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Induction hepatic arterial infusion chemotherapy followed by surgery for hepatocellular carcinoma with massive portal vein tumor thrombosis: a case series of 20 patients

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Abstract

Background The prognosis of hepatocellular carcinoma with portal vein tumor thrombosis is very poor, and the optimal treatment remains controversial. The aim of this study is to examine the safety and feasibility of our multimodal treatment.

Methods This was a single-institution, retrospective case series. From 2013 to 2018, induction hepatic arterial infusion chemotherapy was given to 20 consecutive Japanese patients with hepatocellular carcinoma harboring portal vein tumor thrombosis in the main portal trunk or first branch, even with intrahepatic and extrahepatic metastasis. When the cancers including thrombus and metastatic disease were well controlled, surgical resection was considered. When macroscopic complete resection was achieved, two courses of hepatic arterial infusion chemotherapy were added as adjuvant therapy, whereas patients who had remnant disease after surgery were provided treatment according to the type of lesion.

Results No treatment-related deaths were noted. The objective response rate and disease control rate were 35.0% and 65.0%, respectively. After induction treatment, 10 of 20 patients underwent surgery. Postoperative complications (Clavien-Dindo grade III or more) were observed in three cases, and median postoperative hospital stay was 15.5 days. Median survival time of all 20 patients was 14.5 months and that in patients who underwent surgery was significantly longer than that in patients with unresectable hepatocellular carcinoma (19.5 months versus 9.0 months, $p=0.0018$).

Conclusion Induction treatment followed by surgery was safe and feasible for hepatocellular carcinoma with massive portal vein tumor thrombosis. Surgical resection might be oncologically appropriate for selected patients after induction treatment even with advanced stage hepatocellular carcinoma.

Keywords Combined modality therapy, Hepatic arterial infusion chemotherapy, Hepatocellular carcinoma, Liver resection, Portal vein tumor thrombosis

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Background

Portal vein tumor thrombosis (PVTT) is one of the advanced phases in patients with hepatocellular carcinoma (HCC). Their prognosis is extremely poor, and median survival time (MST) was reported to be 2.7 months with no aggressive treatment [1]. Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system and other guidelines classify the presence of PVTT as advanced stage and recommend systemic therapy with atezolizumab plus bevacizumab [2, 3]. In addition, massive PVTT can cause impairment of liver function by decreasing blood flow, and portal hypertension, which leads to ascites, varices, and encephalopathy [4] and that often makes continuous treatment difficult. On the other hand, treatment outcomes cannot be expected to improve with surgery alone for patients with HCC harboring PVTT, but removing tumor thrombus and reducing tumor volume by surgical resection with prevention of early intrahepatic recurrence by perioperative combination therapy can be effective treatment [5]. Thus, from 2013, we developed a treatment protocol of combination therapy including induction hepatic arterial infusion chemotherapy (HAIC) followed by liver resection (LR) as a systematic approach for HCC with massive PVTT, and this protocol was then used for all patients who met the eligibility criteria in our hospital.

The aim of this study is to assess the acceptability of our multimodal treatment for HCC with PVTT, including the utility of surgical resection.

Methods

This was a single-institution, retrospective case series. This study was approved by the Institutional Review Board of Yamaguchi University Hospital (2020–162).

A total of 20 Japanese patients in Yamaguchi University Hospital who had been diagnosed as having HCC with tumor thrombus in the first branch or main trunk from 2013 to 2018 were reviewed. Macroscopic PVTT was diagnosed by imaging, such as computed tomography, magnetic resonance imaging, or ultrasonography.

Indication for multimodal treatment

Patients who met the following criteria were eligible: (1) the main tumor was located in a unilateral lobe with PVTT, (2) a few nodules in another lobe were acceptable, (3) extrahepatic metastases were none or localized with good control, (4) the Child–Pugh score was 5 or 6, (5) there were no serious comorbidities such as heart, renal, infectious, or other malignant disease, and (6) Eastern Cooperative Oncology Group performance status was 0 or 1. Patients who had diffuse nodules in bilateral lobes were excluded.

Treatment protocol

First, two courses of HAIC were performed as induction treatment in principle. In some cases, concurrent radiotherapy (RT) against tumor thrombus were added to improve resectability.

When the cancers including thrombus and metastatic disease were well controlled and complete resection was expected without decreased liver function after induction treatment, surgical removal of both the main tumor and thrombus was considered. After surgery, two courses of HAIC were added to prevent early intrahepatic recurrence, even though macroscopic complete resection was achieved. The patients who had remnant disease after surgery were provided treatments such as continuous HAIC, transcatheter arterial chemoembolization (TACE), or systemic chemotherapy with molecular targeted drugs according to the type of lesion. The patients who had unresectable disease after induction therapy received systemic therapy such as sorafenib or best supportive care.

In induction HAIC, the chemotherapeutic regimen was low-dose FP (5-fluorouracil/cisplatin). One course consisted of daily administration of cisplatin (10 mg/ body) and 5-fluorouracil (250 mg/ body) on days 1–5, 8–12, 22–26, and 29–33. External radiotherapy with image-guided technique targeting PVTT with a total dose of 50 Gy in 25 fractions was performed at the same time as HAIC. Finally, doses of chemotherapeutic agents, treatment intervals, and number of treatment courses were adjusted after confirming toxicity or tolerability by the patient in the first treatment cycles.

During surgery, en bloc resection of thrombus with main tumor by hemihepatectomy was performed when tumor thrombus was confined to the first branch. If thrombus extended to the main portal trunk or contralateral branch, hemihepatectomy with thrombectomy was performed. In patients with bilobular HCCs, in addition to hemihepatectomy for the dominant side, partial resection for the other side was performed. R0 resection was defined as a complete resection and no remnant disease. R1 was defined as a positive pathological margin, and R2 was defined as macroscopically positive.

Evaluation and statistical analysis

The extent of PVTT was classified into five grades according to the Liver Cancer Study Group of Japan [6]. The grades are defined as follows: Vp0, no tumor thrombus in the portal vein; Vp1, presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein; Vp2, presence of a tumor thrombus in the

second-order branches of the portal vein; Vp3, presence of a tumor thrombus in the first-order branches of the portal vein; and Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both). Preoperative treatment response was assessed by the modified Response Evaluation Criteria in Solid Tumor (mRECIST) [7]. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The severity of postoperative complications was assessed using the Clavien-Dindo classification [8]. Continuous data are presented as median values and range. The statistical significance of the continuous variables was analyzed using Mann–Whitney's *U*-test and χ^2 test was used for the samples of nominal scales. Paired continuous variables were analyzed using the Wilcoxon signed-rank test. Multivariate analysis was performed with logistic regression analysis. The Kaplan–Meier method was used to evaluate overall survival (OS). Differences in survival between groups were compared using the log-rank test. OS was defined as the period from the date of diagnosis of HCC with PVTT to death from any cause or the date of confirmed survival. Disease-free survival (DFS) was defined as the period from complete resection to recurrence. Statistical analysis was performed using JMP version 13.0 software (SAS Institute Japan, Tokyo, Japan).

Results

Patient characteristics

The patients' characteristics are presented in Table 1. Their median age was 64 years (45–79 years), and 16 of 20 were male. Only two cases had a single tumor, and 13 patients had 10 or more tumors. Macroscopic tumor thrombus extended to the main portal trunk in nine cases and the contralateral branch in five of them. Although three patients had extrahepatic metastasis at the time of diagnosis, the metastatic lesions were localized. All 20 patients were considered to be fit for the multimodal treatment.

Table 1 Baseline characteristics of the 20 patients

Case	Age (y)	Sex	Viral infection	Number of tumors	Maximum diameter (cm)	Location	Macroscopic tumor thrombi	Extrahepatic metastasis
1	52	Male	HBV	7	11	Bilateral	Main portal trunk	–
2	54	Male	HBV	6	4.5	Bilateral	SMV-main portal trunk	–
3	77	Male	–	>10	14	Bilateral	Left first branch	Lung
4	59	Female	HBV	3	10	Bilateral	Main portal trunk -Contralateral second branch	–
5	69	Male	HCV	>10	8	Bilateral	Left first branch	–
6	74	Male	–	>10	11.6	Bilateral	Right first branch	–
7	69	Female	–	1	3.8	Unilateral	Left first branch	–
8	60	Female	HCV	>10	13	Bilateral	Main portal trunk -Contralateral second branch	Lymph node
9	52	Male	HBV	>10	13	Bilateral	Left first branch	–
10	45	Male	HBV	>10	3	Bilateral	Main portal trunk -Contralateral third branch	–
11	74	Male	HCV	>10	11.3	Bilateral	Left first branch	–
12	61	Male	–	2	7.5	Bilateral	Main portal trunk -Contralateral second branch	–
13	76	Female	–	>10	13	Unilateral	Main portal trunk	–
14	69	Male	HBV	>10	3	Unilateral	Right first branch IVC	–
15	79	Male	–	>10	8.4	Unilateral	Main portal trunk	–
16	64	Male	–	>10	11	Bilateral	Main portal trunk -Contralateral second branch	–
17	71	Male	–	1	3.9	Unilateral	Left first branch	–
18	64	Male	–	>10	12.5	Unilateral	Left first branch	–
19	63	Male	–	2	5	Bilateral	Right first branch	–
20	53	Male	–	>10	8.5	Bilateral	Right first branch	Lung

HBV, hepatitis B virus; HCV, hepatitis C virus; SMV, superior mesenteric vein; IVC, inferior vena cava

TABLE 2 Outcomes of induction treatment

Case	Number of HAIC courses	Total dose of RT (Gy)	Treatment response	Adverse events (grade 2 or more)	Surgical indication	Reason for being unresectable
1	1	40	PR	Thrombocytopenia	Resectable	–
2	8	50	PR	Thrombocytopenia	Resectable	–
3	1	–	PD	None	Unresectable	Progression
4	2	50	SD	Thrombocytopenia	Resectable	–
5	1	50	PD	Thrombocytopenia	Unresectable	Progression
6	1	50	SD	Leukopenia, anemia	Unresectable	Decline in liver function
7	2	50	PR	Thrombocytopenia	Unresectable	Decline in liver function
8	1	–	PD	Thrombocytopenia	Unresectable	Progression
9	2	–	PD	Cerebral infarction	Unresectable	Progression
10	2	–	PR	Anemia, thrombocytopenia	Resectable	–
11	1	–	PD	None	Unresectable	Progression
12	2	50	SD	Neutropenia, anemia, thrombocytopenia	Resectable	–
13	1	–	PD	None	Unresectable	Progression
14	2	39	SD	Neutropenia, anemia, thrombocytopenia	Resectable	–
15	1	50	SD	Anemia, thrombocytopenia	Resectable	–
16	1	50	SD	Hemobilia	Unresectable	Decline in liver function
17	2	50	PR	Neutropenia, anemia, thrombocytopenia	Resectable	–
18	1	45	PD	None	Unresectable	Progression
19	1	50	PR	Anemia, thrombocytopenia	Resectable	–
20	1	50	PR	Thrombocytopenia	Resectable	–

HAIC, hepatic arterial infusion chemotherapy; RT, radiotherapy; PR, partial response; SD, stable disease; PD, progressive disease

Clinical response and adverse events in induction treatment

Outcomes of induction treatment are presented in Table 2. All patients received at least one course of HAIC, but 12 patients did not proceed to the second course of HAIC due to disease progression ($n = 6$), decreased liver function ($n = 2$), and adverse events ($n = 4$). Concurrent RT was performed for 14 of 20 patients. Regarding the treatment response, seven patients showed partial response, six had stable disease, and seven patients had progressive disease. The objective response rate was 35.0%, and the disease control rate was 65.0%. Grade 2 or greater adverse events were observed in 16 patients. The most frequently observed adverse event was myelosuppression. After induction treatment, 10 of 20 patients were considered resectable and underwent liver resection (LR group). Of these, as an exception, HAIC was effective in case 2, but tumor thrombus still extended widely after two courses of HAIC, and immediate surgery was considered unsuitable. Thus, LR was performed after eight courses of HAIC. The other ten patients were considered unresectable due to disease progression in seven patients and decreased liver function in three (non-LR group). After induction treatment, the levels of tumor markers were significantly lower in the LR group than in the non-LR group (Fig. 1a, b). Although univariate and multivariate analysis were performed to identify the factors influencing resectability such as age, the number of tumors, location, the range of PVTT, RT or not, and preoperative tumor makers, there were no significant factors.

Perioperative outcomes

Table 3 summarizes the surgical procedures and perioperative outcomes. Median surgical time was 550.5 min (422–697 min), and median blood loss was 956 mL (275–3710 mL). R0 resection was achieved in five cases. Tumors remained macroscopically in the five other cases after surgery. Four of them were Vp4 cases in which the tumor thrombus still remained after surgery, and one was Vp3 with lung metastasis. Although Clavien-Dindo grade III or more postoperative complications were observed in three cases, there were no treatment-related deaths. Median postoperative hospital stay was 15.5 days (11–119 days). After surgery, four of five patients could undergo HAIC as postoperative adjuvant treatment in the R0 group, but case 15, who had suffered aspiration pneumonia and bile leakage after R0 resection, required

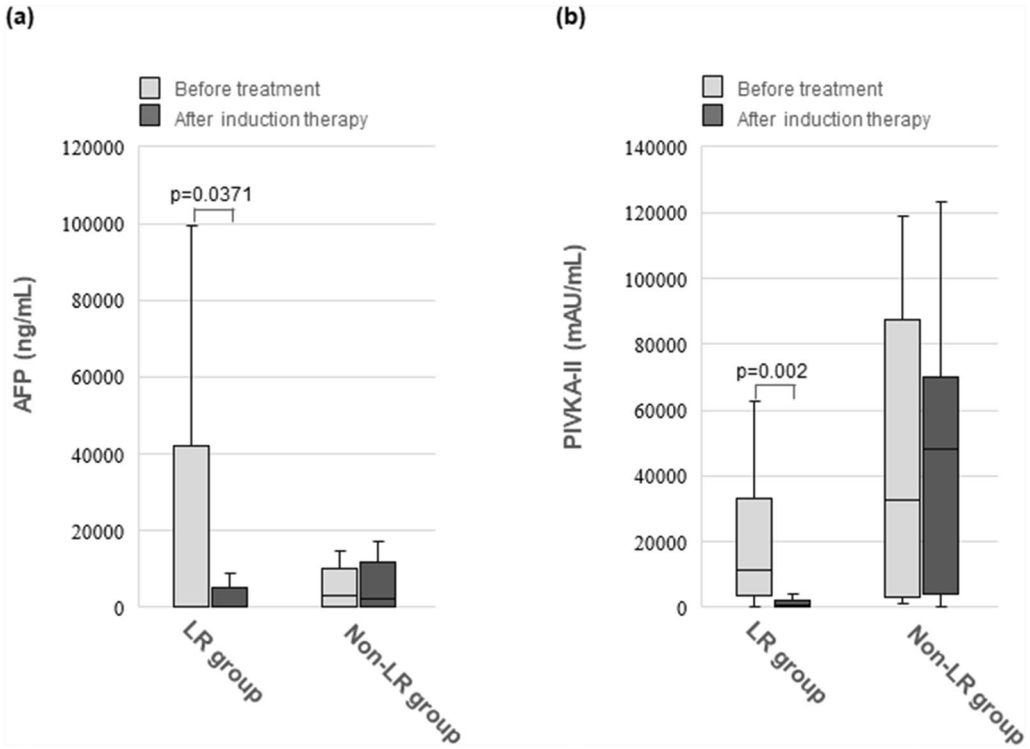

Fig. 1 Changes in serum tumor marker levels after induction treatment. The levels of serum alfa-fetoprotein (ng/mL; **a**) and protein induced by vitamin K absence or antagonist II (mAU/mL; **b**) are lower in the LR group than in the non-LR group after induction treatment. LR, liver resection

Table 3 Perioperative outcomes

Case	Operation	Method of thrombus removal	Surgical time (min)	Blood loss (mL)	Curability	Remnant	Postoperative complications (Grade III or more)	Postoperative hospital stay (days)	Postoperative treatment
1	Extended lobectomy + partial resection	Thrombectomy	697	2250	R0	–	Pleural effusion	24	HAIC
2	Lobectomy	*En bloc* resection	455	337	R2	Liver Portal trunk	–	16	TACE Sorafenib
4	Extended lobectomy + partial resection	Thrombectomy	545	600	R2	Portal vein	–	15	HAIC
10	Lobectomy	Thrombectomy	556	912	R2	Liver Portal vein	–	11	HAIC Sorafenib
12	Lobectomy	Thrombectomy	633	2960	R2	Portal vein	–	15	HAIC
14	Lobectomy	Thrombectomy	502	2010	R0	–	–	15	HAIC
15	Lobectomy	Thrombectomy	571	3710	R0	–	Aspiration pneumoniae Bile leakage	119	–
17	Laparoscopic-assisted lobectomy	Thrombectomy	605	275	R0	–	Intra-abdominal infection	28	HAIC
19	Lobectomy	Thrombectomy	541	1000	R0	–	–	18	HAIC
20	Lobectomy	*En bloc* resection	422	300	R2	Liver Lung	–	12	Lenvatinib

HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization

long-term hospitalization, and adjuvant treatment could not be given.

Survival

In the current study, eight of ten cases in the LR group and all ten cases in the non-LR group died from HCC. Only two cases in the LR group remained alive during the observation period. In fact, one case was alive for 56 months without cancer, and the other case was alive for 30 months with recurrent HCC. The overall survival curve of all 20 patients is shown in Fig. 2a, and MST was 14.5 months. From the point of view of treatment method, MST was longer in the LR group than in the non-LR group (19.5 months versus 8.5 months, $p = 0.0018$; Fig. 2b).

Regarding recurrence, all five patients who had undergone R0 resection recurred after surgery, and DFS varied from one to eight months. Of these patients, only intrahepatic recurrence was observed in three patients, only extrahepatic recurrence in one, and both intrahepatic and extrahepatic recurrences in one. After diagnosis of recurrence, four of five patients underwent aggressive treatment and one received best supportive care. In the LR group, breakdowns of the treatment modality for recurrent or remnant HCC after surgery were HAIC in two, TACE in one, HAIC and systemic therapy in four, TACE and systemic therapy in one, HAIC, TACE, and systemic therapy in one, and best supportive care in one patient. Remarkably, case 12 with a remnant lesion in his contralateral portal branch after surgery showed complete response with postoperative HAIC and remained detectable lesion-free until the time of the analysis. Meanwhile, in the non-LR group, six of ten patients were treated with sorafenib, and four of ten received best supportive care. The flow diagram of the overall clinical course of all patients is shown in Fig. 3.

Discussion

This is the first report that described our systematic strategy for HCC with massive PVTT. The current study shows that our multimodal treatment including LR seemed to be safe and brought survival benefit to patients with HCC harboring PVTT. In the current report, adverse events of preoperative treatment and postoperative complications were controllable, and there were no treatment-related deaths with our multimodal treatment. It was noteworthy that there was no mortality in the LR patients despite the high-difficulty surgical procedure after induction treatment. The MST of all 20 patients who had undergone our multimodal treatment was 14.5 months. Moreover, the MST of patients LR group was 10.5 months longer than that of cases in the non-LR group. In the LR group, the patients received various treatments for remnant or recurrent HCC after surgery. On the other hand, half of the patients in this case series were considered unresectable with limited treatment options because of their tumor progression or liver dysfunction after induction treatment. In fact, these patients were provided only sorafenib as treatment for HCC; they otherwise received best supportive care after induction treatment. Thus, successful preoperative treatment followed by surgical excision provided postoperative

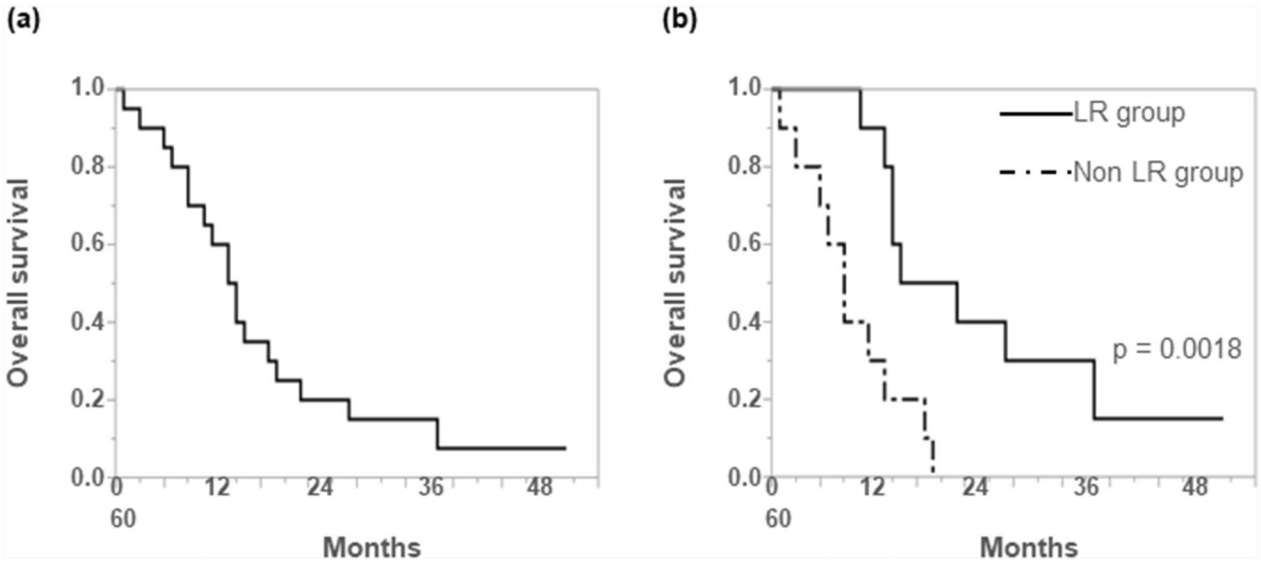

Fig. 2 Kaplan–Meier curves for the overall survival. Overall survival curve of all patients (**a**) and of patients with/without liver resection (**b**) in this study. LR, liver resection

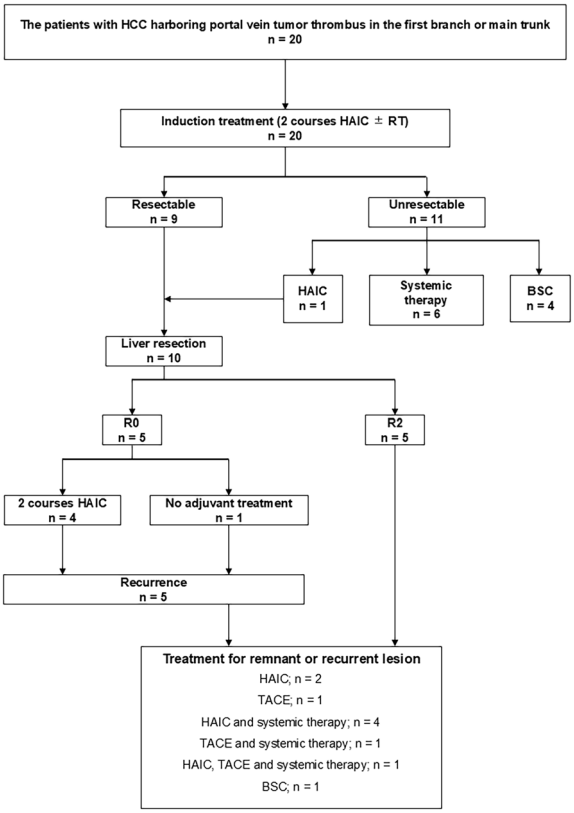

Fig. 3 Flow diagram of this study. R0 is defined as a complete resection and no remnant disease. R2 is defined as a positive macroscopic margin. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; RT, radiotherapy; BSC, best supportive care; TACE, transcatheter arterial chemoembolization

treatment options that could achieve prolonged survival in selected patients with PVTT.

HCC often invades major vessels, especially the portal vein, with tumor progression and forms tumor thrombus. Macrovascular invasion (MVI) was reported in approximately 20% of patients with HCC at the time of diagnosis, and it is a factor associated with a poor prognosis [4]. Moreover, Vp3-4 patients have a particularly poor prognosis [9]. As the reason for this, formation of tumor thrombus causes the spread of tumor cells into the bloodstream and leads to intrahepatic metastasis or recurrence. In addition, PVTT decreases portal flow or develops portal hypertension, which can interfere with continuous aggressive treatment [4]. Treatment outcomes in most patients with HCC have been improving year after year, but the prognosis of patients with PVTT remains poor, and the 1-year survival rate was reported to be 37.5% even with various treatments [10]. Recently, atezolizumab plus bevacizumab significantly improved survival in patients with advanced HCC [11], and subgroup analysis showed that MST of the patients with MVI was 14.2 months [12]. In the current study, induction treatment followed by surgery could provide repeated treatment for remnant or recurrent HCC after removal of main tumor with PVTT, and MST of the LR group was 19.5 months. Thus, multimodal treatments may improve prognosis more in this dreaded disease.

Surgical approaches for HCC with PVTT were already reported in the 1990s [13]. Afterward, several reports showing the effectiveness of surgery were published, mainly from Japan and other Asian countries [14]. Kokudo *et al.* [15] analyzed 6474 cases with HCC harboring PVTT (Vp1-4) on a nationwide scale and reported that MST of the LR group was 0.88 years longer than that of the non-LR group in the propensity score-matched cohort. However, it should be noted that they included Vp1-2 patients and excluded patients with extrahepatic metastasis. Moreover, the surgical indications for Vp4 patients are still controversial [16]. In the previous study by Kokudo *et al.* [15], it was reported that the survival benefit of LR in Vp4 cases was not significantly different from non-LR, and the R2 resection rate was relatively higher compared with Vp1-3 patients. Thus, it seems that the patients with massive PVTT cannot be cured by surgery alone, and the effectiveness of combination therapy with other modalities added to surgery has been reported [5, 17]. In this study, MST was significantly longer in the LR group than in the non-LR group, even though the majority of patients in the LR group had Vp4. In other words, the patients who had good response to induction treatment could expected surgical benefit even in Vp4 cases. In addition, importance has been placed on a smooth transition to postoperative medical treatment in our multimodal treatment. The purpose of our strategy is to extend the treatable period by reducing tumor volume and reopening portal flow, avoiding liver failure and portal hypertension by surgical resection. Although almost all cases in the LR group were provided postoperative treatment for HCC as soon after surgery as possible, there was a case, case 15, in which we abandoned postoperative adjuvant treatment due to complications. Thus, it was necessary to select appropriate patients and reduce surgical error to minimize postoperative complications.

It is considered that HAIC can theoretically administer anticancer drugs to the liver at high concentrations and reduce their systemic distribution, which is expected to have a stronger antitumor effect and lower incidence of adverse events than systemic chemotherapy [18]. HAIC has been used widely for advanced patients with HCC, especially in the Asia–Pacific region, and its efficacy has been reported [19–23]. It was also reported that the response rate to HAIC of advanced HCC patients was 30–40% [18], and the high response rate was the main reason for selecting HAIC as induction therapy at

that time, before the advent of powerful therapies such as atezolizumab or lenvatinib. In the current study, the objective response rate and the disease control rate of induction HAIC for patients with HCC harboring PVTT, of which 14 patients also underwent RT, were 35.0% and 65.0%, respectively. Meanwhile, hematological toxicity was observed frequently as grade 2 or more adverse events. Although the completion rate of two-course induction HAIC was only 40% due to adverse events or disease progression, at least one course of induction HAIC was conducted safety in all patients, and all operable patients could achieve LR by adjusting doses of agents, treatment intervals, and number of treatment courses. Moreover, RT was also used against tumor thrombus with an expectation of regression and reduced viability of PVTT. On the other hand, one of the complications associated with RT is tissue inflammation and fibrosis, which can occur 4–12 months after RT [24], and it sometimes seems to make surgery difficult. However, in the current study, LRs were performed about 1 month later at the end of preoperative treatment including RT, and there was no negative effect of RT found during surgery. Surgical difficulties caused by delayed radiation injury can be avoided by early surgical intervention after RT.

Based on the powerful evidence of atezolizumab plus bevacizumab, treatment with novel systemic agents including molecularly targeted agents and immunotherapies will continue to be mainstream in the treatment for advanced HCC. On the other hand, surgery may also improve survival in limited cases who show benefit from these systemic therapies. In fact, patients who had been able to undergo LR after induction therapy showed a better prognosis than non-LR cases in the present study. In other words, a response to induction therapy could lead to selection of surgical cases. In the current study, HAIC was provided as induction treatment because there had been few effective agents for advanced HCC in that era; however, the novel systemic agents may be substituted for HAIC and turn this treatment concept into reality in the future. Recently, the prospective phase II study aimed to evaluate the efficacy and safety of preoperative lenvatinib for patients with advanced HCC including PVTT showed that the surgical resection rate was 67.3% [25]. Compared with HAIC, lenvatinib, an oral drug, seems to be a feasible treatment because it is less invasive and has a high resection rate. In addition, another prospective phase II study evaluating the efficacy of combination therapy of atezolizumab and bevacizumab for conversion surgery in patients with technically and/or oncologically unresectable HCC was also performed [26]. The results of the final analysis are awaited in the future. Thus, with recent advances in systemic therapies, the development of more powerful multimodal treatment is expected hereafter.

One of the limitations of the present study was that it was a small-scale, single institute, retrospective case series. It should be noted that this was a preliminary study to examine the safety and feasibility of multimodal treatment combining liver resection with HAIC for HCC with PVTT, and accumulation of cases and long-term observation are now required.

Conclusion

Our multimodal treatment seemed safe and acceptable. To maximize treatment outcomes, it is essential to select patients for surgery based on their response to induction therapy, and then provide them with postoperative medical treatment.

Abbreviations

PVTT	Portal vein tumor thrombosis
HCC	Hepatocellular carcinoma
MST	Median survival time
HAIC	Hepatic arterial infusion chemotherapy
LR	Liver resection
RT	Radiotherapy
OS	Overall survival
DFS	Disease-free survival
MVI	Macrovascular invasion

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Author contributions

Conception and design: YK, YT, and HN. Collection of data: YK, YT, YS, HM, SM, IS, TT, TY, and TI. Analysis and interpretation of data: YK, YT, and SM. Drafting of the manuscript: YK and YT. Review and revision of the manuscript: All authors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol for this research project was approved by a suitably constituted Ethics Committee of Yamaguchi University (approval no. 2020–162). Informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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