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EDITORIAL
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Role of liver resection in the era of advanced systemic therapy for hepatocellular carcinoma

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Abstract: The recent dramatic progress in systemic therapy for hepatocellular carcinoma (HCC) provides the possibility of a combination of surgery and systemic therapy including adjuvant, neoadjuvant, or conversion settings. Since the turn of the century, at least three negative studies have tested adjuvant therapies after curative resection or ablation, including uracil-tegafur, which is an oral chemotherapeutic drug, sorafenib, and peretinoin, which a synthetic retinoid that may induce the apoptosis and differentiation of liver cancer cells. Using more potent immuno-checkpoint inhibitors (ICIs), at least 4 phase III trials of adjuvant immunotherapy are ongoing: nivolumab, durvalumab/bevacizumab, pembrolizumab, and atezolizumab+bevacizumab. Very recently, the last trial indicated a significantly better recurrence-free survival (RFS) for adjuvant atezolizumab+bevacizumab. Another promising combination of surgery and systemic therapy is neoadjuvant therapy for potentially resectable cases or a conversion strategy for oncologically unresectable cases. There are 2 neoadjuvant trials for technically or oncologically unresectable HCCs ongoing in Japan: the LENS-HCC trial using lenvatinib and the RACB study using atezolizumab+bevacizumab. A longer follow-up may be needed, but the overall survival (OS) in resected cases seems much higher than that in unresectable cases. Recently, the Japan Liver Cancer Association (JLCA) and the Japanese Society of HPB Surgery (JSHPBS) created a joint working group on "so-called borderline resectable HCC". They obtained a Japanese consensus on this issue that has been published on the websites of JLCA and JSHPBS. The definition of resectability or borderline resectability provides a common language regarding advanced HCC for investigators and is a useful tool for future clinical trials.

***Keywords*:** hepatocellular carcinoma (HCC), adjuvant systemic therapy, neoadjuvant systemic therapy, conversion strategy

As of January 2023, the Food and Drug Administration (FDA) has approved nivolumab, pembrolizumab, ramucirumab, nivolumab/ipilimumab, atezolizumab/bevacizumab, and tremelimumab/durvalumab as first- or second-line monoclonal antibodies (mAbs) for unresectable hepatocellular carcinoma (HCC) in the USA (*1*). In Japan, atezolizumab/bevacizumab was approved in 2020, and it became the regimen of choice for first-line treatment. Durvalumab/tremelimumab was approved as first-line treatment in 2023. In total, 6 or 7 regimens are available for HCC in Japan as of January 2024. The recent dramatic progress in systemic therapy for HCC provides the possibility of a combination of surgery and systemic therapy; *i.e.*, adjuvant, neoadjuvant, or conversion settings.

Adjuvant systemic therapy

The first type of combination is the adjuvant setting: systemic therapy after liver resection. Tumor recurrence is known to be very common even after curative liver resection. The reported 5-yr recurrence rate was as high as 70 to 80% (*2*). There are two peaks for recurrence-free survival (RFS) hazard after liver resection. The first peak is recurrence because of residual micro metastases. The second peak may be because of so-called multi-centric carcinogenesis. Adjuvant therapy is targeted to lower the first wave of recurrence.

There have been several trials on adjuvant therapy to solve this issue. Takayama's adaptive immunotherapy was probably one of the oldest and milestone studies which indicated the impact of adaptive immunotherapy as reported by the National Cancer Center Japan (*3*). They used autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and antibodies against CD3. After culturing for two weeks, they obtained enough T cells with CD3, 4, and 8 markers. The primary endpoint was met, and this immunotherapy significantly reduced the risk of tumor recurrence after resection. However, this adjuvant therapy was not feasible in daily practice

because of the complex procedure for cell preparation and probably the cost. After this study, there have been at least three studies that tested adjuvant therapies after curative resection or ablation, including uracil-tegafur (UFT), which is an oral chemotherapeutic drug (*4*), sorafenib (*5*), and peretinoin, which is a synthetic retinoid that may induce the apoptosis and differentiation of liver cancer cells (*6,7*). All of the subsequent studies were negative in reducing tumor recurrence (*8*).

In the uracil-tegafur study, RFS curves of the UFT arm and control were almost identical. However, overall survival looked even worse in the UFT arm, with a *p*-value of 0.08. As a result, UFT was not recommended as an adjuvant therapy after curative resection (*4*). Subjects of the STORM trial were patients with a moderate risk of recurrence. Sorafenib was administered for as long as 4 years in the experimental arm. Both RFS and overall survival (OS) curves were almost overlapping, and the study was negative. A point worth noting is that the 5-yr OS was as high as 70% even for the placebo arm (*5*).

There are several reasons why most of the previous adjuvant trials for HCC failed. First, defining optimal patient populations was difficult. The outcome of the control arm has been generally too good in previous studies, and there have been no biomarkers for patient selection. Second, there is no set duration for adjuvant therapy. Figure 1A compares the duration among the previous studies and ongoing studies using immuno-checkpoint inhibitors (ICIs). Of note, there is no set duration for this setting. This is probably because peaks in the hazard curve for recurrence are not very steep compared to those for other cancer types (*2*). Severe adverse events (AE) are not acceptable for seemingly healthy patients after curative treatment. Finally, previous studies might have simply indicated insufficient efficacy.

Since the introduction of ICIs, at least 4 phase III trials of adjuvant immunotherapy after liver resection or radiofrequency ablation (RFA) are ongoing. Experimental arms are nivolumab, durvalumab/bevacizumab, pembrolizumab, and atezolizumab+bevacizumab (Table 1). The inclusion criteria for these trials are "a high risk of recurrence" patient subgroup. Macroscopic vascular invasion may have been regarded as "a very high risk of recurrence", and this patient condition was excluded in 3 studies. Only IMbrave 050, a study of atezolizumab+bevacizumab, accepted Vp1 or Vp2 patients.

Very recently, the IMbrave 050 study indicated a significantly better RFS for adjuvant atezolizumab +bevacizumab (*9*). This is the first phase III study showing the benefit of adjuvant therapy after liver resection or RFA. However, reaching a conclusion on survival benefits would be premature. IMbrave 050 is the only adjuvant study that included patients with limited vascular invasion, Vp1 and 2. However, they accounted

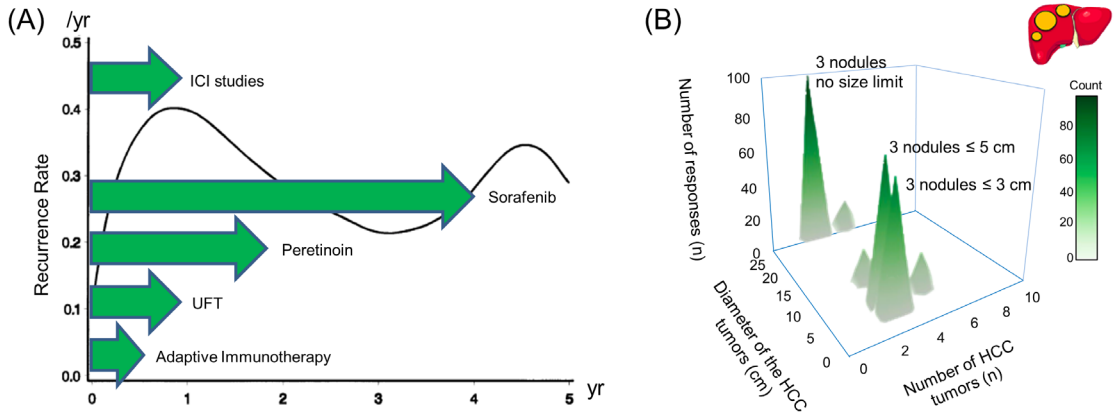

Figure 1. (A) Duration of adjuvant therapy superimposed on a risk of recurrence curve. (B) Upper limit of oncologically resectable (R) for multiple lesions in terms of the size and number of tumors. The x-axis shows the number of HCC tumors, the y-axis shows the maximum diameter of the HCC tumors (cm), and the z-axis shows the number of responses. Source: *Modified from Reference 2,15.*

Table 1. On-going phase III trials of adjuvant immunotherapy for HCC

Trial name	Drug	Target molecule	Duration of treatment	Primary endpoint	Target number of patients	Study start date
CheckMate 9DX	Nivolumab	PD1	1 yr	RFS	530	Dec. 2017
EMERALD-2	Durvalumab +/- Bevacizumab	PD-L1, VEGF	1 yr	RFS	888	Apr. 2019
KEYNOTE-937	Pembrolizumab	PD-L1	1 yr	RFS	950	May 2019
IMbrave 050	Atezolizumab + Bevacizumab	PD-L1, VEGF	1 yr	RFS	662	Dec. 2019

for only 6–8% of cases, and subgroup analysis was done only for cases with micro- instead of macro-vascular invasion. Further evaluation of the impact of ICIs after liver resection for HCC with macrovascular invasion may be needed.

After reviewing a long history of failures in adjuvant trials for HCC, there are several keys to success including appropriate patient selection, appropriate duration of adjuvant therapy, sufficient efficacy of the regimen, acceptable AEs, maintained performance status (PS), and liver function. Most of the ongoing trials might fulfill these conditions and their final results are awaited.

Neoadjuvant systemic therapy or conversion strategy

Another promising combination of surgery and systemic therapy is neoadjuvant therapy for potentially resectable cases or conversion strategy for oncologically unresectable cases. The conversion strategy for unresectable colorectal liver metastases (CRLM) was established more than a decade ago. After the introduction of FOLOX, FOLFIRI +/- mAbs, we could expect marked tumor shrinkage, making unresectable tumors into resectable ones. This strategy may not be simply applicable to HCC because the anti-tumoral action of systemic therapy on HCC differs slightly because dramatic tumor shrinkage is rare and a decrease in vascularity is more common.

Since lenvatinib was approved in 2018, there have been several reports on effective cases. For example, Matsuki *et al*. reported a case that initially involved a large tumor in the right liver and a lung metastasis. After lenvatinib administration, there was a marked shrinkage of the tumors and the metastatic lesion in the lung disappeared. This patient was ultimately able to undergo curative liver resection (*10*). The relatively high response rate (RR) to lenvatinib led us to plan a neoadjuvant trial for technically or oncologically unresectable HCCs (LENS-HCC trial: jRCT s031190057). There were 5 categories for patient inclusion. Category A is cases with macrovascular invasion, followed by category B, synchronous extrahepatic disease (EHD). Category C is a combination of A and B. Category D is cases with very large tumor loads where R0 resection is unlikely. The last category E is metachronous EHD. Forty-nine patients were recruited, and 33 patients (67%) were able to undergo liver resection and 16 were not. Although we may need a longer follow-up, the 24-month survival rate was over 75% in resected cases, which was much higher than that for unresectable cases (*11*).

A similar study is ongoing in Japan: the neoadjuvant atezolizumab plus bevacizumab RACB study, UMIN000046634). The inclusion criteria are the same as those for the lenvatinib trial. The target number of patients is 50, and it is expected to close soon (*12*). Recently, Kaseb *et al*. conducted a prospective study in a neoadjuvant setting to compare nivolumab and nivolumab plus ipilimumab: the blockade of the PD-1/PD-L1 and CTLA-4 pathways (*13*). Although efficacy was not a primary endpoint, CR was achieved in 29% of cases and there was no delay in surgery because of severe AEs. Patients with a major pathological response (MPR) has a significantly better RFS after liver resection.

Concept of borderline resectable HCC

In the field of pancreatic cancer, the concept of a borderline resectable tumor (BR) has been well established. Neoadjuvant therapy is usually used for BR pancreatic cancer according to National Center for Global Health and Medicine (NCGM) guidelines (14). Recently, the Japan Liver Cancer Association (JLCA) and the Japanese Society of HPB Surgery (JSHPBS) created a joint working group on "so-called borderline resectable HCC". First, they surveyed expert Japanese HBP surgeons to clarify their perceptions of the resectability of HCC. Then, an expert panel was organized to reach a consensus on oncological resectability for advanced HCC.

Akahoshi *et al*. analyzed a total of 351 responses from the aforementioned survey (*15*). Resectability for single tumors was broad in that 64.7% of the respondents considered solitary tumors to be R (resectable), irrespective of size. However, opinions diverged on the upper limit of the number of tumors/tumor size for R among multiple tumors: *i*) up to three nodules with no size limit (27.9%), *ii*) up to three nodules ≤ 5 cm in diameter each (21.4%), and *iii*) up to three nodules ≤ 3 cm in diameter each (19.4%, Figure 1B. Resectability for HCC with portal vein invasion depended on the extent of vascular invasion: Vp1, Vp2, Vp3, and Vp4 were considered to be R by 90.9%, 70.7%, 39.0%, and 8.0% of respondents, respectively. Half of the respondents indicated they would consider resection even for cases with extrahepatic spread under limited conditions.

Based on the aforementioned survey data, the expert panel (*i.e.*, joint working group) reached a Japanese consensus on "so-called borderline resectable HCC" that has been published on the websites of JLCA and JSHPBS. Here are the definitions for R: resectable, BR1, and BR2. Surgery may offer better survival outcomes for the R category compared to other treatments. Surgical intervention as a part of multi-disciplinary treatment may offer survival benefits for the BR1 category. The effectiveness of surgery is indeterminate and surgical indications should be carefully determined under the standard multidisciplinary management for the BR2 category. We decided not to use the term "UR or unresectable" for the BR2 category because "UR" may be misleading since most of the cases are technically resectable and the patient's surgical option may be limited from the beginning due to the label UR.

In conclusion, recent dramatic progress in systemic therapy has harkened the advent of an era

of a combination strategy for HCC. Several adjuvant ICI regimens are being studied, and IMbrave 050 demonstrated a promising clinical benefit. Neoadjuvant or perioperative systemic therapy for advanced HCC is another clinical question that warrants further investigation. The definition of resectability or borderline resectability provides a common language regarding advanced HCC for investigators and is a useful tool for future clinical trials.

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