Review

DOI: 10.5582/bst.2024.01372

Advances in systemic therapy leading to conversion surgery for advanced hepatocellular carcinoma

Hiroyuki Hakoda, Akihiko Ichida, Kiyoshi Hasegawa*

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

SUMMARY Recently, a systemic therapy for advanced hepatocellular carcinoma (HCC) has been developed. The regimen for unresectable HCC varies and includes single or multi-tyrosine kinase inhibitors, monoclonal antibodies, immune checkpoint inhibitors, or their combinations. Treatment with these agents begins with sorafenib as the first-line drug for unresectable HCC. Subsequently, several systemic therapies, including lenvatinib, ramucirumab, cabozantinib, and regorafenib have been investigated and established. With advances in systemic therapy for unresectable HCC, the prognosis of patients with unresectable HCC has improved significantly than previously. Conversion surgery, consisting of systemic therapy and surgery, showed the possibility of improving the prognosis than systemic therapy alone. Although a combination of atezolizumab and bevacizumab is mostly used for initially unresectable HCC to conduct conversion surgery because of the high response rate and fewer adverse events compared to others, many trials are being conducted to assess their efficacy for initially unresectable HCC. However, the appropriate timing of surgery and interval between systemic therapy and surgery remain controversial. To address these issues, a multidisciplinary team can play a vital role in determining the strategies for treating unresectable HCC. This review describes previous and current trends in the treatment of HCC, with a particular focus on conversion surgery for initially unresectable HCC.

Keywords conversion therapy, liver resection, unresectable hepatocellular carcinoma, immune checkpoint inhibitor

1. Introduction

Systemic therapy has advanced hepatocellular carcinoma (HCC) (*1*). The treatment strategies for advanced HCC have remarkably changed over the past few decades (*2*). Treatments for advanced HCC vary according to guidelines. The Barcelona Clinic Liver Cancer (BCLC) staging system, which is widely used in Western countries, recommends systemic therapy for intermediate- and advanced-stage HCC (*3*). However, Asian guidelines, such as the Japanese or Chinese guidelines and guidelines of the Asian Pacific Association for the Study of the Liver, recommend surgery for selected patients with advanced HCC (*4-7*). One of the main reasons why Asian guidelines are more aggressive than Western guidelines is surgeons' consensus on surgical indications for HCC (*7*). Some studies have reported that hepatectomy for advanced HCC without systemic therapy offered five-year overall survival (OS), ranging between 20-53% (*8,9*). Hepatectomy offered better median survival time (MST) than systemic therapy (15.1 *vs*. 4.5 months) in patients with portal vein tumor thrombus (*10,11*). Hepatectomy plays an important role in the treatment of advanced HCC, particularly in the conversion from systemic therapy to resection.

Systemic therapy for HCC begins with sorafenib, a multikinase inhibitor for unresectable advanced HCC (*12,13*). Phase III trials of sorafenib and the SHARP trial (ClinicalTrials.gov number, NCT00105443) showed that the median OS was 10.7 *vs*. 7.9 months in sorafenib and placebo, respectively ($p < 0.001$) (*14*). However, the efficacy of sorafenib is not significant, with an MST of < 1 year and a tumor response rate of < 5% (*14,15*). Trials of other agents have shown no superiority or non-inferiority to sorafenib in patients with advanced HCC (*16-18*).

Approximately 10 years after the appearance of sorafenib, new treatments with multitargeted tyrosine kinase inhibitors (TKIs) have been started, with lenvatinib as the first-line treatment (*14,19*). Lenvatinib is an orally active inhibitor of multiple receptor tyrosine

kinases (*20-22*). The REFLECT trial (*ClinicalTrials.gov*, NCT01761266) compared the efficacies of sorafenib and lenvatinib in patients with unresectable advanced HCC (*20*). It revealed that lenvatinib was significantly superior to sorafenib in the progression-free survival (PFS) (median of 7.4 *vs*. 3.7 months in Lenvatinib and placebo, respectively), and that objective response rate (ORR) based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (*23*) were of 29.6 *vs*. 6.9% ($p < 0.0001$), respectively. Lenvatinib has the potential to play a key role in tumor downstaging because of its high response rate (40.6%) to mRECIST and antiangiogenic effects (*20,24,25*).

Furthermore, immune checkpoint inhibitors (ICIs), such as anti-programmed death receptor-1 (PD-1), anti-programmed death ligand (PD-L1), and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, have been adopted as treatments for HCC. The combination of atezolizumab, which is an anti-PD-L1 antibody, and bevacizumab (a monoclonal antibody against vascular endothelial growth factor) showed a better prognosis than single therapy of sorafenib alone in a phase III trial for unresectable HCC (*26*). Recently, the combination of durvalumab and tremelimumab has also been shown to result in better OS than sorafenib (*27*). The CheckMate 040 randomized clinical trial of nivolumab plus ipilimumab showed an improved OS (median, 22.2 months) and 60-month OS rate of 29% in patients with HCC previously treated with sorafenib. Many guidelines worldwide recommend these combination therapies for the treatment of advanced HCC (*3*).

Trials and studies on advanced HCC are increasingly being performed to investigate treatments with better prognosis, especially in advanced or unresectable HCC (*13,20-22,24-26,28-34*). The combination of hepatectomy and systemic therapies is a promising treatment expected to improve OS and reduce HCC recurrence.

In this review, we discuss the development of treatments for advanced HCC, including state-of-the-art treatment strategies and ongoing trials, and compare the differences in HCC treatments between Western and Eastern countries.

2. Combination therapies for advanced HCC

2.1. Atezolizumab plus bevacizumab

The IMbrave 150 study reported that a combination therapy with atezolizumab plus bevacizumab resulted in better OS than sorafenib (*31*). Patients were treated with atezolizumab plus bevacizumab and sorafenib. Overall survival rates at 12 months were 67.2% with atezolizumab plus bevacizumab and 54.6% with sorafenib, and median PFS was 6.8 *vs*. 4.3 months, respectively. Atezolizumab plus bevacizumab is now recommended as the first-line systemic therapy for patients with advanced HCC (*12*).

2.2. Durvalumab plus tremelimumab

Combination treatment with durvalumab (an anti-programmed cell death ligand-1) and tremelimumab (an anti-cytotoxic T-lymphocyte-associated antigen 4) showed promising results in a phase II trial in patients with unresectable HCC (*27*). A phase III trial, the HIMALAYA trial, was conducted to evaluate combination treatment in patients with unresectable HCC (*27,30*). Patients were assigned to receive durvalumab plus tremelimumab (STRIDE regimen), durvalumab, and sorafenib treatment. The trial revealed that median OS was 16.43 with STRIDE *vs*. 16.56 with durvalumab *vs*. 13.77 months with sorafenib. A four-year update of the HIMARAYA trial reported that a 48-month OS rate was higher with STRIDE than with sorafenib (25.2 *vs*. 15.1% , respectively) (*30*). Another study that included 44 patients treated with STRIDE for unresectable HCC reported a disease control rate of 53.3%, which was significantly better when used as a first-line therapy than when used as a second or later line (65.8 *vs*. 45.9%, respectively, $p = 0.034$) (*35*). In an Asian subgroup analysis of the HIMALAYA trial, STRIDE demonstrated that ORRs based on RECIST ver1.1. were 28.2% with STRIDE, 18.6% with durvalumab, and 9.0% with sorafenib (*36*). These results suggested that STRIDE is a promising treatment option for unresectable HCC.

2.3. Other promising therapies

Many trials and studies have investigated promising therapies for unresectable HCC. Combination therapy with novel agents, such as an anti-programmed death-1 antibody, showed a better response rate or prognosis than sorafenib. For example, camrelizumab plus revoceranib (*37*), sintilimab plus bevacizumab biosimilars (*38*), and lenvatinib plus pembrolizumab (*32*) have shown better prognoses in advanced HCC. Among these, treatment with lenvatinib plus hepatic intra-arterial infusion chemotherapy (HAIC) with cisplatin for advanced HCC showed prospective results in the LEOPARD trial (*39*). This phase II trial enrolled 36 patients with advanced HCC and evaluated 34 patients. The patients received the following treatments: lenvatinib, 12 mg/day for patients ≥ 60 kg and 8 mg/day for patients < 60 kg; HAIC with cisplatin: 65 mg/m^2, day 1, every 4-6 weeks, and a maximum of six cycles. The ORRs were 64.7% (95% confidence interval (CI): 46.5-80.3%) and 45.7% (95% CI: 28.8-63.4%) in mRECIST and RECIST ver1.1, respectively. Median PFS and OS were 6.3 and 17.2 months, respectively. According to these results, the LEOPARD-NEO trial, a multicenter phase II trial, aimed at assessing the safety and efficacy of lenvatinib plus HAIC using cisplatin for borderline resectable HCC, is now ongoing and is expected to show better results. Transarterial chemoembolisation (TACE) plus lenvatinib (LEN-TACE) is a promising treatment (*40*). The phase

II TACTICS-L trial, which included 62 patients with unresectable HCC, revealed a high response (ORR, 88.7%) and complete response rate (67.7%) based on the Response Evaluation Criteria in Cancer of the Liver as defined by the Liver Cancer Study Group of Japan (*41*). These promising therapies have the potential to change treatment strategies or provide better prognoses than those in the near future.

3. Outlines of conversion surgery

3.1. Conversion surgery versus neoadjuvant chemotherapy

Conversion therapy should be distinguished from neoadjuvant chemotherapy (*42*). There are significant differences between the neoadjuvant chemotherapy and conversion therapy. Conversion surgery is a treatment strategy that involves surgery following systemic therapy for initially unresectable or borderline resectable tumors that undergo radical resection, and is established for other solid cancers (*15,43,44*). Conversion surgery aims to downstage tumor burden in patients with initially unresectable cancer, providing better survival, reducing recurrence (*15,29,45*), and achieving complete resection. Recently, conversion surgery has been increasingly performed to provide better prognosis in patients with solid tumors (*15*).

Neoadjuvant chemotherapy is administered to patients with resectable tumors to decrease tumor size before hepatectomy (*46,47*). Generally, it aims to decrease the possibility of recurrence or increase the remnant liver volume to ensure safety after hepatectomy (*46*).

3.2. Conversion surgery for hepatocellular carcinoma

The treatment for patients with initially unresectable HCC after systemic therapy has not been established yet (*22,48*). In general, after a tumor is downstage from advanced or unresectable to an early stage (for example, the BCLC stage A or Chinese National Liver Cancer (CNLC) stage I), curative surgery is indicated (*12,49,50*). Patients with tumors that meet the criteria for technical resectability are also indicated for curative surgery or local treatment. Conversion surgery for initially unresectable HCC consists of a combination of systemic therapy and resection (*12,19,51*). In patients with advanced HCC, a combination of hepatectomy with sorafenib or lenvatinib reportedly improved OS compared with systemic therapy alone (*14,21,52*). However, the low response rate to systemic therapy contributed to a few patients undergoing conversion therapy (*15,53*). An improvement in the response rate would enable more patients to undergo conversion surgery than ever before (*53*).

3.3. Candidate selection for conversion surgery using a staging system

The BCLC staging system has been adopted globally for HCC treatment, particularly in Europe and the United States. According to the staging system, liver resection is limited to early-stage cases. In contrast, the CNLC staging system, established in 2017 and updated, proposes a more aggressive candidate for liver resection (*5*). The stages were defined as follows: Ia, single ≤ 5 cm; Ib, single > 5 cm or up to three tumors ≤ 3 cm; IIa, up to three tumors > 3 cm; IIb, ≥ 4 tumors; IIIa, tumor with vascular invasion; IIIb, tumor with metastases; IV, end stage.

During conversion therapy, tumors are classified into two groups: technically resectable and technically unresectable. Patients with technically unresectable HCC (CNLC stages Ia-IIa) and technically resectable HCC (CNLC stages IIb-IIIa) are potential candidates for conversion surgery. Moreover, patients with technically unresectable HCC (CNLC stages IIb-IIIa) initially undergo systemic therapy with or without local therapy, and resection is recommended if the tumor shrinks to a resectable condition. A previous study reported improved recurrence-free survival after hepatectomy following systemic therapy in patients with CNLC stage IIb/IIIa (*54*).

3.4. Candidate selection for conversion surgery based on resectability

Candidacy for conversion therapy is limited to patients with initially unresectable HCC, who have the possibility of being treated by surgery after systemic therapy (*55*). Several definitions of HCC resectability have been proposed. In one proposal, HCC was divided into three groups: resectable, borderline resectable, and unresectable, depending on four factors: distant metastasis, macroscopic curative resectability, indocyanine green clearance of a remnant liver, and macrovascular invasion (*56*). Another study also proposed a three-group classification, but it consisted of three similar factors (distant metastasis, macroscopic curative resection, and macrovascular invasion) and two different factors (ratio of future liver remnant to modified albumin-bilirubin score and tumor size) (*25,57*). However, there is no international consensus regarding the resectability of HCC. These situations make it difficult to discriminate conversion surgery from surgery after neoadjuvant therapy (*25,56*). Candidates for conversion therapy should be selected by a multidisciplinary team because many factors, including general condition, liver function, remnant liver volume, vascular invasion, and tumor size, should be considered to determine whether surgery is suitable (*50,58*). According to previous reports and trials, the conversion therapy rates differ, depending on the type and duration of systemic therapy (Table 1) (*47,58,59*). Conversion surgery may offer a better prognosis in patients with unresectable HCC who achieve pathological complete

Table 1. Conversion rates after treatments for initially unresectable hepatocellular carcinoma

Authors	Study design	Treatment (number)	Conversion rate
Takeyama *et al*. (*62*)	Retrospective	Sorafenib (*n* = 32)	12.5%
Shindoh *et al*. (*25*)	Retrospective	Lenvatinib (*n* = 107)	8.4%
Kudo *et al*. (*69*)	Retrospective	Atezolizumab plus Bevacizumab (*n* = 38)	31.8%
Ichida *et al*. (*22*)	Prospective	Lenvatinib (*n* = 49)	67.3%
Kaneko *et al*. (*53*)	Retrospective	Sofarenib (*n* = 292)	1.4%
Kaneko *et al*. (*53*)	Retrospective	Lenvatinib (*n* = 72)	2.7%
Peng *et al*. (*82*)	Prospective	Lenvatinib (*n* = 338)	1.8%

response (*60*). Advances in systemic therapy for HCC have promoted conversion therapy and its efficacy has been investigated worldwide.

3.5. Resectability for HCC

There are no established criteria for the oncological resectability of HCC or the concept of borderline resectable tumors in the field of pancreatic cancer. There has been an increasing demand for consensus on these criteria because conversion surgery has become common in recent years.

To precisely determine the operative indication for initially unresectable HCC after systemic therapy, it is necessary to clarify the definition of "unresectable" (*41,59*).

Generally, unresectable HCC is classified into two groups according to the cause: oncologically and technically unresectable HCC (*23,49*). Oncologically unresectable tumors indicate that treatments other than surgery are expected to provide better survival rates. Oncologically unresectable HCC has a poor prognosis, even if hepatectomy is successfully performed. Technically, tumors are unresectable owing to factors, such as their general condition, liver function, and insufficient liver remnant volume. Technically unresectable tumors extend to a large extent and cannot be completely and safely removed (41). In such cases, tumor shrinkage is due to the response to systemic therapy to safely undergo radical resection. These patients are eligible for conversion therapy. However, it is often difficult to clearly divide them because the two unresectable statuses partly overlap (*50*).

Recently, the Working Group of the Japan Liver Cancer Association and Japanese Society of Hepatobiliary-pancreatic Surgery proposed oncological resectability in HCC and classified the resectability of HCC into three grades: resectable, borderline resectable 1 (BR1), and borderline resectable 2 (BR2) (Figure 1) (*1*). These classifications were defined as follows: resectable, the status in which surgery alone may be expected to provide better OS compared with other treatments; BR1, the status in which surgical intervention may be expected as a part of multidisciplinary treatment to provide survival benefit; and BR2, the status in which the efficacy of surgery is unclear and the indication for surgery should be decided with discretion under standard multidisciplinary treatment (*1*). Additionally, BR2 is synonymous with initial unsuitability for surgery.

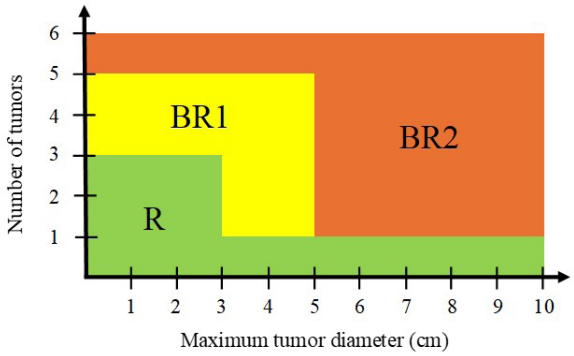

Figure 1. Resectability criteria for hepatocellular carcinoma based on the number and maximum diameter of tumors. The vertical and horizontal axes represent the number (*n*) of tumors and maximum diameter of tumors (cm), respectively. R, resectable; BR, borderline resectable 1; BR2, borderline resectable 2. Created based on the previous article (*1*).

The treatment of patients with BR2 or unresectable HCC should be carefully determined by a multidisciplinary team to offer a better prognosis.

4. Outcomes of conversion surgery

4.1. Conversion surgery with sorafenib

There have been no large cohort reports on conversion surgery after systemic sorafenib (*42*). Previous studies with a small number of patients or case reports showed that patients with initially unresectable HCC who underwent surgery after sorafenib achieved pathological response, better prognosis, and disease-free survival (*53,61,62*). However, there is no strong evidence to support sorafenib as a systemic therapy after curative conversion surgery for initially unresectable HCC. Sorafenib is not adopted as systemic therapy before conversion surgery because of its low response rate, accounting for only approximately 3% (*61,63,64*). Therefore, a few patients who have undergone conversion therapy after systemic therapy with sorafenib and have achieved a complete response can have a better prognosis (*42,61,64*). Considering these results,

conversion surgery using sorafenib is unrealistic for patients with unresectable HCC.

4.2. Conversion surgery with lenvatinib

Lenvatinib is thought to be suitable for conversion surgery because of its properties, such as suppression of tumor progression and tumor necrotic effect. A greater response rate to lenvatinib could contribute to more opportunities for conversion surgery in patients with unresectable or borderline resectable HCC. A retrospective study revealed that surgical resection after lenvetinib treatment had better disease-specific survival compared to no additional treatment after lenvatinib (hazard ratio (HR), 0.04; 95% CI, 0.01-0.30; $p = 0.002$) with a conversion surgery rate of 8.4% (*65*). In the comparison of additional treatments including surgery, ablation, TACE, and transcatheter arterial infusion chemotherapy after lenvatinib treatment, complete surgical resection showed a better prognosis than others in PFS (HR, 0.30; 95% CI, 0.16-0.58) and time-to-treatment failure (HR, 0.08; 95% CI, 0.02-0.39) (*25*). Another single-center study reported an improvement in the prognosis of patients with initially unresectable HCC after conversion surgery with lenvatinib (*66*). Successful conversion surgery with lenvatinib has been reported in some cases with survival benefits after surgery and preserved liver function, even in patients with metastases to other organs (*44,67,68*).

These results suggest that complete resection after lenvatinib treatment may offer a better prognosis than previous treatments. The prospective LENS-HCC trial was conducted to evaluate the efficacy of surgery after lenvatinib treatment in unresectable HCC (*22*). This trial revealed a high conversion rate of 67.3%. These results support conversion therapy, especially conversion surgery, after lenvatinib treatment for initially unresectable HCC.

The LENS-HCC trial is a multicenter, phase II trial performed in Japan to evaluate the efficacy and safety of preoperative lenvatinib therapy in patients with initially unresectable HCC (the Japan Registry of Clinical Trials (s031190057)) (*22*). This trial was conducted in response to the results of the phase III REFLECT trial, which showed that lenvatinib is superior to sorafenib in terms of PFS, time to progression, and ORR in patients with initially unresectable HCC (*24*). In this trial, a high response rate of 40.6% based on mRECIST for sorafenib was reported.

This trial enrolled patients with advanced HCC without a history of systemic therapy for HCC and with at least one factor suggestive of a poor prognosis as follows: macroscopic vascular invasion, extrahepatic metastasis, or multinodular tumors. The endpoint of this trial was surgical resection rate. This trial enrolled 49 patients from 11 centers in Japan. Among them, 42 patients were oncologically unresectable, and seven were technically unresectable. The patients underwent treatment with lenvatinib (12 mg/body weight/day ≥ 60 kg, or 8 mg/body weight/day < 60 kg) for eight weeks. Subsequently, resectability was evaluated by a multidisciplinary team, and the patients underwent tumor resection one or more times after the last lenvatinib administration.

The results of the trial demonstrated a high disease control rate of lenvatinib in patients with unresectable HCC, leading to a high surgical resection rate of 67.3%, and the safety and feasibility of lenvatinib therapy in conversion surgery. The trial also reported the safety and feasibility of lenvatinib because there were no cases of severe worsening of the liver functional reserve, no mortality in patients who underwent surgery, and no serious perioperative complications associated with lenvatinib administration. Although the long-term outcome remains unclear because the follow-up period was not very long (median, 9.3 months), this trial is expected to report long-term outcomes in the near future. In this trial, the patients with technically or oncologically unresectable HCC were treated with lenvatinib. However, there may be differences in the possibility of conversion surgery between the patients with technically and oncologically unresectable HCC because those with technically unresectable HCC received systemic therapy until the tumor becomes resectable, whereas those with oncologically unresectable HCC receive systemic therapy until the tumors showed a better response to systemic therapy; surgery was recommended by a multidisciplinary team from the perspective of oncology. Therefore, each patient should have a different appropriate treatment duration of systemic therapy depending on tumor conditions.

4.3. Conversion surgery with atezolizumab plus bevacizumab

Atezolizumab plus bevacizumab is widely used as the first-line treatment for advanced HCC because the IMbrave150 trial revealed the superiority of atezolizumab plus bevacizumab over sorafenib in advanced HCC (*31*). Based on the results of this trial, another study was performed to evaluate the efficacy of a combination of curative treatments after atezolizumab plus bevacizumab. In this study, 39 patients received conversion therapy. Among them, 25 achieved complete response at a rate of 35% based on RECIST ver1.1 (*69,70*). Moreover, 23% of the patients achieved a drug-free status. However, conversion therapy included liver resection, ablation, selective TACE, or their combination. The criteria for conversion surgery were unclear, and patients who did not achieve complete response underwent surgery. These conditions must be considered when results are interrupted. Seven patients underwent liver resection in this study. Other studies, including case reports, have reported complete response and better survival benefits in

Table 2. Time to progression and response according to previous reports

Authors	Treatment (number)	Assessment	Time to progression (months)	Time to response (months)
Llovet *et al*. (*14*)	Sorafenib (*n* = 299)	RECIST ver1.1	5.5 (4.1-6.9)	NA
Abou-Alfa *et al*. (*27*)	STRIDE (*n* = 393)	RECIST ver1.1	22.34	2.17 (1.84-3.98)
Abou-Alfa *et al*. (*27*)	Sorafenib (*n* = 389)	RECIST ver1.1	18.43	3.78 (1.89-8.44)
Cainap *et al*. (*16*)	Sorafenib (*n* = 521)	RECIST ver1.1	4.0 (2.8-4.2)	NA
Kudo *et al*. (*26*)	Atezolizumab plus bevacizumab (*n* = 46)	mRECIST	14.2 (10.9-16.6)	4.1 (1.3-12.3)
Kudo *et al*. (*26*)	Sorafenib (*n* = 23)	mRECIST	12.4 (4.7-NE)	4.2 (1.2-5.7)
Kudo *et al*. (*20*)	Lenvatinib (*n* = 478)	mRECIST	8.9 (7.4-9.2)	NA
Kudo *et al*. (*20*)	Sorafenib (*n* = 476)	mRECIST	3.7 (3.6-5.4)	NA
Yamashita *et al*. (*24*)	Lenvatinib (*n* = 81)	mRECIST	7.2 (5.4-9.2)	NA
Yamashita *et al*. (*24*)	Sorafenib (*n* = 87)	mRECIST	4.6 (3.5-5.4)	NA

STRIDE, Single Tremelimumab Regular Interval Durvalumab (300 mg of tremelimumab for one dose plus 1500 mg of durvalumab every four weeks); RECTST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NA, not available; NE, not estimated. The time to progression and response are shown with 95% confidence intervals.

patients with initially unresectable HCC after conversion surgery following treatment with atezolizumab plus bevacizumab (*71-76*). These results imply that liver resection after atezolizumab plus bevacizumab treatment offers a better prognosis for patients with initially unresectable HCC.

The RACB trial is an ongoing, prospective, multicenter phase II trial in Japan to evaluate the efficacy of combination therapy of atezolizumab plus bevacizumab in achieving conversion surgery in patients with unresectable HCC (the Japan Registry of Clinical Trials (s031190057)) (*45*). Inclusion criteria for this study were as follows: unresectable HCC without a history of systemic therapy, at least one target lesion based on RECIST ver. 1.1 (*70*), and a Child-Pugh score of 5 or 6. In this study, macroscopic vascular invasion, extrahepatic metastasis, and massive distribution of intrahepatic tumors were classified as unresectable HCC.

As a treatment protocol, patients diagnosed with unresectable HCC underwent systemic therapy with atezolizumab (1,200 mg/kg body weight) plus bevacizumab (15 mg/kg body weight) every three weeks. The patients were assessed radiologically using computed tomography or magnetic resonance imaging at twelve weeks after the first systemic therapy. If the tumor became resectable during the assessment, the patient received a single treatment with atezolizumab and tumor resection three weeks later. If the tumors are unresectable, the patients continue systemic therapy until they become resectable or show progression.

To assess the response of the tumors to systemic therapy, radiographic assessments were conducted every nine weeks until the tumor became resectable or progressed after the second assessment (12 weeks). The follow-up period was 18 months after inclusion.

Primary endpoint was PFS assessed by RECIST ver. 1.1 (*70*).

This study aimed to determine the efficacy of conversion surgery with atezolizumab plus bevacizumab in patients with initially unresectable HCC.

4.4. Timing of conversion surgery

The timing of surgery remains unestablished and controversial (*47,64,77,78*). Previous reports suggested that the timing of surgery should be after five cycles of ICI plus an anti-angiogenic drug (*51,79*). Other recommended patients with complete tumor remission should receive ICI treatment for six months, and patients with partial remission should receive combined treatment for 6-12 months prior to surgery (*47*). Determining the precise timing of surgery is difficult because it is not necessarily better to perform surgery as soon as possible. Early surgery can contribute to failure, whereas late surgery can lead to drug resistance and tumor progression (*53*). Time to progression and time to response have been reported for some agents, showing wide range (Table 2). The differences in time to progression and response between trials seemed to come from differences, such as patients' background, liver function, number of patients, and study design because patients' background and liver function had an influence on tolerance to systemic therapy, and the small number of patients and study design influenced data reliability. To avoid missing the ideal timing for conversion surgery, the effects on the tumor should be carefully assessed, and liver function should be preserved enough for surgery, referring to the results, such as the time to progression and time to response may be useful.

4.5. Cessation interval between systemic therapy and conversion surgery

The interval between systemic therapy and surgery should be recommended based on the half-lives of the agents used in the treatment. Patients who have undergone treatment with a TKI and bevacizumab should stop them one and 6-9 weeks before surgery, respectively (*64,80*). Wound-healing complications are well known to

be related to bevacizumab (*81*). If the cessation interval is not sufficiently long, a shorter interval may cause wound-healing complications. Patients treated with lenvatinib can safely undergo surgery one week after lenvatinib cessation (*22*). Patients who have undergone ICI treatment should stop it at the same time as anti-angiogenic drugs for > 2 weeks before surgery (*50,51*). It is not necessarily better to increase the interval between systemic therapy and surgery because of the possibility of tumor progression during the interval.

5. Conclusions

This article reviews advancements in systemic therapy for HCC and highlights the progression of a combination of surgery and systemic therapy. Prognosis has been rapidly improving since the introduction of sorafenib, and its efficacy in providing a better prognosis for unresectable HCC was revealed in a trial. Subsequently, new types of systemic therapies and novel regimens for HCC have emerged, and further investigations of their combinations have been conducted worldwide. Although systemic therapy for HCC has remarkably advanced recently, the selection of patients eligible for systemic therapy remains under investigation. The number of patients receiving systemic therapy and surgery is increasing. The timing of conversion therapy, including surgery, should be carefully determined, and the response to systemic therapy should also be evaluated with discretion. To deal with these subjects, a multidisciplinary plays an important and critical role in the treatment of HCC. Therefore further investigations are required to solve these problems.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Akahoshi K, Shindoh J, Tanabe M, *et al*. Oncological resectability criteria for hepatocellular carcinoma in the era of novel systemic therapies: The Japan Liver Cancer Association and Japanese Society of Hepato-Biliary-Pancreatic Surgery Expert Consensus Statement 2023. Liver Cancer. 2024; 13:0-10.
2. Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, Kamel IR, Ghasebeh MA, Pawlik TM. Hepatocellular carcinoma: From diagnosis to treatment. Surg Oncol. 2016; 25:74-85.
3. Reig M, Forner A, Rimola J, *et al*. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76:681-693.
4. Omata M, Cheng AL, Kokudo N, *et al*. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: A 2017 update. Hepatol Int. 2017; 11:317-370.
5. Xie DY, Ren ZG, Zhou J, Fan J, Gao Q. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: Updates and insights. Hepatobiliary Surg Nutr. 2020; 9:452-463.
6. Kudo M, Kawamura Y, Hasegawa K, *et al*. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer. 2021; 10:181-223.
7. Cho, Y., B.H. Kim, and J.W. Park, Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: An Asian perspective comparison. Clin Mol Hepatol. 2023; 29:252-262.
8. Glantzounis GK, Paliouras A, Stylianidi MC, Milionis H, Tzimas P, Roukos D, Pentheroudakis G, Felekouras E. The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review. Eur J Surg Oncol. 2018; 44:195-208.
9. Liu W, Wang K, Bao Q, Sun Y, Xing BC. Hepatic resection provided long-term survival for patients with intermediate and advanced-stage resectable hepatocellular carcinoma. World J Surg Oncol. 2016; 14:62.
10. Komatsu S, Kido M, Kuramitsu K, Tsugawa D, Gon H, Fukushima K, Urade T, Yanagimoto H, Toyama H, Fukumoto T. Impact of hepatectomy for advanced hepatocellular carcinoma with major portal vein tumor thrombus. J Gastrointest Surg. 2022; 26:822-830.
11. Komatsu S, Ueshima K, Kido M, Kuramitsu K, Tsugawa D, Yanagimoto H, Toyama H, Ku Y, Kudo M, Fukumoto T. Hepatectomy versus sorafenib for advanced hepatocellular carcinoma with macroscopic portal vein tumor thrombus: A bi-institutional propensity-matched cohort study. J Hepatobiliary Pancreat Sci. 2023; 30:303-314.
12. Gordan JD, Kennedy EB, Abou-Alfa GK, *et al*. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. J Clin Oncol. 2020; 38:4317-4345.
13. Kudo M, Ueshima K, Ikeda M, *et al*. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. 2020; 69:1492-1501.
14. Llovet JM, Ricci S, Mazzaferro V, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378-390.
15. Zhu XD, Huang C, Shen YH, Ji Y, Ge NL, Qu XD, Chen L, Shi WK, Li ML, Zhu JJ, Tan CJ, Tang ZY, Zhou J, Fan J, Sun HC. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. Liver Cancer. 2021; 10:320-329.
16. Cainap C, Qin S, Huang WT, *et al*. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: Results of a randomized phase III trial. J Clin Oncol. 2015; 33:172-179.
17. Llovet JM, Decaens T, Raoul JL, *et al*. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: Results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013; 31:3509-3516.
18. Ikeda M, Morizane C, Ueno M, Okusaka T, Ishii H, Furuse J. Chemotherapy for hepatocellular carcinoma: Current status and future perspectives. Jpn J Clin Oncol. 2018; 48:103-114.
19. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022; 400:1345-1362.
20. Kudo M, Finn RS, Qin S, *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised

phase 3 non-inferiority trial. Lancet. 2018; 391:1163-1173.
21. Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, Tamai T, Suzuki T, Hisai T, Hayato S, Okita K, Kumada H. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017; 52:512-519.
22. Ichida A, Arita J, Hatano E, *et al*. A multicenter phase 2 trial evaluating the efficacy and safety of preoperative lenvatinib therapy for patients with advanced hepatocellular carcinoma (LENS-HCC Trial). Liver Cancer. 2023; 13:322-334.
23. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30:52-60.
24. Yamashita T, Kudo M, Ikeda K, *et al* REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: An analysis of Japanese subset. J Gastroenterol. 2020; 55:113-122.
25. Shindoh J, Kawamura Y, Kobayashi Y, Kobayashi M, Akuta N, Okubo S, Suzuki Y, Hashimoto M. Prognostic impact of surgical intervention after lenvatinib treatment for advanced hepatocellular carcinoma. Ann Surg Oncol. 2021; 28:7663-7672.
26. Kudo M, Finn RS, Galle PR, Zhu AX, Ducreux M, Cheng AL, Ikeda M, Tsuchiya K, Aoki KI, Jia J, Lencioni R. IMbrave150: Efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in patients with Barcelona Clinic Liver Cancer Stage B unresectable hepatocellular carcinoma: An exploratory analysis of the phase III study. Liver Cancer. 2022; 12:238-250.
27. Abou-Alfa GK, Lau G, Kudo M, *et al*. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid. 2022; 1:EVIDoa2100070.
28. Llovet JM, Kudo M, Merle P, *et al*. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): A randomised, double-blind, phase 3 trial. Lancet Oncol. 2023; 24:1399-1410.
29. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. Ann Surg. 2004; 240:299-305.
30. Sangro B, Chan SL, Kelley RK, *et al*. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol. 2024; 35:448-457.
31. Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020; 382:1894-1905.
32. Finn RS, Ikeda M, Zhu AX, *et al*. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020; 38:2960-2970.
33. Zhu AX, Kang YK, Yen CJ, *et al*. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20:282-296.
34. Zhu AX, Park JO, Ryoo BY, *et al*. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015; 16:859-870.
35. Shimose S, Saeki I, Tomonari T, *et al*. Initial clinical experience with durvalumab plus tremelimumab in patients with unresectable hepatocellular carcinoma in real-world practice. Oncol Lett. 2024; 28:397.
36. Lau G, Abou-Alfa GK, Cheng AL, *et al*. Outcomes in the Asian subgroup of the phase III randomised HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. J Hepatol. 2024:S0168-8278(24)02424-3.
37. Qin S, Chan SL, Gu S, *et al*. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): A randomised, open-label, international phase 3 study. Lancet. 2023; 402:1133-1146.
38. Ren Z, Xu J, Bai Y, *et al*. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): A randomised, open-label, phase 2-3 study. Lancet Oncol. 2021; 22:977-990.
39. Ikeda M, Yamashita T, Ogasawara S, *et al*. Multicenter phase II trial of lenvatinib plus hepatic intra-arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma: LEOPARD. Liver Cancer. 2024; 13:193-202.
40. Kudo M, Ueshima K, Saeki I, *et al*. A phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable intermediate-stage hepatocellular carcinoma: TACTICS-L trial. Liver Cancer. 2023; 13:99-112.
41. Kudo M, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, Furuse J, Nakamura K, Makuuchi M; Liver Cancer Study Group of Japan (Committee for Response Evaluation Criteria in Cancer of the Liver, Liver Cancer Study Group of Japan). Response evaluation criteria in cancer of the liver (RECICL) proposed by the liver cancer study group of Japan (2009 revised version). Hepatol Res. 2010; 40:686-692.
42. Arita J, Ichida A, Nagata R, Mihara Y, Kawaguchi Y, Ishizawa T, Akamatsu N, Kaneko J, Hasegawa K. Conversion surgery after preoperative therapy for advanced hepatocellular carcinoma in the era of molecular targeted therapy and immune checkpoint inhibitors. J Hepatobiliary Pancreat Sci. 2022; 29:732-740.
43. Ma YN, Jiang X, Liu H, Song P, Tang W. Conversion therapy for initially unresectable hepatocellular carcinoma: Current status and prospects. Biosci Trends. 2024; 17:415-426.
44. Sano S, Asahi Y, Kamiyama T, *et al*. Conversion surgery after lenvatinib treatment for multiple lung metastases from hepatocellular carcinoma. Int Cancer Conf J. 2022; 12:7-13.
45. Okuno M, Ishii T, Ichida A, Soyama A, Takemura N, Hirono S, Eguchi S, Hasegawa K, Sasaki Y, Uemura K, Kokudo N, Hatano E. Protocol of the RACB study: A multicenter, single-arm, prospective study to evaluate the efficacy of resection of initially unresectable hepatocellular carcinoma with atezolizumab combined with bevacizumab. BMC Cancer. 2023; 23:780.
46. Liu K, McCaughan GW. How to select the appropriate "neoadjuvant therapy" for hepatocellular carcinoma. Expert Opin Pharmacother. 2018; 19:1167-1170.
47. Bai J, Huang M, Song B, Luo W, Ding R. The current status and future prospects for conversion therapy in the treatment of hepatocellular carcinoma. Technol Cancer Res Treat. 2023; 22:15330338231159718.

48. Goto Y, Hisaka T, Sakai H, Takagi K, Fukutomi S, Akagi Y, Okuda K. Salvage surgery for initially unresectable locally advanced hepatocellular carcinoma downstaged by hepatic arterial infusion chemotherapy. Anticancer Res. 2020; 40:4773-4777.
49. Chen LT, Martinelli E, Cheng AL, *et al*. Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with intermediate and advanced/relapsed hepatocellular carcinoma: A TOS-ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and SSO. Ann Oncol. 2020; 31:334-351.
50. Sun HC, Zhou J, Wang Z, *et al*. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). Hepatobiliary Surg Nutr. 2022; 11:227-252.
51. Tang H, Cao Y, Jian Y, Li X, Li J, Zhang W, Wan T, Liu Z, Tang W, Lu S. Conversion therapy with an immune checkpoint inhibitor and an antiangiogenic drug for advanced hepatocellular carcinoma: A review. Biosci Trends. 2022; 16:130-141.
52. Itoh S, Toshida K, Morita K, Kurihara T, Nagao Y, Tomino T, Toshima T, Harada N, Mori M, Yoshizumi T. Clinical effectiveness of surgical treatment after lenvatinib administration for hepatocellular carcinoma. Int J Clin Oncol. 2022; 27:1725-1732.
53. Kaneko S, Tsuchiya K, Yasui Y, *et al*. Conversion surgery for hepatocellular carcinoma after tyrosine kinase inhibitor treatment. JGH Open. 2022; 6:301-308.
54. Ma Z, Xiao Z, Yin P, Wen K, Wang W, Yan Y, Lin Z, Li Z, Wang H, Zhang J, Mao K. Comparison of survival benefit and safety between surgery following conversion therapy versus surgery alone in patients with surgically resectable hepatocellular carcinoma at CNLC IIb/IIIa stage: A propensity score matching study. Int J Surg. 2024; 110:2910-2921.
55. Kishi Y, Shimada K, Nara S, Esaki M, Kosuge T. Role of hepatectomy for recurrent or initially unresectable hepatocellular carcinoma. World J Hepatol. 2014; 6:836-843.
56. Yoh T, Ishii T, Nishio T, Koyama Y, Ogiso S, Fukumitsu K, Uchida Y, Ito T, Seo S, Hata K, Hatano E. A conceptual classification of resectability for hepatocellular carcinoma. World J Surg. 2023; 47:740-748.
57. Nakamura I, Yoh T, Nishimura T, Okuno M, Okamoto T, Sueoka H, Iida K, Tada M, Ishii T, Seo S, Fujimoto Y, Iijima H, Hirono S, Hatano E. A classification model for resectability in hepatocellular carcinoma patients. Hepatol Res. 2024. doi: 10.1111/hepr.14108.
58. Long Y, Huang J, Liao J, Zhang D, Huang Z, He X, Zhang L. Safety and survival outcomes of liver resection following triple combination conversion therapy for initially unresectable hepatocellular carcinoma. Cancers (Basel). 2023; 15:5878.
59. Zhang J, Zhang X, Mu H, Yu G, Xing W, Wang L, Zhang T. Surgical conversion for initially unresectable locally advanced hepatocellular carcinoma using a triple combination of angiogenesis inhibitors, anti-PD-1 antibodies, and hepatic arterial infusion chemotherapy: A retrospective study. Front Oncol. 2021; 11:729764
60. Jia J, Ding C, Mao M, Gao F, Shao Z, Zhang M, Zheng S. Pathological complete response after conversion therapy in unresectable hepatocellular carcinoma: A retrospective study. BMC Gastroenterol. 2024; 24:242.
61. Yoshimoto T, Imura S, Morine Y, Ikemoto T, Arakawa Y, Iwahashi S, Saito YU, Takasu C, Ishikawa D, Teraoku H, Bando Y, Shimada M. The outcome of sorafenib therapy on unresectable hepatocellular carcinoma: Experience of conversion and salvage hepatectomy. Anticancer Res. 2018; 38:501-507.
62. Takeyama H, Beppu T, Higashi T, *et al*. Impact of surgical treatment after sorafenib therapy for advanced hepatocellular carcinoma. Surg Today. 2018; 48:431-438.
63. Zhang Z, Zhang E. Conversion therapy for advanced hepatocellular carcinoma with vascular invasion: A comprehensive review. Front Immunol. 2023; 14:1073531.
64. Yamamura K, Beppu T, Miyata T, Okabe H, Nitta H, Imai K, Hayashi H, Akahoshi S. Conversion surgery for hepatocellular carcinoma following molecular therapy. Anticancer Res. 2022; 42:35-44.
65. Shindoh J, Kawamura Y, Kobayashi M, Akuta N, Okubo S, Matsumura M, Suzuki Y, Hashimoto M. Prognostic advantages of individual additional interventions after lenvatinib therapy in patients with advanced hepatocellular carcinoma. J Gastrointest Surg. 2022; 26:1637-1646.
66. Hidaka M, Hara T, Soyama A, Sasaki R, Matsushima H, Tanaka T, Hamada T, Imamura H, Adachi T, Kanetaka K, Miyaaki H, Okano S, Eguchi S. The outcome of conversion liver resection surgery by lenvatinib treatment: A single center experience. Anticancer Res. 2022; 42:3049-3054.
67. Tomonari T, Sato Y, Tanaka H, Tanaka T, Taniguchi T, Sogabe M, Okamoto K, Miyamoto H, Muguruma N, Saito Y, Imura S, Bando Y, Shimada M, Takayama T. Conversion therapy for unresectable hepatocellular carcinoma after lenvatinib: Three case reports. Medicine (Baltimore). 2020; 99:e22782.
68. Takahashi K, Kim J, Takahashi A, *et al*. Conversion hepatectomy for hepatocellular carcinoma with main portal vein tumour thrombus after lenvatinib treatment: A case report. World J Hepatol. 2021; 13:384-392.
69. Kudo M, Aoki T, Ueshima K, *et al*. Achievement of complete response and drug-free status by atezolizumab plus bevacizumab combined with or without curative conversion in patients with transarterial chemoembolization-unsuitable, intermediate-stage hepatocellular carcinoma: A multicenter proof-of-concept study. Liver Cancer. 2023; 12:321-338.
70. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.
71. Sato S, Aoki T, Matsumoto T, Shiraki T, Mori S, Iso Y, Nemoto T, Onishi T, Iijima M, Ishida K. Pathological complete response of hepatocellular carcinoma confirmed by conversion hepatectomy following atezolizumab plus bevacizumab therapy: A case report and literature review. Clin J Gastroenterol. 2024; 17:292-299.
72. Miyata T, Sugi K, Horino T, Ono A, Tagayasu Y, Nomoto D, Inoue M, Mizumoto T, Kubota T, Yanagida E, Murayama T, Miyanari N, Baba H. Conversion surgery after atezolizumab plus bevacizumab for primary and peritoneal metastasis after hepatocellular carcinoma rupture. Anticancer Res. 2023; 43:943-947.
73. Hoshino T, Naganuma A, Furusawa A, Suzuki Y, Hirai K, Sakamoto I, Ogawa T, Ogawa A, Hatanaka T, Kakizaki S. A case of conversion hepatectomy for huge hepatocellular carcinoma with adrenal metastasis and vascular invasion after atezolizumab-bevacizumab treatment. Clin J Gastroenterol. 2022; 15:776-783.

74. Matsuoka T, Fujikawa T, Uemoto Y, Aibe Y, Hasegawa S. Conversion to curative resection and pathological complete response following targeted therapies with atezolizumab and bevacizumab for initially unresectable hepatocellular carcinoma: A case report. Cureus. 2023; 15:e45176.
75. Fukunaga A, Takata K, Itoh S, Yamauchi R, Tanaka T, Yokoyama K, Shakado S, Kohashi K, Yoshizumi T, Hirai F. Complete tumor necrosis confirmed by conversion hepatectomy after atezolizumab-bevacizumab treatment for advanced-stage hepatocellular carcinoma with lung metastasis. Clin J Gastroenterol. 2023; 16:224-228.
76. Hidaka Y, Tomita M, Desaki R, Hamanoue M, Takao S, Kirishima M, Ohtsuka T. Conversion surgery for hepatocellular carcinoma with portal vein tumor thrombus after successful atezolizumab plus bevacizumab therapy: A case report. World J Surg Oncol. 2022; 20:228.
77. Wang MD, Xu XJ, Wang KC, Diao YK, Xu JH, Gu LH, Yao LQ, Li C, Lv GY, Yang T. Conversion therapy for advanced hepatocellular carcinoma in the era of precision medicine: Current status, challenges and opportunities. Cancer Sci. 2024; 115:2159-2169.
78. Hatanaka T, Yata Y, Naganuma A, Kakizaki S. Treatment strategy for intermediate-stage hepatocellular carcinoma: Transarterial chemoembolization, systemic therapy, and conversion therapy. Cancers (Basel). 2023; 15:1798.
79. Luo L, He Y, Zhu G, Xiao Y, Song S, Ge X, Wang T, Xie J, Deng W, Hu Z, Shan R. Hepatectomy after conversion therapy for initially unresectable HCC: What is the difference? J Hepatocell Carcinoma. 2022; 9:1353-1368.
80. Lu JF, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol. 2008; 62:779-786.
81. Sharma K, Marcus JR. Bevacizumab and wound-healing complications: Mechanisms of action, clinical evidence, and management recommendations for the plastic surgeon. Ann Plast Surg. 2013; 71:434-440.
82. Peng Z, Fan W, Zhu B, *et al*. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: A phase III, randomized clinical trial (LAUNCH). J Clin Oncol. 2023; 41:117-127.

Received November 19, 2024; Revised December 3, 2024; Accepted December 6, 2024.

**Address correspondence to:*
Kiyoshi Hasegawa, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
E-mail: hasegawa-2su@h.u-tokyo.ac.jp

Released online in J-STAGE as advance publication December 8, 2024.