC [50]. In the BCLC staging system, all patients with multiple HCC outside the Milan criteria without distant metastasis or vascular invasion are classified as intermediate stage, and TACE is uniformly recommended. However, there are a wide variety of patients, some of whom may benefit from liver transplantation, and some may benefit from regional therapy such as liver resection or RFA compared to TACE [51–54]. In 2019, Fukami et al. reported a nationwide study of the treatment outcomes of 3246 cases of multiple HCC in Japan [10]. Among them, subgroup analysis of the 1309 patients with HCC larger than 3 cm in size revealed that the 90-day mortality rate in the liver resection group was extremely low at 0.57%, and a five-year overall survival rate was significantly better in the liver resection group than the TACE group (53% vs. 32.7%). For subclassification of these heterogeneous populations, it has been reported that the combinatorial use of the number of tumors, size, tumor markers, and liver function can be useful [22,23,51,55–57].

5. Minimally Invasive Surgery for HCC

Laparoscopic liver resection (LLR) was first reported in 1991, and since then, LLR has rapidly spread with an increasing number of reports about its feasibility, safety, and usefulness. Today, about a quarter of all liver resections in Japan were performed laparo-

scopically [58]. In 2014, the second International consensus conference on Laparoscopic Liver Resection (ICLLR) was held in Japan, and laparoscopic partial liver resection for HCC located the peripheral portion of the anterolateral segments of the liver was considered as standard clinical practice [59].

The advantages of LLR can be summarized in four points: a good field of view with minimal disruption of the body wall, magnified vision, hemostasis by buffer effect of pneumoperitoneum, and preservation of portosystemic venous and lymphatic collaterals. The laparoscopic approach could provide a good field of view for surgery on the liver, which is located within the thorax without large incisions [60]. In addition, the magnification effect allows us to observe the fine vascular structures, and managing pneumoperitoneum pressure reduces bleeding from the hepatic veins, which enables more delicate surgical procedures with a dry surgical field [61]. However, if the pneumoperitoneum pressure is higher than the central venous pressure, the risk of pulmonary gas embolism increases [62]. In terms of short-term surgical outcomes, a recent meta-analysis comparing 4026 open liver resection (OLR) and 2786 LLR patients revealed that the R0 resection rate was comparable between the two groups and blood transfusion rate, hospital stay in days, 30-day mortality rate and morbidity were significantly lower in LLR compared to OLR [63]. Among the postoperative complications, superficial surgical site infections were reported to be significantly reduced in the LLR group [64]. In terms of long-term surgical outcomes, it has been reported that there may be no difference between the two groups; however, caution is required in interpretation due to the strong influence of background factors [63]. Other advantages include the possibility of reducing the frequency of postoperative complications such as ascites and liver failure by minimizing the transection of the ligament and liver mobilization [65]. In addition, postoperative adhesions are reduced after LLR, and LLR with its magnified view enables more careful dissection of adhesions strained by the pneumoperitoneum when performing repeat LLR. An additional possible advantage of repeat LLR is reported that complete adhesiolysis could be avoided when the adhesion does not affect the current operative procedure [66].

However, it is still not a well-established procedure. It is essential to determine the indication based on a learning curve and preoperative evaluation of surgical difficulty to safely perform the operation. In 2014, Ban et al. reported the Difficulty scoring system, which predicts the surgical difficulty of LLR based on five factors (tumor location, tumor size, tumor proximity to major vessels, the extent of liver resection, and liver function) [67,68]. After that, this difficulty scoring system was revised after discussion at the Second ICLLR and renamed the IWATE criteria [69,70]. Although this scoring system could predict short-term surgical outcomes, the surgical difficulty assessment system is still not perfect, and various new difficulty assessment systems are even being proposed [71–74].

6. The Impact of HCV Eradication on Surgical Outcomes for HCC

HCV infection is a major risk factor for the development of HCC in Europe, the United States, and Japan, as well as a risk factor for the progression of liver dysfunction (liver fibrosis and cirrhosis) [75]. It is now clear that elimination of HCV and achievement of sustained virological response (SVR) prevents or delays the progression of fibrosis/cirrhosis, decompensation, and the incidence of primary HCC, leading to improved survival [76]. However, the true impact of SVR on surgical outcomes of HCV related HCC remained controversial. Today HCV can be eliminated in almost all cases, and it is necessary to clarify that at least antiviral treatment has not worsened the surgical outcomes of HCC. Therefore, in a multicenter study, we investigated the impact of SVR before and after hepatectomy on the long-term surgical outcomes of HCV-related HCC after statistically minimizing bias arising from patients' background characteristics [77]. Two hundred ninety-six patients underwent radical hepatectomy for primary HCV related HCC, of which 58 achieved SVR before hepatectomy (Pre-SVR group), 54 achieved SVR after hepatectomy, and 186 without achieving SVR (Non-SVR group). All patients in the pre-SVR group received interferon (IFN) treatment. OS and RFS were significantly better in Pre-SVR group than

the Non-SVR group in a propensity-matched cohort. In terms of recurrence, both early intrahepatic metastases and multicentric carcinogenesis were suppressed in the SVR group. The post-SVR group also showed significantly better OS and RFS than the non-SVR group. Furthermore, histopathological evaluation using surgically resected specimens revealed that only the patients with SVR (about 30%) had regression of liver fibrosis. There have been several similar reports, and achievement of SVR before or after hepatectomy by IFN therapy is essential for improving long-term surgical outcomes in patients with HCV-related HCC [78–81].

Currently, the majority of treatments for HCV have replaced IFN with direct-acting antivirals (DAA). As data accumulation progresses, it has become clear that DAA treatment as well as IFN treatment associated reduced risk of mortality and HCC [82]. Concern was transiently raised that DAA treatment might increase the risk of HCC recurrence after hepatectomy; however, it is now clear that HCV elimination with DAAs does not have a significant impact on the course of established HCC [83,84]. On the other hand, whether HCV exclusion by DAA treatment can improve the surgical outcomes of HCC still needs further investigation due to the small number of cases and short follow-up period [85].

7. Liver Transplantation for HCC

Liver transplantation for HCC can cure underlying cirrhosis, the origin of multicentric carcinogenesis, while removing the tumor by total hepatectomy. The Milan criteria, defined by the size and number of the tumor, is the most commonly used and accepted indication criteria for patients with HCC [86]. Subsequently, various expanded criteria based on tumor size and number have been reported with comparable long-term outcomes compared to the Milan criteria [87–90]. In addition, a combination of alfa-fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) values as factors other than tumor size and number has been reported to improve the prognostic value of transplantation compared to the Milan criteria [91–93]. Recently, new expanded criteria, the so-called “5-5-500 rule”, was proposed by the Japanese Liver Transplantation Society based on a retrospective data analysis of the Japanese nationwide survey [94]. In the study of 965 living donor liver transplants for HCC, patients with nodule size ≤ 5 cm in diameter, nodule number ≤ 5 , and AFP value ≤ 500 ng/mL without extrahepatic disease or vascular invasion showed a 95% confidence interval of a five-year recurrence rate of 7.3% with an increase in number of eligible liver transplant candidates by 19% compared to the Milan criteria. In 2020, the “5-5-500 rule” was accepted as inclusion criteria for liver transplantation by the Japanese Social Insurance Coverage. There have been several reports on downstaging, and relatively good results have been obtained in terms of overall survival. Still, the recurrence rate is somewhat higher than that of cases within the Milan criteria. Therefore, the search for biomarkers, such as AFP and FDG-PET values after pretreatment, that can accurately assess the indication for liver transplantation after downstaging has been actively underway [95–100].

8. Conclusions

We have reviewed current topics in the treatment of HCC, with a focus on surgical treatment. The importance of liver resection has increased with the widespread use of minimally invasive surgery, the advent of DAA, and the development of multidisciplinary treatment. Accordingly, a growing number of different treatment options can be customized for individual HCC patients. In the future, it is most desirable to develop uniform and flexible treatment guidelines based on new high-quality evidence so that patients can choose the optimal HCC treatment regardless of country, and, above all, further improvement of surgical outcomes for HCC is expected.

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