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EDITORIAL
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What liver surgeons have achieved in the recent decade for patients with hepatocellular carcinoma?

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Abstract: In the past decade, there has been remarkable progress in surgical treatment for hepatocellular carcinoma (HCC) based on evidence created by epoch-making prospective trials or national registry big data analysis. A head-to-head randomized controlled trial comparing liver resection and local ablation for small oligo HCCs (SURF trial) demonstrated comparable recurrence-free survival provided both modalities are feasible. Survival benefit of liver resection for HCC with vascular invasion was demonstrated by two propensity scored matched analyses based on Japanese national data. Furthermore, expanded HCC criteria for living donor liver transplantation were developed based on Japanese national data, and this "5-5-500 rule" was accepted by the social insurance system in Japan. The recent remarkable progress in promising new anti-HCC agents may open the door for effective neoadjuvant or adjuvant treatment in combination with surgery.

***Keywords*:** hepatocellular carcinoma, liver resection, vascular invasion, living donor transplantation, molecular targeted agents, immune-check point inhibitors

In the past decade, there has been remarkable progress in surgical treatment of hepatocellular carcinoma (HCC) based on evidence created by epoch-making prospective trials or national registry big data analysis. Here we focus on three recent major developments from Japan: *i*) a head-to-head randomized controlled trial comparing liver resection and local ablation, *ii*) survival benefit of liver resection for HCCs with vascular invasion, and *iii*) expanded HCC criteria for living donor liver transplantation. Future outlook of combining surgery with promising new anti-HCC agents are also discussed.

Role of liver resection for small oligo HCCs

Although both liver resection and local ablation (radiofrequency ablation: RFA) are considered potentially curative treatments for small oligo HCCs, retrospective studies have suggested better local tumor control by liver resection (*1,2*). There have been at least 5 randomized controlled trials (RCTs) conducted to compare liver resection and RFA (*3-7*, Table 1). Most of the previous studies were reports from mainland China, Hong Kong, or Taiwan where hepatitis B is a major etiology. Three of the studies failed to show the benefits of liver resection over RFA for patients with small oligo HCCs on the long-term outcome in terms of recurrence free survival (RFS) nor overall survival (OS), and only one reported a significantly better outcome for surgery (*5*). Since inclusion criteria for the latter study was within Milan criteria, RFA for tumors over 3 cm may have inferior local control which may have affected the outcome of the RFA arm. In general, patient numbers for the previous studies were relatively small and could be under-powered.

Since 2008, a similar head-to-head multicenter study called SURF trial (Comparison between SUrgery and RFA) has been conducted in Japan. Inclusion criteria were primary HCC ≤ 3 cm in diameter with ≤ 3 nodules. Liver function should be ≤ Child-Pugh 7. Before randomization, patient condition and tumor location were reviewed by both surgeons and hepatologists to check the feasibility of liver resection and RFA. Once informed consent was obtained, patients were randomized with stratification by trial site, age, HCV infection, tumor number, and size. Primary co-endpoints were RFS and OS. Although the targeted patient number (n = 600) was not achieved, 308 cases were registered, which is larger than any of the previous trials (Table 1). Surgical resection and RFA were both safe therapeutic approaches and both of them provided similar RFS after a 3-year follow-up period (*7*). It would be safe to conclude curability for small oligo HCCs is similar between liver resection and RFA, however, technical feasibility of RFA in terms of proximity to major vessels should be carefully evaluated before selecting the optimal treatment option for each patient.

Table 1. Randomized clinical trials comparing resection and RFA for small oligo HCCs

Author (*Ref.*)	Year	Sites	Size	Tumor No.	Child-Pugh	Patient No.	Conclusion
Huang, *et al*. (*3*)	2005	Taiwan	≤ 3 cm	≤ 2	A,B	76	N.S.
Chen, *et al*. (*4*)	2006	Hong Kong, Guangzhou	≤ 5 cm	1	A	180	N.S.
Huang, *et al*. (*5*)	2010	Chengdu	≤ 3 cm (Milan criteria)	≤ 3	A,B	230	Favor SUR
Feng, *et al*. (*6*)	2012	Chongqing, Ji'nan	≤ 4 cm	≤ 2	A,B	168	N.S.
Izumi, *et al*. (*7*)	2019	Japan 118 sites	≤ 3 cm	≤ 3	A,B	308	N.S.

N.S.: not significant, SUR: surgery.

Surgery for vascular resection

HCCs with vascular invasion are considered as very advanced stage and liver resection is not recommended in treatment guidelines in Western countries (*8,9*). In Asian countries, liver resection has been attempted for selected cases and is recommended in APSL (*10*) and Japanese guidelines (*11*) as long as it's technically feasible. However, there have been no randomized controlled trials or even large-scale registry data analysis to address this issue. Recently, propensity score analyses using Japanese national registry data were conducted to investigate the survival benefit of liver resection for HCC patients with vascular invasion in portal vein (PVTT) or hepatic vein (HVTT) (*12,13*).

Data for 6,474 HCC patients with PVTT registered between 2000 and 2007 were analyzed. Of these patients, 2,093 who underwent liver resection (LR) and 4,381 who received other treatments were compared. The median survival time (MST) of the LR group was 1.93 years longer than that of the non-LR group (2.74 years *vs*. 0.81 years; $p < 0.001$) and 1.03 years longer than the non-LR group (2.41 years *vs*. 1.38 years; $p < 0.001$) in a propensity score-matched cohort (*12*). Similarly, data for 1,021 Child-Pugh A HCC patients with HVTT without inferior vena cava invasion were analyzed. The median survival time of the LR group ($n = 540$) was 2.89 years longer than that of the non-LR group ($n = 481$, 4.47 *vs*. 1.58 years, $p < 0.001$) and 1.61 years longer than the non-LR group (3.42 *vs*. 1.81 years, $p = 0.023$) in a propensity score-matched cohort (*13*). These studies provide a second best level of evidence for this clinical question. The randomized controlled study may not be feasible for the patient population due to heterogeneity of the disease and technical difficulty.

Expanded criteria

Since 1994, Milan criteria have been the gold standard for selecting HCC patients for successful liver transplantation (*14*), however, these criteria are too strict and expansion of indication criteria has long been debated. Due to a very severe scarcity of deceased donors in Japan, living donor liver transplantation (LDLT) has been a mainstay in this setting. Table 2 shows a list of expanded criteria proposed by Japanese centers. Exclusion of HCC with vascular invasion and extrahepatic disease was consistent among all of the expanded criteria. The University of Tokyo proposed a so-called 5-5 criteria (≤ 5 nodules, ≤ 5 cm in diameter) (*15*), and Kyoto University group proposed ≤ 10 nodules, ≤ 5 cm in diameter, and des-gamma-carboxy prothrombin (DCP) ≤ 400 mAU/mL (*16*). Kyushu University group also proposed their own expanded criteria: no limitation in tumor number, ≤ 5 cm in diameter, or DCP ≤ 300 mAU/mL (*17*). They reported non-inferior long-term outcome for patients fulfilling their expanded criteria compared to that for Milan criteria.

Table 2. Expanded LDLT Criteria for HCC in Japan*

Institution (*Ref.*)	Number	Size (cm)	Tumor marker
Tokyo Univ. (*15*)	≤ 5	≤ 5	Any
Kyoto Univ. (*16*)	≤ 10	≤ 5	DCP ≤ 400
Kyushu Univ. after 2007 (*17*)	Any	≤ 5	or DCP ≤ 300
Kyoto Univ. before 2006 (*16*)	Any	Any	Any
All-Japan (*18*)	≤ 5	≤ 5	AFP ≤ 500

*Exclusion of HCC with vascular invasion and extrahepatic disease is consistent among all of the expanded criteria. AFP: alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

Recently, new expanded criteria were proposed by the Japanese Liver Transplantation Society based on a retrospective data analysis of the Japanese nationwide survey. A total of 965 HCC patients undergoing LDLT were included, and 301 (31%) were beyond the Milan criteria. The Greenwood formula was applied to investigate new criteria, which enabled a maximal enrollment of candidates while securing a 5-year recurrence rate below 10%, by examining various combinations of tumor numbers and serum alpha-fetoprotein values, and maintaining the maximal nodule diameter at 5 cm. After thorough statistical scrutiny, new expanded criteria for LDLT candidates with HCC, the "5-5-500 rule" (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and alfa-fetoprotein value ≤ 500 ng/mL), were established as a new condition with a 95% confidence interval of a 5-year recurrence rate of 7.3%. These criteria expanded the eligible patient pool by 19% (*18*). In 2019, the "5-5-500 rule" was applied as inclusion criteria for listing HCC patients by the Japanese Organ Sharing System. This rule was also accepted for Japanese Social Insurance Coverage for LDLT in 2020.

Table 3. Randomized controlled trials on adjuvant treatment after curative treatment for HCC

Intervention (*Ref.*)	Title of the Study	Registry code	Recruitment	Result
Uracil-Tegafur (*21*)	–	UMIN C000000445	Aug. 1997-2002	N.S.
Sorafenib (*22*)	STORM	NCT00692770	Aug. 2008-Nov. 2014	N.S.
Peretinoin (*23*)	NIK-333 phase 2/3	JapicCTI-060250	Feb. 2005-Dec.2009	N.S.
Nivolumab	ONO-4538-70	NCT03383458	Dec. 2017-	Ongoing
Duravalumab ± Bevacizumab	EMERALD-2	NCT03847428	April 2019-	Ongoing
Atezolizumab + Bavacizumab (*24*)	IMbrave 050	NCT04102098	Dec. 2019-	Ongoing

N.S.: not significant.

Future surgery and new drugs

Since the introduction of sorafenib in 2007 (*19*), there has been tremendous progress in molecular targeted drug or immuno-checkpoint inhibitors for advanced HCC. A combination of liver resection and advanced drug therapy may work in two ways: adjuvant therapy after curative resection and neoadjuvant or conversion therapy for initially unresectable HCC. The 5-year recurrence rate is known to be as high as 70-80% even after curative resection (*20*), and there has been a number of adjuvant treatments including Uracil-Tegafur (*21*), sorafenib (*22*), and peretinoin (*23*) to reduce tumor recurrence, but without success (Table 3). Following introduction of immuno-checkpoint inhibitors, there have been at least 3 randomized trials, which are still ongoing, to test adjuvant therapy using these agents (*24*, Table 3). Results of these trials are expected to be available within a few years.

Initial response rate (RR) of the first molecular targeted drug, sorafenib, was only 3% and strategy of conversion surgery was not feasible with such a low RR (*19*). RR of the second approved 1st line agent Lenvatinib jumped up to 24% (*25*), and more recent combination therapies demonstrated RR at around 30-40%. Currently, a few prospective studies for neoajuvant therapy are ongoing with results expected soon.

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