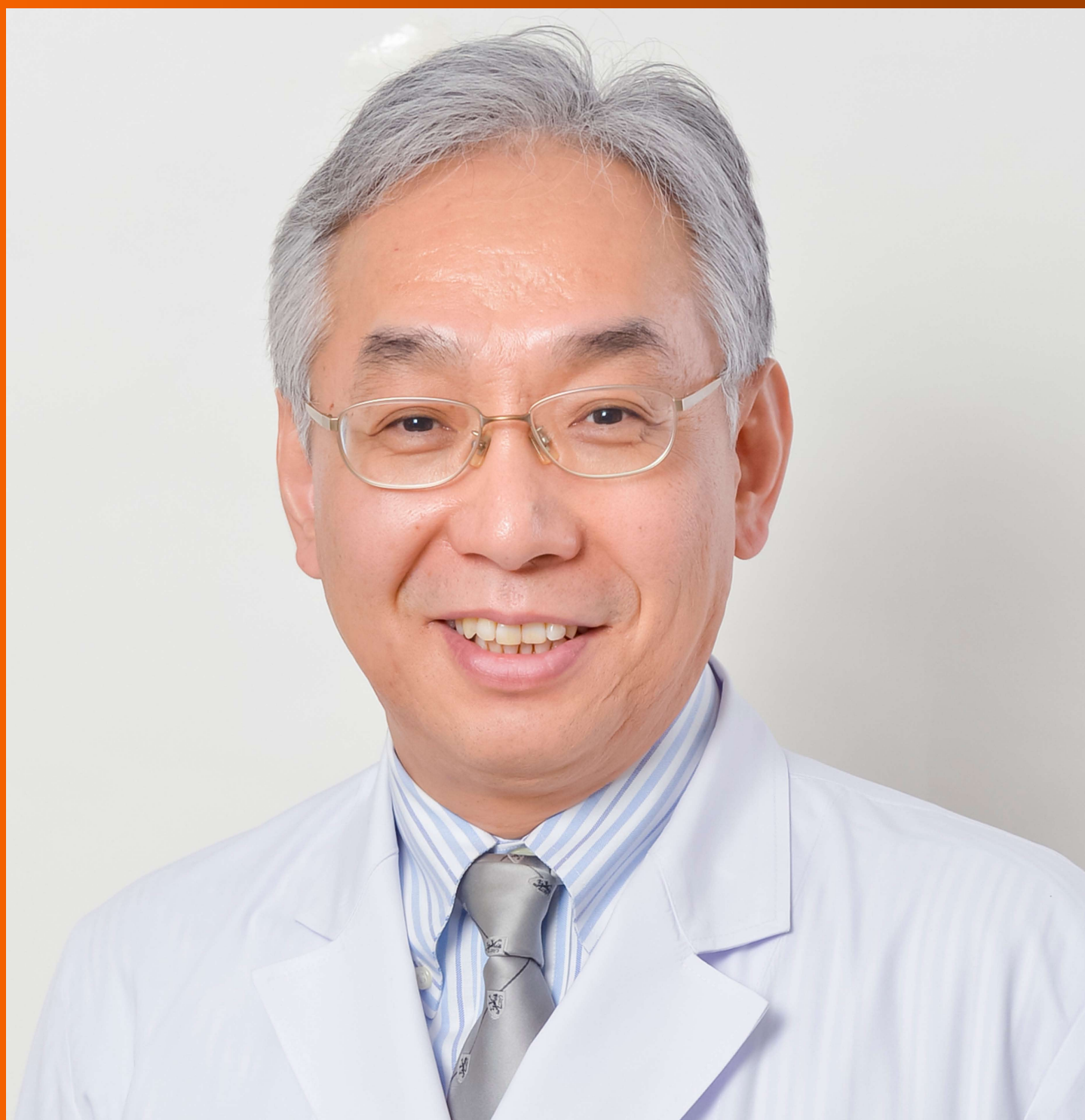


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Editorial Board Member of *World Journal of Hepatology*, Toshiya Kamiyama, MD, PhD, Assistant Professor, Surgeon, Surgical Oncologist, Department of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan

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Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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## Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus

Toshiya Kamiyama, Tatsuhiko Kakisaka, Tatsuya Orimo, Kenji Wakayama

Toshiya Kamiyama, Tatsuhiko Kakisaka, Tatsuya Orimo, Kenji Wakayama, Department of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan

ORCID number: Toshiya Kamiyama (0000-0002-9157-7811); Tatsuhiko Kakisaka (0000-0002-8556-5945); Tatsuya Orimo (0000-0003-4398-0697); Kenji Wakayama (0000-0002-2979-8461).

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and approval of the final version.

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Correspondence to: Toshiya Kamiyama, MD, PhD, Assistant Professor, Surgeon, Surgical Oncologist, Department of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido University, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan. [t-kamiya@med.hokudai.ac.jp](mailto:t-kamiya@med.hokudai.ac.jp)  
Telephone: +81-11-7065927  
Fax: +81-11-7177515

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### Abstract

Despite surgical removal of tumors with portal vein tumor thrombus (PVTT) in hepatocellular carcinoma (HCC) patients, early recurrence tends to occur, and overall survival (OS) periods remain extremely short. The role that hepatectomy may play in long-term survival for HCC with PVTT has not been established. The operative mortality of hepatectomy for HCC with PVTT has also not been reviewed. Hence, we reviewed recent literature to assess these parameters. The OS of patients who received hepatectomy in conjunction with multidisciplinary treatment tended to be superior to that of patients who did not. Multidisciplinary treatments included the following: preoperative radiotherapy on PVTT; preoperative transarterial chemoembolization (TACE); subcutaneous administration of interferon-alpha (IFN- $\alpha$ ) and intra-arterial infusion of 5-fluorouracil (5-FU) with infusion chemotherapy in the affected hepatic artery; cisplatin, doxorubicin and 5-FU locally administered in the portal vein; and subcutaneous injection of IFN- $\alpha$ , adjuvant chemotherapy (5-FU + Adriamycin) administration *via* the portal vein with postoperative TACE, percutaneous isolated hepatic perfusion and hepatic artery infusion and/or portal vein chemotherapy. The highest reported rate of operative mortality was 9.3%. In conclusion, hepatectomy for patients affected by HCC with PVTT is safe, has low mortality and might prolong survival in conjunction with multidisciplinary treatment.

**Key words:** Hepatocellular carcinoma; Portal vein tumor thrombus; Hepatectomy; Multidisciplinary treatment; Operative mortality

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**Core tip:** Hepatocellular carcinoma (HCC) is characterized by early formation of portal vein tumor thrombus (PVTT). Even after surgical removal of the tumors with PVTT in HCC patients, early recurrence has been frequently



reported due to intrahepatic metastasis from PVTT. There have been reports of long-term survival after hepatectomy in patients with macroscopic PVTT. The operative mortality of major hepatectomy for HCC patients with macroscopic PVTT has not been well documented or discussed. To this end, we reviewed recent literature on the significance of hepatectomy in HCC with macroscopic PVTT with respect to the long-term survival and mortality.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is characterized by early formation of portal vein tumor thrombus (PVTT)<sup>[1]</sup>. An important prognostic factor and predictor for HCC recurrence is PVTT<sup>[2,3]</sup>. The effectiveness of transarterial chemoembolization (TACE) for HCC with PVTT remains unclear<sup>[4,5]</sup> though TACE is included in the treatment for HCC with tumor thrombus in the main portal branch<sup>[6]</sup>. However, it was suggested that hepatic arterial infusion chemotherapy might be a hopeful approach<sup>[7,8]</sup>. Because the median survival for untreated patients with PVTT is only 2.7 mo, this suggestion is especially relevant<sup>[9]</sup>. Hepatectomy for advanced HCC with removal of PVTT might also warrant consideration as an adjuvant treatment though it is usually performed as an emergency operation to avoid lethal complications<sup>[10]</sup>. Early recurrence has been reported in many cases due to intrahepatic metastasis from PVTT<sup>[11]</sup> even after tumors with PVTT in HCC patients was surgically removed. On the other hand, there have been reports of long-term survival after hepatectomy in patients with macroscopic portal invasion<sup>[12,13]</sup>, but whether this treatment is optimal for patients with major PVTT remains controversial. Moreover, the operative mortality of major hepatectomy for HCC with macroscopic PVTT has not been well documented and reviewed. Therefore, we review literature published after January 2000 about the significance of hepatectomy in HCC with macroscopic PVTT with respect to long-term survival and mortality.

## SURGICAL GUIDELINES FOR RESECTION IN HCC WITH PVTT

Because the cancer has already disseminated at this stage, leading to high rates of recurrence, hepatectomy for HCC with portal invasion is not recommended in the barcelona clinic liver cancer (BCLC) staging and treatment strategy. Portal invasion is associated with

the development of metastatic nests, with higher incidence in tumors exhibiting microvascular invasion and/or satellite lesions<sup>[14]</sup>.

According to the BCLC staging classification, sorafenib is the treatment of choice for HCC with macroscopic portal invasion (BCLC stage C). The efficacy of sorafenib in the treatment of advanced HCC was recently confirmed by the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial. In that report, the median overall survival was 7.9 mo in the placebo group compared to 10.7 mo in the sorafenib group. The benefit of sorafenib was consistent in the pre-specified stratification groups that included patients with the worst prognosis, such as those with macroscopic vascular invasion<sup>[15]</sup>. According to the BCLC staging classification, hepatectomy is contraindicated in HCC with Vp3 (tumor thrombus in the first branch of the portal vein) or Vp4 (tumor thrombus extension to the trunk or to the opposite side branch of the portal vein) and should only be performed in patients with small single tumors without signs of portal hypertension or hyperbilirubinemia. On the other hand, the proposed treatment for HCC with minimal portal invasion, such as Vp1 (tumor thrombus distal to the second branches of the portal vein) and Vp2 (tumor thrombus in the second branches of the portal vein), is hepatectomy combined with TACE in the Japan Society of Hepatology (JSH) algorithm<sup>[16]</sup>. Indeed, when hepatectomy was performed in selected patients affected by HCC with macroscopic PVTT, in combination with either postoperative arterial infusion therapy or preoperative TACE, long-term survival was achieved<sup>[13,17]</sup>.

In the 17<sup>th</sup> Nationwide Follow-up Survey of Primary Liver Cancer report in Japan, it was stated that the survival rates of 976 hepatectomized HCC patients with Vp3 or Vp4 were 50.4%, 25.8% and 18.4% at 1, 3 and 5 years, respectively<sup>[1]</sup>.

## HEPATECTOMY WITH MULTIDISCIPLINARY TREATMENT FOR PVTT

The prognosis of the HCC patients with PVTT in the first branch or main trunk is very poor, with a median survival of only 2.7 mo if appropriate treatments are not employed<sup>[9]</sup>. However, in the present literature search, we identified instances of long-term survival after hepatectomy. The range of overall survival (OS) rates for patients who received hepatectomy without multidisciplinary treatment were from 14.2% to 86.5% at 1 year, 0% to 60.4% at 3 years and 0 to 33.3% at 5 years (Table 1). On the other hand, the range of the OS rates for patients who received hepatectomy with multidisciplinary treatment were from 0% to 100% at 1 year, 14.0% to 74.0% at 3 years and 21.5% to 42.0% at 5 years (Table 1). From these data, we can see that the OS rates of patients who received hepatectomy with multidisciplinary treatment tended to be superior to those of patients who did not receive multidisciplinary treatment. This favorable

**Table 1** Surgical outcome of hepatectomy for hepatocellular carcinoma patients with portal vein thrombus

Ref.	Vp type	Patients	Child-Pugh A (%)	HBV (%)	OS, 1 yr (%)	OS, 3 yr (%)	OS, 5 yr (%)	Treatment
Ohkubo <i>et al</i> <sup>[11]</sup> 2000	Vp234	47	91.5	42.6	53.9	33.2	23.9	
Minagawa <i>et al</i> <sup>[13]</sup> 2001	Vp234	18	NS	44.4	82	42	42	Preop TACE
Fan <i>et al</i> <sup>[26]</sup> 2003	Vp34	19	78.9	NS	14.2	0	0	
	Vp34	64	78.1	NS	37.6	14	NS	Postop PVI HAI
Capussotti <i>et al</i> <sup>[42]</sup> 2004	Vp234	13	NS	NS	NS	18.5	18.5	
Zhou <i>et al</i> <sup>[19]</sup> 2006	Vp234	381	NS	90	47	16	12	
Ikai <i>et al</i> <sup>[27]</sup> 2006	Vp34	78	NS	30.8	45.7	21.7	10.9	
Chen <i>et al</i> <sup>[49]</sup> 2006	Vp234	438	NS	NS	52.1	16	11.8	
	Vp23	286	13.3	60.1	58.7	22.7	18.1	
	Vp34	152	NS	62.5	39.5	5.7	0	
Nagano <i>et al</i> <sup>[17]</sup> 2007	Vp3	15	NS	66.7	100	74	NS	Postop 5-FU/IFN
	Vp3	15	NS	40	41	22	NS	
Kamiyama <i>et al</i> <sup>[12]</sup> 2007	Vp34	15	100	66.7	86.2	43.5	34.8	Preop radiation
	Vp34	28	85.7	64.3	39	13.1	13.1	
Liang <i>et al</i> <sup>[20]</sup> 2008	Vp34	33	54.5	93.9	46.8	14.4	NS	Postop PIAF
	Vp34	53	69.8	92.5	23.4	5.8	NS	
Peng <i>et al</i> <sup>[22]</sup> 2009	Vp34	51	86.3	NS	50.9	33.8	21.5	Postop TACE
	Vp34	53	86.8	NS	33.3	17	8.5	
Ban <i>et al</i> <sup>[57]</sup> 2009	Vp34	45	66.7	42.2	69.6	37.4	22.4	
Shi <i>et al</i> <sup>[48]</sup> 2010	Vp3	169	99.4	81.1	38.2	17.7	NS	
	Vp4	78	97.4	87.2	24.7	3.6	NS	
	Vp4 <sup>1</sup>	20	95	90	18.3	0	NS	
Zhou <i>et al</i> <sup>[21]</sup> 2011	Vp34	21	NS	NS	47	22	NS	
	Vp34	38	NS	NS	70	20	NS	Adjuvant chemotherapy via portal vein
Matono <i>et al</i> <sup>[45]</sup> 2012	Vp34	19	NS	55.2	62.1	24.1	17.2	
	Vp34 <sup>2</sup>	10	NS	NS	38.5	0	0	
Chen <i>et al</i> <sup>[50]</sup> 2012	Vp34	88	84.1	89.8	31.1	18.3	15.2	
Peng <i>et al</i> <sup>[46]</sup> 2012	Vp3	68	NS	NS	46.3	17.2	17.2	
	Vp4	83	NS	NS	32.5	3.6	3.6	
	Vp4 <sup>1</sup>	23	NS	NS	21.7	0	0	
Tang <i>et al</i> <sup>[43]</sup> 2013	Vp234	186	91.9	85.5	40.1	17	13.6	
Li <i>et al</i> <sup>[58]</sup> 2013	Vp3	10	100	100	43	16	NS	
	Vp3 <sup>3</sup>	20	100	90	32	11	NS	
Chok <i>et al</i> <sup>[47]</sup> 2014	Vp3	71	95.8	90.1	45.8	22.7	11.2	
	Vp3 <sup>4</sup>	10	90	100	50	12.5	12.5	
	Vp34 <sup>5</sup>	7	85.7	100	28.6	14.3	14.3	
Fukumoto <i>et al</i> <sup>[25]</sup> 2014	Vp234	41	NS	NS	80.5	32.4	NS	Postop PIHP
Yamamoto <i>et al</i> <sup>[44]</sup> 2015	Vp34	10	NS	NS	NS	NS	30	
Pesi <i>et al</i> <sup>[59]</sup> 2015	Vp3	21	NS	NS	60	39	10	
Kojima <i>et al</i> <sup>[18]</sup> 2015	Vp34	27	92.6	33.3	77.8	48.2	25.9	Postop HAIC (FP, epi- ADM)
	Vp34	25	88	32	68	32	12	
Xiao <i>et al</i> <sup>[60]</sup> 2015	Vp2	28	NS	NS	53.6	25	25	
	Vp3	38	NS	NS	39.5	15.8	5.3	
Bai <i>et al</i> <sup>[23]</sup> 2016	Vp23	51	92.2	22	19.6	NS	NS	
	Vp23	31	96.8	19	53.3	NS	NS	Postop TACE
	Vp23	10	100	30	71.1	NS	NS	Postop radiation
Zheng <i>et al</i> <sup>[51]</sup> 2016	Vp234	96	78.1	58.3	86.5	60.4	33.3	
Li <i>et al</i> <sup>[30]</sup> 2016	Vp4	39	88.9	82.2	69	NS	NS	Preop radiation
	Vp23	50	84	88	35.6	NS	NS	
Ye <i>et al</i> <sup>[24]</sup> 2016	Vp4	54	NS	85.2	0	NS	NS	Postop TACE
Hamaoka <i>et al</i> <sup>[33]</sup> 2017	Vp34	7	100	NS	100	71	NS	Preop radiation, HAIC (FP, IFN/5-FU)

<sup>1</sup>Tumor thrombi involving the superior mesenteric vein; <sup>2</sup>Non-curative resection; <sup>3</sup>Hepatectomy with caudate lobe; <sup>4</sup>PVTT extending to or beyond the portal vein bifurcation, treated by en bloc resection followed by portal vein reconstruction; <sup>5</sup>PVTT extending to or beyond the portal vein bifurcation, treated by thrombectomy. OS: Overall survival; HBV: Hepatitis B virus; Vp2: Tumor thrombus in the second branches of the portal vein; Vp3: Tumor thrombus in the first branch of the portal vein; Vp4: Tumor thrombus extension to the trunk or the opposite-side branch of the portal vein; TACE: Transarterial chemoembolization; PVI: Portal vein infusion; HAI: Hepatic arterial infusion; PIAF: Cisplatin, doxorubicin and 5-fluorouridine (5-FU) locally administered in the portal vein with subcutaneous injection of interferon- $\alpha$ ; PIHP: Percutaneous isolated hepatic perfusion; FAIT: FU arterial infusion and interferon therapy; HAIC: Hepatic arterial infusion chemotherapy; FP: Cisplatin+5-FU; ADM: Adriamycin; NS: Not stated.

outcome was achieved when hepatectomy was pre- or postoperatively combined with multidisciplinary treatment. The multidisciplinary treatments included

the following: Preoperative radiotherapy (RT) on PVTT in the main trunk or first branch<sup>[12]</sup>; preoperative TACE<sup>[13]</sup>; subcutaneous administration of interferon- $\alpha$  (IFN- $\alpha$ )

and intra-arterial infusion of 5-fluorouracil (5-FU)<sup>[17]</sup>; Epi-Adriamycin/cisplatin+5-FU<sup>[18]</sup>; cisplatin+5-FU infused in the portal vein or in the proper hepatic artery<sup>[19]</sup>; PIAF regimen (cisplatin, doxorubicin and 5-FU locally administered in the portal vein with subcutaneous injection of IFN- $\alpha$ )<sup>[20]</sup>; adjuvant chemotherapy (5-FU and Adriamycin) *via* the portal vein<sup>[21]</sup>; postoperative TACE<sup>[22-24]</sup>; percutaneous isolated hepatic perfusion (PIHP)<sup>[25]</sup>; and hepatic artery infusion and/or portal vein chemotherapy<sup>[26]</sup>.

It was reported that the survival periods of approximately 10% of patients with tumor thrombi in the first branch and the portal trunk is more than 5 years following hepatectomy and that postoperative multidisciplinary treatments, including local and systemic adjuvant chemotherapy, are required in addition to hepatectomy to prevent intrahepatic metastasis<sup>[27]</sup>. Fukumoto *et al*<sup>[25]</sup> described that the efficacy of PIHP for hepatectomized patients with macroscopic PVTT had a median OS of 23 mo compared with a 6.5 mo median survival for patients treated with sorafenib<sup>[15]</sup>. However, PIHP treatment requires special equipment/expertise that is not currently available outside of Kobe University. On the other hand, Minagawa *et al*<sup>[13]</sup> reported the survival rate of 42% at 5 years for patients who underwent hepatectomy with preoperative TACE, which can be easily performed in any center, with only 9 cases exhibiting portal vein invasion in the second-order branches. It was reported that treating 15 cases of HCC with PVTT using FU arterial infusion and interferon therapy (FAIT) in addition to surgery, and 100% of the patients survived more than 1 year. In contrast, 10 patients (67%) died within 1 year without FAIT and surgery<sup>[17]</sup>. Peng *et al*<sup>[22]</sup> conducted a randomized controlled trial and showed that postoperative TACE enhances the effect of liver resection combined with PVTT removal. Estimated 1-, 3- and 5-years survival rates were better in the TACE group (50.9%, 33.8%, and 21.5%, respectively) than in the control group (33.3%, 17.0%, and 8.5%, respectively).

Liang *et al*<sup>[20]</sup> reported that the efficacy of intra-portal infusion chemotherapy using the PIAF regimen. They describe their procedure for administration of chemotherapeutic agents into portal vein as an attempt to kill the residual cancer cells in the portal venous system and subsequently curtail postoperative cancer recurrence. Moreover, another randomized controlled trial reported that postoperative TACE combined with portal vein chemotherapy is beneficial for patients with HCC complicated by PVTT but that the long-term efficacy of this approach is uncertain<sup>[28]</sup>. A combination of hepatectomy and preoperative RT has been reported to be effective for PVTT in the first branch or main trunk<sup>[12]</sup>. The survival rates at 1-, 3-, and 5-year were 100%, 53.3%, and 40.0%, respectively. Therefore, one of the abovementioned perioperative treatments combined with hepatectomy for HCC with PVTT might be necessary to prolong patient survival, though which of these options are superior cannot be concluded from

this review. More appropriate regimens of perioperative treatment continue to be developed. Because Ando *et al*<sup>[7]</sup> reported that hepatic arterial infusion chemotherapy (HAIC) with 5-FU and low-dose cisplatin may be a beneficial therapeutic option for patients with HCC with PVTT in the main portal trunk or in the first portal branch or in the second portal branch; this regimen may be promising as adjuvant therapy for hepatectomy in HCC with macroscopic PVTT.

As a curative treatment for HCC with PVTT, only hepatectomy might be insufficient, and multidisciplinary treatments must be required because portal invasion is associated with the development of metastatic nests.

### Significance of local treatment for PVTT

What about targeting PVTT for local treatment? Yamanaka *et al*<sup>[29]</sup> reported that the portal pedicles should be divided before liver parenchymal dissection during segmentectomy and lobectomy to decrease the chance of dissemination of the intravasated cancer cells because the cancer cells can dislodge into the portal venous stream during hepatectomy for HCC. From this point of view, targeting the PVTT to prevent cancer cell dissemination is a desirable approach. It was reported that preoperative radiation on the PVTT caused the tumor thrombus to become completely necrotic based on pathological examination, and 5 (83.3%) of the 6 patients survived for over 2 years after treatment<sup>[12]</sup>. Li *et al*<sup>[30]</sup> also demonstrated that better postoperative survival outcomes were provided by neoadjuvant radiotherapy before partial hepatectomy than partial hepatectomy alone for patients with HCC containing the main portal tumor thrombus. In 12 of 45 patients, the extent of PVTT after radiotherapy was significantly reduced, with the remaining 31 showing partial response (PR) and stable disease (SD) or two with progressive disease (PD)<sup>[30]</sup>. Because the tolerance of the liver for RT is low, RT for HCC has been limited to palliative treatment<sup>[31,32]</sup>. However, for the treatment of HCC, the effects of a high dose of local RT have been investigated<sup>[12,30]</sup>. Minagawa *et al*<sup>[13]</sup> described that radiation hepatitis did not occur in any of their patients and no apparent late radiation-induced complications were noted in any patients. For this reason, preoperative external RT was targeting the PVTT, not the whole tumor. By their method of RT, the irradiation in the normal liver tissue was minimized and the RT dose was increased without significantly increasing toxicity. Good survival outcome of hepatectomy with preoperative TACE for HCC patients with PVTT was reported<sup>[13]</sup>. Pathological examination detected necrosis of the PVTT in these patients. Therefore, the dissemination of HCC cells in the portal vein decrease because preoperative TACE or RT in PVTT induces necrosis. Consequently, these preoperative treatments might prevent HCC recurrence. Moreover, Hamaoka *et al*<sup>[33]</sup> reported that hepatectomy after down-staging with 3D-CRT for PVTT combined with HAIC for advanced HCC is safe and results in long-term survival outcomes. Hepatectomy for patients affected



by HCC with PVTT might prolong survival in conjunction with local treatment targeting PVTT: RT or TACE.

### Operative mortality of hepatectomy for PVTT

Hepatectomy was indicated for living donor liver transplantation and the following liver tumors: Metastatic liver tumor, HCC, biliary malignancy. Of all the local treatments, hepatectomy for HCC had the highest local controllability and yielded a good survival outcome<sup>[34,35]</sup>. The liver functional reserve was decreased in almost all the patients with HCC because almost of patients with HCC had hepatitis B and/or hepatitis C viral infection and therefore had chronic hepatitis or cirrhosis<sup>[1]</sup>. Patients with liver cirrhosis decreased reticuloendothelial system functions, had elevated portal venous pressures, and impaired liver regeneration and coagulopathy<sup>[36]</sup>. Therefore, the mortality rates of hepatectomy in patients with liver cirrhosis was high from 8.9% to 19.6%<sup>[37]</sup>. On the other hand, recent advances in pre- and postoperative care, the decision criteria for hepatectomy and indications for hepatectomy and surgical techniques have been applied to extended hepatectomy<sup>[38-40]</sup>. Although operative mortality is not avoided even in donor hepatectomy for living donor liver transplantation, major hepatectomy become more safe by these preoperative evaluations<sup>[41]</sup>.

There were 6 papers that reported mortality within 30 d. In Ohkubo *et al.*<sup>[11]</sup>'s series, one patient died within 1 mo of the operation due to liver failure. In Capussotti *et al.*<sup>[42]</sup>'s report, two patients died within 30 d due to postoperative bleeding and liver failure. In Ikai *et al.*<sup>[27]</sup>'s report, patients who died within 30 d were 3, two from growth of the extrahepatic metastases and another because of pulmonary bleeding. There were 2 deaths (2.3%) recorded within 30 d after the operation due to operative mortality in Liang *et al.*<sup>[20]</sup>'s paper. Two patients died within 30 d of surgery due to hepatic decompensation in Tang *et al.*<sup>[43]</sup>'s study. Yamamoto *et al.*<sup>[44]</sup> described one patient dying within 30 d of the operation due to acute renal failure. Thirteen papers mentioned mortality or operative mortality without reporting times. No mortality was described in six of these papers. The other 7 papers showed the number of patients or percentage of mortality. Fan *et al.*<sup>[26]</sup> reported an operative mortality of 4.8%. In the control group, two patients died from operative complications in Peng *et al.*<sup>[22]</sup>'s study. One patient in Matono *et al.*<sup>[45]</sup>'s report died of operative morbidity. In Peng *et al.*<sup>[46]</sup>'s report, there was one in-hospital postoperative death due to liver failure. The overall hospital mortality was 3.4% ( $n = 3$ ) in Chock *et al.*<sup>[47]</sup>'s study. There was one in-hospital death after the operation caused by postoperative bleeding ( $n = 169$ ) in Shi *et al.*<sup>[48]</sup>'s series. Operative mortality of Group A was 0% and that of Group B was 2.6% in Chen *et al.*<sup>[49]</sup>'s paper. Chen *et al.*<sup>[50]</sup> reported a mortality of 4.5%. Ye *et al.*<sup>[24]</sup> reported that 5 patients died (9.3%) (liver failure: 3, serious infection: 1, and heart failure: 1). Zheng *et al.*<sup>[51]</sup> reported that 1 in-hospital postoperative

death (1.0%) occurred in the hepatic resection group, caused by a serious postoperative infection. Mortality on postoperative day 38 and 58 was described in studies by Capussotti *et al.*<sup>[42]</sup> and Minagawa *et al.*<sup>[13]</sup>, respectively (Table 2).

When an HCC with major PVTT is surgically resected, a major hepatectomy should be performed with removal of the parenchyma fed by the portal vein obstructed by the PVTT vein. This operative procedure is quite technically complicated. In Asiyanbola *et al.*<sup>[52]</sup>'s report, the type of operative procedure (more than or equal to hemi-hepatectomy *vs* less than hemi-hepatectomy) was related with in-hospital mortality and, specifically, patients who underwent more than or equal to a hemi-hepatectomy had a mortality rate of 6.5% compared with 4.1% for patients who underwent less than a hemi-hepatectomy. Therefore, major hepatectomy requires a very refined technique<sup>[52]</sup>. However, the operative mortality for hepatectomy in HCC with macroscopic PVTT has not been discussed. In the present review, the highest rate of operative mortality found in the literature was 9.3%<sup>[24]</sup>. The rest were not as high compared to the rates reported by Asiyanbola *et al.*<sup>[52]</sup>, though the mortality data were represented in a variety of ways. Major hepatectomy for HCC with macroscopic PVTT has been safely performed in many cases. The estimated cause was that the majority of patients described in this review paper had a Child-Pugh A and were infected with HBV (Table 1) and thus had a good liver function reserve. Therefore, we propose that the indication for hepatectomy in HCC with major PVTT should be expanded.

## LONG-TERM SURVIVAL-RELATED FACTORS: THE EXTENT OF THE TUMOR THROMBUS

What are the long-term survival-related factors? Shi *et al.*<sup>[48]</sup> previously classified PVTT into 4 groups by the extent of the tumor thrombus. Patients of types I and II: PVTT located in the segmental, sectoral, or right and/or left portal veins showed significantly better survival than those of types III and IV: PVTT extended to the main trunk of the portal vein or the superior mesenteric vein. Therefore, they concluded that hepatectomy with thrombectomy is justified in selected patients with HCC and PVTT located in the first, second, or lower branch of the portal vein. Zheng *et al.*<sup>[51]</sup> also reported that the long-term survival in patients with type I and II PVTT was remarkably improved compared with in patients with type III and IV PVTT. Moreover, Kokudo *et al.*<sup>[53]</sup> reported data from the nationwide survey of patients with primary liver cancer performed by the Liver Cancer Study Group of Japan, which stated that the survival benefit of liver resection was statistically significant only in patients with PVTT invading the main trunk or contralateral branch. From these data, while HCC with PVTT located in the first or second branch of the portal vein might be a relatively

Table 2 Patient mortality

	Ref.	Patient number or percent	Cause of death
Within 30 d	Ikai <i>et al</i> <sup>[27]</sup>	3	Pulmonary bleeding
			Extrahepatic growth
	Yamamoto <i>et al</i> <sup>[44]</sup>	1	Renal failure
	Ohkubo <i>et al</i> <sup>[11]</sup>	1	Liver failure
	Capussotti <i>et al</i> <sup>[42]</sup>	2	Postoperative bleeding
			Liver failure
38 d	Liang <i>et al</i> <sup>[20]</sup>	2	
	Tang <i>et al</i> <sup>[43]</sup>	2	Decompensation
58 d	Capussotti <i>et al</i> <sup>[42]</sup>	1	Sepsis
	Minagawa <i>et al</i> <sup>[13]</sup>	1	Liver failure
Operative mortality	Fan <i>et al</i> <sup>[26]</sup>	4.80%	
	Peng <i>et al</i> <sup>[22]</sup>	2	Operative complication
	Matono <i>et al</i> <sup>[45]</sup>	1	
	Peng <i>et al</i> <sup>[46]</sup>	1	Liver failure
	Chock <i>et al</i> <sup>[47]</sup>	3.40%	
	Shi <i>et al</i> <sup>[48]</sup>	1	Postoperative bleeding
	Zheng <i>et al</i> <sup>[51]</sup>	1	Serious postoperative infection
	Ye <i>et al</i> <sup>[24]</sup>	9.30%	Liver failure, serious infection, heart failure
Mortality	Chen <i>et al</i> <sup>[49]</sup>	0%	
		2.60%	
	Nagano <i>et al</i> <sup>[17]</sup>	0%	
	Kamiyama <i>et al</i> <sup>[12]</sup>	0%	
	Ban <i>et al</i> <sup>[57]</sup>	0%	
	Chen <i>et al</i> <sup>[50]</sup>	4.50%	
	Fukumoto <i>et al</i> <sup>[25]</sup>	0%	
	Li <i>et al</i> <sup>[30]</sup>	0%	

good indication for hepatectomy, hepatectomy for HCC combined with PVTT in the contralateral branch or main trunk should be performed after careful consideration.

#### Long-term survival-related factors: Liver function

Ikai *et al*<sup>[27]</sup> reported that the absence of ascites, prothrombin activity, and tumor diameter are independent prognostic factors reflecting portal hypertension, liver function and tumor status, respectively. Kondo *et al*<sup>[54]</sup> reported negative prognostic factors of hepatectomized patients with PVTT, including age < 60 years and factors related to liver function: Total serum bilirubin > 0.8 mg/dL and serum alkaline phosphatase > 300 IU/mL. Pawlik *et al*<sup>[55]</sup> concluded that patients with HCC and the major vascular invasion of the main portal or hepatic vein branches derive long-term resection benefits if they have no, or minimal, underlying fibrosis. In another report, the presence of fibrosis: Moderate to severe was the individual significant predictive factor on multivariate analysis that was related with worse short-term ( $\leq 6$  mo) and long-term ( $> 6$  mo) survival. In this paper, the authors argued that this result is due to postresection hepatic decompensation and to a "field cancerization"<sup>[56]</sup> effect in the cirrhotic liver, which places these patients at a higher risk for metachronous or synchronous disease. Most of the patients described in the studies

we reviewed had a Child-Pugh A and were infected HBV (Table 1). This status might be a requirement for adaptation to hepatectomy to prevent postoperative hepatic decompensation. Moreover, increased liver function reserve might lead to a better prognosis for patients with HCC complicated by PVTT after hepatectomy due to the prevention of synchronous or metachronous tumors. Of the HCC patients with macroscopic PVTT, the indication of hepatectomy should be restricted within good liver function reserve.

A limitation of this review is that most of the articles selected were published from Eastern Asian countries, and the findings may not be applicable to other regions of the world. A more comprehensive review of the global literature would be very valuable in the future.

## CONCLUSION

Hepatectomy might prolong the survival of patients with HCC with PVTT when the liver function reserve is preserved, such as in Child-Pugh score A cases. Effective multidisciplinary treatments may improve the prognosis and prevent recurrence due to disseminated cancer cells in these patients. Moreover, hepatectomy may be a feasible adjunct treatment for HCC with PVTT due to the current mortality rates after hepatectomy being quite low.

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