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Review

Surgery for Hepatocellular Carcinoma With Macroscopic Vascular Invasion in the Era of Modern Molecular Therapy

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Abstract. *It has been reported that patients with macroscopic vascular invasion accompanying hepatocellular carcinoma have a poor prognosis. Modern molecular therapy with multitargeted tyrosine kinase inhibitors and immune checkpoint inhibitors has shown promising results in patients with metastatic hepatocellular carcinoma; however, molecular therapy is limited to patients with Child-Pugh class A disease. This review summarizes the present status of surgical therapies, including conversion hepatectomy, for patients with MVI in the developing era of novel molecular therapy. Phase III studies showed patients with macroscopic vascular invasion had significant survival benefits from sorafenib [hazard ratio (HR)=0.68] and regorafenib (HR=0.67) versus placebo, and nivolumab (HR=0.74) versus sorafenib. Lenvatinib and atezolizumab plus bevacizumab showed marginal effects. It is currently widely assumed that molecular therapy alone will not cure the disease but that additional conversion hepatectomy will be required. A response other than progressive disease is essential but a pathological complete response is not always required. A significant randomized controlled trial has already started in China to assess the necessity for conversion hepatectomy after effective atezolizumab plus bevacizumab treatment, and the results are still awaited. According to Japanese national data, upfront hepatectomy can be recommended for patients with initially resectable disease and macroscopic vascular invasion other than for those with tumors in the main portal vein and the inferior vena cava. In addition, adequate adjuvant therapies with hepatic arterial chemotherapy and transarterial chemoembolization may be beneficial but an effective adjuvant molecular therapy is currently unavailable. In conclusion, novel molecular therapies with higher response rates customized to the oncologic characteristics of each hepatocellular carcinoma with macroscopic vascular invasion are needed to increase the likelihood of conversion surgery and improve long-term outcomes.*

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Patients with hepatocellular carcinoma (HCC) undergo therapy with various treatments and combinations based on their liver functional reserve, clinical stage and malignancy grade (1-3). One of the most critical factors in selecting a treatment strategy is the presence of macroscopic vascular invasion (MVI). Approximately 20% of patients with HCC have MVI at diagnosis (4). MVI is typically categorized for the portal vein, hepatic vein and bile duct by the classification system from the Liver Cancer Study Group of Japan (5). Furthermore, patients with HCC with MVI are classified as having stage C of the Barcelona Clinic Liver Cancer classification (3).

MVI is one of the most significant poor prognostic factors after various treatments for patients with HCC such as hepatic resection, transarterial chemoembolization (TACE), and systemic therapy (6-9). Furthermore, local ablation therapy and liver transplantation have been ruled out for patients with HCC with MVI (10-12). However, the treatment strategy has been changing. Patients with HCC, other than those with tumor within a main portal vein (Vp4) and tumor within the inferior vena cava (Vv3), are good candidates for liver

resection (13, 14), and liver transplantation is recommended after a significant response to locoregional therapies (11).

In the past decade, modern molecular therapy with multitargeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) was introduced for patients with advanced HCC and has shown promising results (15-20). However, molecular therapy is limited to patients with good liver function of Child-Pugh class A. In the HCC management guidelines of Western countries, systemic therapy is recommended for HCC with MVI (21). However, recent evidence has established that the long-term prognosis after molecular therapy alone is insufficient (15-20). In contrast, the Japanese guideline recommends hepatic resection, hepatic arterial chemotherapy (HAIC), and systemic therapy (5). Patients with HCC with MVI have unsatisfactory prognosis after hepatic resection alone; therefore, several perioperative adjuvant therapies have been recommended (22-24).

Conversion hepatectomy is one of the essential options for prolonging survival in patients with initially unresectable HCC that has been down-staged to being resectable by conversion therapy (25-44). The number of articles on the advantages of conversion surgery after molecular therapy has increased. Conversion rates from sorafenib to lenvatinib, atezolizumab plus bevacizumab (ATEZO/BEV), and combinations of other molecular drugs or TACE have improved. Patients with HCC with MVI are among the main candidates for conversion hepatectomy. In China, a pioneering randomized controlled trial (RCT) to assess the efficacy of conversion hepatectomy for patients with MVI has started (45). A future topic is whether conversion hepatectomy benefits patients with MVI by HCC.

This article summarizes the present status of surgical therapies, including conversion hepatectomy, for patients with MVI in the developing era of novel molecular therapy. We selected papers cited in PubMed until March 2023 using the key words hepatocellular carcinoma, macroscopic vascular invasion, portal vein tumor thrombosis, surgery, conversion, and systemic therapy (chemotherapy, molecular therapy).

Classification of MVI

Classification of MVI using diagnostic imaging is summarized by the Liver Cancer Study Group of Japan (5). MVI of the portal vein includes Vp1: tumor within third-order branches; Vp2: tumor within second-order branches; Vp3: tumor in first-order branches; and Vp4: tumor in the central portal vein. MVI of the hepatic vein includes Vv1: tumor within the peripheral hepatic vein; Vv2: tumor within the major hepatic vein; and Vv3: tumor within the inferior vena cava. MVI of the bile duct includes B1: tumor within third-order branches; B2: tumor within second-order branches; B3: tumor in first-order branches; and B4: tumor in the common bile duct or opposite bile duct).

Recent Progress in Molecular Therapy for HCC With MVI

Unresectable HCC accompanied by MVI is associated with poor prognosis; the median survival time (MST) ranges from 2-5 months with best supportive care (4). TKIs were developed and have been used worldwide for such patients. In 2008, sorafenib was shown to provide significant survival benefits compared with placebo (MST: 10.7 *vs*. 7.9 months) in the SHARP study of 602 patients with advanced HCC (15). After that, lenvatinib was found to be non-inferior to sorafenib as a first-line therapy with a comparable survival benefit (MST: 13.6 *vs*. 12.3 months) and toxicity profile in the REFLECT trial of 954 patients with advanced HCC (16). Notably, Vp4 patients were excluded from the REFLECT trial, resulting in only 21% having MVI compared with 38% in the SHARP study. Molecular therapy with ICIs (nivolumab and pembrolizumab) and combination therapy with ICIs and TKIs have achieved a better prognosis as first-line therapy (15-20). A subgroup analysis of patients with MVI in several phase III studies found that sorafenib [hazard ratio (HR)=0.68, 95% confidence interval (CI)=0.49-0.93, compared with placebo], regorafenib (HR=0.67, 95% CI=0.46-0.98, compared with placebo) and nivolumab (HR=0.74, 95% CI=0.61-0.90, compared with sorafenib) showed significant survival benefits, and lenvatinib (MST=11.5 months, HR=0.87, 95% CI=0.73-1.04, compared with sorafenib) showed a marginal benefit (4). However, the nivolumab and lenvatinib studies included patients with extrahepatic metastases (18, 20).

Recently, ATEZO/BEV was shown to improve survival significantly (MST=16.4 months) compared with sorafenib in first-line therapy in the updated data on the phase III IMbrave150 study (46). In a subgroup analysis of the updated data, patients with MVI had significant survival benefits (MST=14.2 months, HR=0.68, 95% CI=0.47-0.98). At the 2021 American Society of Clinical Oncology meeting, marginally better overall survival (OS) in Vp4 patients (HR=0.62, 95% CI=0.34-1.11) treated with ATEZO/BEV compared with sorafenib was reported, but the MST was only 7.6 months (47). Even with modern molecular therapy, the prognosis of patients with MVI needs to be improved and better investigated.

A patient with initially unresectable disease with the possibility of conversion surgery needs to know that molecular characteristics of HCC might cause a failure of the ATEZO/BEV treatment. Aoki *et al*. showed that ICIs can be ineffective due to intratumoral active beta-catenin signaling, known as green hepatoma, with sustained expression of bile acid transporter, organic anion transporting polypeptide 1B3, and a high-intensity nodule on the hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine-enhanced magnetic resonance imaging (48). Therefore, lenvatinib should be replaced immediately after treating physicians

become aware of the ineffective clinical course so as not to miss the chance of conversion surgery.

Upfront Liver Resection for HCC With MVI

HCC management guidelines in Western countries demonstrate that systemic therapy is the first-line treatment for HCC with MVI (3), but the maximum MST after systemic therapy was 14 months (17). In contrast, the Japanese guidelines recommend hepatic resection and systemic therapy for patients with MVI (5). A nationwide survey by the Liver Cancer Study Group of Japan revealed that liver resection provided significant survival benefits for patients with HCC with MVI in the portal and hepatic vein (13, 14). One propensity score-matching study of 6,474 patients with HCC with portal MVI demonstrated that surgical resection was associated with better median survival than nonsurgical patients (2.9 *vs*. 1.1 years) (13). However, the subgroup analysis found that patients with Vp4 disease received no survival benefit. Another propensity score-matching study examined 1,021 patients with Child-Pugh A grade HCC with hepatic MVI (14). The MST was significantly longer in the group that underwent liver resection than in the non-resection group (3.42 *vs*. 1.81 years, p=0.023). According to Vv class, the MST was as follows: Vv1, 4.85 years; Vv2, 4.67 years; and Vv3, 1.37 years. Patients without portal vein tumor thrombosis (PVTT) showed significantly better survival compared with those with PVTT (5.67 *vs*. 1.88 years, p<0.001).

An international multicenter study was completed for patients with bile duct MVI undergoing liver resection (49). MST and 5-year OS were excellent (45.8 months and 43.6%, respectively), and liver resection as hemi-hepatectomy or greater (HR=0.61, 95% CI=0.38-0.99) and combined bile duct resection (HR=0.51, 95% CI=0.31-0.84) significantly increased OS. The 5-year OS rates in the B3 and B4 groups were equivalent at 46.9% and 39.2%, respectively (p=0.29). Another study compared the long-term survival of patients with bile duct MVI based on their initial treatment (50). Liver resection, TACE, systemic chemotherapy, and conservative therapy led to MSTs of 11.5, 6.0, 2.4 and 1.6 months, respectively. After adjusting for confounders, liver resection and repeated TACE were also significant good prognostic factors (HR=0.47 and 0.39, respectively).

Adjuvant Therapies in Combination With Liver Resection for HCC With MVI

For selected patients with HCC with MVI, liver resection can provide higher OS than systemic therapy; however, the survival rate remains unsatisfactory (13, 14). Several adjuvant therapies have been developed to reduce recurrence and increase survival rates. The STORM RCT was conducted to determine the usefulness of adjuvant sorafenib administration after hepatic resection, with negative results (51). This study excluded patients with HCC with MVI. Several similar RCTs using new molecular drugs have been conducted. However, they also excluded almost patients with HCC with MVI (52). At the annual American Association for Cancer Research meeting in 2023, the phase III study of liver resection or ablation therapy followed by adjuvant ATEZO/BEV (IMbrave050) demonstrated recurrence-free survival improvement. However, the study included only 6-8% of patients with minor MVI (Vp1/Vp2) (53, 54).

Several interventional approaches have been attempted in an adjuvant setting. We previously reported the significant effectiveness of short-term adjuvant HAIC with 5-fluorouracil plus cisplatin, followed by mild embolization with mitomycin C starch microspheres in patients with HCC with Vp3 (22). This hepatic arterial adjuvant therapy was unnecessary for patients with HCC with Vp2 and ineffective for those with Vp4. Another Japanese multicenter study showed the apparent survival benefit of adjuvant HAIC for patients with MVI (Vp3 and Vp4). The MST was significantly longer for the HAIC group than the non-HAIC group (28.1 *vs*. 18.7 months, p=0.0024) (23). A recent meta-analysis showed that postoperative adjuvant TACE may improve long-term outcomes in patients with HCC with MVI or PVTT (24). In the subgroup analyses, the HRs for OS were 0.62 and 0.49, and for disease-free survival were 0.67 and 0.58, in patients with HCC with MVI and PVTT, respectively. Future RCTs limited to patients with HCC with MVI must define the benefit of adjuvant HAIC and TACE.

Conversion Hepatectomy for HCC With MVI After Molecular Therapy

After the initiation of molecular therapy, the number of patients with complete response (CR) by response evaluation criteria in solid tumors (RECIST) and modified RECIST (mRECIST) criteria in diagnostic imaging increased; in contrast, complete remission of HCC is rarely achieved by molecular therapy alone (36). Conversely, many long-term survivors, including those completely cured, have been reported in patients with initially unresectable HCC after molecular therapy followed by conversion surgery (25-43). Partial response (PR) or stable disease after molecular therapy is required for patients to undergo conversion surgery, but CR is not always required (31). Furthermore, it is necessary to perform curative surgery, not reduction surgery. The selection of postoperative therapy for such patients is still under investigation.

Patients with HCC with MVI are one of the main candidates for such conversion surgery. Data for patients with MVI by HCC undergoing curative conversion surgery are summarized in Table I (26-38). All patients were male,

Table I. *Clinical characteristics of patients (all male) with hepatocellular carcinoma with macrovascular invasion undergoing conversion surgery after effective molecular therapy.*

Case (Ref)	Year published	Molecular therapy	Age, years	Etiology	Tumor, n	Tumor size, cm	Vascular invasion	Distant metastasis	Additional preoperative treatment	BCLC stage	Child-Pugh grade/ score	Duration of molecular therapy, months (Combination drug)	mRECIST/ RECIST	Conversion surgery	Pathological CR	Adjuvant therapy	Survival after initial therapy/ surgery, months	Recurrence, status
1 (26)	2011	Sorafenib	59	Hemochromatosis	1	10	Vp4	Lymph node	None	C	A/5	6	CR/PR	Left-hepatectomy	Yes	None	22/16	None, alive
2 (26)	2011	Sorafenib	59	HBV	1	8	Vp4	None	None	C	A	12	CR/PR	Left-hepatectomy	Yes	None	24/12	None, alive
3 (27)	2011	Sorafenib	78	Alcohol	1	12	Vp3	None	None	C	A	9	ND/SD	Right-hepatectomy	No	None	27/18	Recurrence/ alive
4 (27)	2011	Sorafenib	68	ND	1	10	Vv3	None	None	C	A	9	ND/SD	Right-hepatectomy HVTT extraction	No	None	25/6	None, alive
5 (28)	2013	Sorafenib	68	NBNC	1	15.7	Vp3	None	None	C	A/6	9	PR/PR	Left-hepatectomy	Yes	None	23/14	None, alive
7 (29)	2015	Sorafenib	54	HCV	2	10.1	Vp3/ Vv3	Lung	External-beam RT	C	A/6	5	PR/PR	Central bi-segmentectomy HVTT extraction	Yes	6 Months with sorafenib	14/9	None, alive
6 (30)	2015	Sorafenib	45	HBV	1	9.3	Vv3	None	TACE+ RT before sorafenib	C	A/5	3	PR/PR	Posterior sectionectomy HVTT extraction	No	Sorafenib	123/ 120	None, alive
8 (31)	2020	Sorafenib/ regorafenib	79	HBV	1	13	Vv3	None	None	C	A/6	1/12	PR/SD	Extended S8 HVTT extraction	No	None	24/8	None, alive
9 (32)	2020	Lenvatinib	58	HBV	1	10	Vp2	Lung	None	C	A/5	3	PR/PR	Hepatectomy	No, except PVTT	Lenvatinib	12/9	None, alive
10 (33)	2021	Lenvatinib	59	HCV	1	6	Vp4	None	None	C	A/5	3	PR/SD	Left-hepatectomy PVTT extraction	No	None	11/8	None, alive
11 (34)	2022	Lenvatinib	80	HCV	Many	10	Vp4	None	TACE after lenvatinib	C	A/5	6	PR/PR	Laparoscopic right-hepatectomy	Nearly CR	None	20/14	None, alive

Table I. *Continued*

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Case (Ref)	Year published	Molecular therapy	Age, years	Etiology	Tumor, n	Tumor size, cm	Vascular invasion	Distant metastasis	Additional preoperative treatment	BCLC stage	Child-Pugh grade/ score	Duration of molecular therapy, months (Combination drug)	mRECIST/ RECIST	Conversion surgery	Pathological CR	Adjuvant therapy	Survival after initial therapy/ surgery, months	Recurrence, status
12 (35)	2021	Lenvatinib	69	ND	1	3.5	Vp2-3	None	None	C	A	2	CR/PR	Hepatectomy	ND	None	7.4	None, alive
13 (35)	2021	Lenvatinib	70/	ND	1	5.4	Vp2-3	None	None	C	B	2	PR/SD	Hepatectomy	ND	Lenvatinib	5	None, alive
14 (36)	2021	Lenvatinib+ nivolumab	Median 52	HBV	1	10.2	Vp4	None	None	C	A	2	CR/PR	Major hepatectomy	Yes	ND	ND	ND
15 (36)	2021	Lenvatinib+ pembrolizumab		HBV	>3	9	Vp4	None	None	C	A	4	SD/SD	Major hepatectomy	No	ND	ND	ND
16 (36)	2021	Lenvatinib+ sintilimab		HBV	>3	9	Vp4	None	None	C	A	2	CR/PR	Major hepatectomy	Yes	ND	ND	ND
17 (36)	2021	Lenvatinib+ pembrolizumab		HBV	1	9.6	Vv2	None	None	C	A	3	SD/SD	Minor hepatectomy	No	ND	ND	ND
18 (36)	2021	Apatinib+ sintilimab		HBV	>3	17.6	Vp3	None	None	C	A	3	PR/PR	Major hepatectomy	Yes	ND	ND	ND
19 (36)	2021	Apatinib+ camrelizumab		HBV	1	6.8	Vv3	None	None	C	A	2	PR/PR	Minor hepatectomy	Yes	ND	ND	ND
20 (36)	2021	Apatinib+ sintilimab		HBV	1	15.4	Vp3	None	None	C	A	8	PD/PD	Minor hepatectomy	No	ND	ND	ND
21 (37)	2021	Apatinib+ camrelizumab	64	ND	1	13.9	Vp3/ Vv2	ND	ND	C	ND	2	SD/SD	Laparoscopic right-hepatectomy	Yes	Apatinib+ camrelizumab 6 months	11/9	None, alive
22 (38)	2022	Atezolizumab+ bevacizumab	79	NBNC	1	NE	Vp4	None	TACE before lenvatinib	C	A/6	6	PR/SD	Left-hepatectomy	No	No	15/5	None, alive

BCLC: Barcelona Clinic Liver Cancer class; CR: complete response; HBV: hepatitis B virus; HCV: hepatitis C virus; HVTT: hepatic vein thrombus; mRECIST: modified RECIST; NBNC: non-hepatitis B virus and non-hepatitis C virus; ND: not described; PR: partial response; PVTT: portal vein thrombus; RECIST: response evaluation criteria in solid tumours; SD: stable disease; TACE: transarterial chemoembolization.

and the median age was 59 (range=45-80) years. Of the 17 patients with a known etiology, 11 had hepatitis B virus-associated hepatitis, and three had hepatitis C virus-associated hepatitis. Seventeen patients (77.2%) had solitary HCC, and the median maximal size of the tumor was 10.2 (range=3.5-17.6) cm. Vp2-3, Vp4, Vv2, and Vv3 were observed in nine, eight, two, and five patients, respectively. Two patients had both Vp and Vv. Only three patients (6%) had extrahepatic metastasis. Preoperative combination therapy included two patients undergoing TACE, one TACE plus radiotherapy, and one external beam radiotherapy. All patients were classified as having Barcelona Clinic Liver Cancer stage C HCC. Child-Pugh grade was A in all cases but one. The median duration of preoperative molecular therapy was 3 (range=1.5-13) months. Twelve patients received monotherapy, and 10 received combination therapy. According to mRECIST and RECIST criteria, 15 (68.2%; 5 with CR and 11 with PR) and 12 (54.5%; all PR) patients were defined as responders, respectively. All patients were treated with liver resection, including five patients with combined MVI extraction, and two underwent a laparoscopic approach. Pathological CR was observed in nine patients (40.1%). Four patients (22.7%) received the same molecular therapy after surgery. The observation period was limited, but the median OS was 22 (range=5-123) months and 14 (range=5-120) months from the start of molecular therapy and conversion surgery, respectively, and all patients remained alive. Recurrence in one patient was confirmed. Our team is still following patient 6, who has been cancer-free for more than 10 years (30).

Three extensive cohort studies focusing on conversion surgery have recently been reported. Firstly, the prognostic impact of conversion surgery after lenvatinib therapy was reported (35). Among 107 patients, 16 were treated with surgical intervention, including nine with curative liver resection. Therefore, the conversion rate for curative resection was 8.4%. The successful conversion to curative resection was independently associated with better disease-specific survival (HR=0.04, 95% CI=0.01-0.30; p=0.002) than in those with no additional treatment. Based on the RECIST and mRECIST criteria, the response rates for the nine patients with curative resection were 33% and 89%, respectively. There were no patients with progressive disease using either criterion. However, this study only included two patients with MVI treated with curative surgery (Table I). Secondly, 10 (15.9%) out of 63 consecutive patients underwent curative resection at a median of 3.2 (range=2.4-8.3) months after initiation of combination molecular therapy (36). Seven patients (70%) had MVI and six (60%) achieved pathological CR. After a median follow-up of 11.2 (range=7.8-15.9) months, eight survived without disease recurrence, and one experienced tumor recurrence. Thirdly, a recent cohort study of 107 initially unresectable HCCs treated with lenvatinib plus anti-programmed cell death protein 1 showed excellent results (55). A total of 30 patients (28%) underwent conversion surgery, including 20 patients with MVI. According to RECIST and mRECIST criteria, half of the patients showed PR and the remaining half showed stable disease. Pathological CR was observed in 10 patients. The 1-year OS and disease-free survival rates were 95.7% and 61.6%, respectively. Those who were responders before surgery or had pathological CR had a more prolonged tumor-free survival, while those with pathological vascular invasion had a significantly higher recurrence rate and poorer OS.

The TALENTop study is now ongoing in China (45), with ATEZO/BEV as conversion therapy. It is a crucial RCT that assesses the utility of conversion surgery at the point that the conversion surgery is feasible. In a control group, ATEZO/BEV will be continued. ICIs sometimes lead to CR and durable responses; therefore, this study is being conducted. Patients with HCC with a portal and hepatic vein or inferior vena cava MVI and without extrahepatic spread who were amenable to surgical resection after initial ATEZO/BEV induction treatment are included. The results of this RCT are awaited with great interest.

Conclusion and Future Perspectives

Novel molecular therapy, consisting mainly of multiple drugs, is effective for patients with HCC with MVI; however, patients assessed as having CR on diagnostic imaging do not always show complete remission. Upfront hepatectomy is limitedly recommended for patients with resectable HCC with MVI other than those with Vp4 or Vv3. Although adjuvant therapies with HAIC and TACE may be beneficial, effective adjuvant molecular therapy is currently unavailable.

At present, timely conversion surgery is strongly recommended for patients with initially unresectable HCCs when curative resection becomes possible. Being a responder is desirable, but CR status is only rarely necessary. Furthermore, dual immunotherapy with tremelimumab plus durvalumab is available for patients with unresectable HCCs (56). Novel molecular therapies and treatment strategies with higher response rates tailored to the oncological characteristics of each advanced HCC are required to increase the possibility of conversion surgery and improve long-term outcomes. The TALENTop RCT study (45) will hopefully resolve the question of the necessity for conversion surgery at the conversion point for patients with HCC with MVI.

Conflicts of Interest

The Authors declare no conflicts of interest for this article.

Authors' Contributions

KY and TB designed and drafted the article. TM, HO, KM, HN, KI, EO, RK, NO, and TI collected data and assisted in preparing the article. All Authors read and approved the final article.

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