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Indication of Surgical Hepatectomy for the Patients of Hepatocellular Carcinoma with Inferior Vena Cava Tumor Thrombosis

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The prognosis of hepatocellular carcinoma (HCC) presenting with inferior vena cava tumor thrombus (IVCTT) is extremely poor. The aim of this study was to reveal the postoperative course and to identify patients who have survived surgical hepatectomy among HCC patients with IVCTT. Between January 2006 and December 2018, 643 patients underwent surgical hepatectomy for HCC at Kobe University Hospital. Among them, 20 patients were categorized as Vv3 according to the Japanese staging system. We retrospectively collected detailed data on these patients. The statistical, clinical, and pathological data were recorded prospectively and analyzed retrospectively. The median survival time was 9.8 months. Among all patients, 11 (55%) achieved R0 resection, and only two survivors were from this group. The number of tumors (solitary vs. multiple; p=0.050) and pathological Vp (pVp0 vs. other; p=0.009) were identified as risk factors for overall survival in the univariate analysis. In the multivariate analysis, pathological Vp (pVp0 vs. other; p=0.037) was identified as a significant prognostic factor for survival. Pathological Vp affected overall survival among IVCTT patients; the median survival time was 53.7 months with pVp0, 10.2 months with pVp1, and 8.8 months with pVp2-4 (p=0.035). For patients with IVCTT, surgical hepatectomy should be indicated only for those who do not have portal vein invasion and could achieve R0 resection.

INTRODUCTION

Hepatocellular carcinoma (HCC) was ranked as the sixth most incident neoplasm and the fourth leading cause of cancer-related death worldwide in 2018 (2). Along with advanced stages, HCC invades intrahepatic vessels such as the portal vein or hepatic vein and forms tumor thrombi (14). Further extension of tumor thrombi exceeds three main hepatic veins and gives rise to the inferior vena cava (IVC) or right atrium. The prognosis of HCC patients presenting with IVC or right atrium thrombosis is extremely poor, and can result in comorbid intrapulmonary dissemination, pulmonary embolism, or even sudden death (4) (13) (19). According to the guidelines of the American Association for the Study of Liver Diseases, patients who present with vascular invasion have a shorter life expectancy and are candidates to enter therapeutic trials with new agents (3). As new information emerged, the guidelines were updated in 2010. For patients with more advanced HCC, new data indicates the efficacy of sorafenib in prolonging survival, with a median overall survival of 10.7 months (15). However, even based on the novel guideline, surgical resection remains the first option for patients with optimal profiles. The reason for the narrow indications for surgical resection is the poor long-term outcomes in patients with advanced HCC (1) (16) (20). Recent advances in liver surgery have rapidly improved outcomes, and surgical resection has become a reasonable and safe treatment option for patients with HCC (5) (8). However, because of the low prevalence, there are still only a few reports with very small sample sizes from single centers investigating the outcome and prognosis of advanced HCC patients. In 2014, the prognostic impact of 187 patients with hepatic vein tumor thrombosis was reported from the Tokyo group (10). In 2017, liver resection for 1266 HCC patients with hepatic vein invasion was reported as a Japanese nationwide survey (9). However, in both manuscripts, HCC with tumor thrombosis in the inferior vena cava (IVCTT) was discussed as part of the hepatic vein tumor thrombus, and the postoperative course after hepatectomy for IVCTT patients has not been described in detail.

The aim of this study was to reveal the postoperative course and to identify patients who have survived surgical hepatectomy among HCC patients with IVCTT from the experience of a single center.

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MATERIALS AND METHODS

Patients

Based on the database, there were 643 patients with HCC who underwent surgical hepatectomy at Kobe University Hospital from 2006 to 2018. The presence of hepatic vein tumor thrombosis (HVTT) was diagnosed based on the final pathological findings. HVTT was categorized into three groups based on the existence of tumor thrombosis in the peripheral hepatic vein; Vv1, includes microvascular invasion (pHVTT); Vv2, includes in a major hepatic vein (mHVTT); and Vv3, includes IVCTT according to the Japanese staging system. Among the 643 patients, 582 patients were categorized as Vv0, 28 patients as Vv1, 13 patients as Vv2, and 20 patients as Vv3. In this study, we retrospectively collected detailed data on 20 Vv3 patients. The statistical, clinical, and pathological data were recorded prospectively and analyzed retrospectively. This study has been approved by the research ethics committee of Kobe University.

The preoperative diagnosis of IVCTT and surgical treatment indication was described previously (11). In short, IVCTT was diagnosed based on the identification of an intraluminal filling defect in the IVC by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Several imaging modalities were used to assess the status of disease progression and determine indications for treatment. Indications of surgical hepatectomy were selected based mainly on the general condition of the patient, liver function, and local tumor involvement. Liver function was assessed by biochemical tests, Child-Pugh classification, and indocyanine green retention rate at 15 minutes (ICGR15); poor liver function and multiple extrahepatic metastases are contraindications for surgical hepatectomy. Major hepatectomy included hepatectomy with resection of at least three Couinaud segments. After surgery, all patients underwent physical examinations, blood tests, CT, or MRI every 3 months and were followed until death or December 31, 2019.

Statistical analysis

Survival rate was evaluated by the Kaplan-Meier method and compared using the log-rank test. For all statistical analyses, numerical values are expressed as median (range) or mean ± standard deviation. P-values<0.05 was considered as statistically significant. In addition, all statistical analyses were performed using the JMP 13 statistical package. The present study was conducted in accordance with the ethical standards set forth by the Declaration of Helsinki, and all patients provided written informed consent.

RESULTS

Patients characteristics

A total of 20 patients who underwent surgical hepatectomy for HCC with IVCTT were enrolled in the study. Patients' demographic and clinical characteristics are described in Table I. The median age was 67.5 years. Most of the patients were classified as Child-Pugh classification A (n=19), and background liver diseases were mainly hepatitis B (n=8) or not virus-related disease (n=8). Approximately 90% of the operative procedures was major hepatectomy. Among them, nine cases (45%) required thoracotomy and there were four cases of extended right hepatectomy, four cases of extended left hepatectomy, and one case of left hepatic trisegmentectomy. Moreover, three cases (15%) required extracorporeal circulation and there were two cases of extended left hepatectomy and one case of left hepatic trisegmentectomy.

Table I. Demographic and clinical characteristics of the 20 patients.

Patient characteristics	Overall population
Age (year)	67.5 (42-81)
Sex (M/F)	19/1
Child Pugh classification (A/B)	19/1
Hepatitis virus type (HBV/HCV/NBNC)	8/4/8
ICGR15 (%)	11.2 (3.7-23.9)
Number of tumors	3 (1-11)
Maximal tumors size (cm)	9.9 (3.5-23)
Serum AFP (ng/ml)	472 (3-107343)
Serum PIVKAII (mAU/ml)	8513 (236-746100)
Operative time (min)	638±177
Blood loss (ml)	1605 (580-6650)
Operative procedure	
(extended) Right hepatectomy	10 (50%)
(extended) Left hepatectomy	7 (35%)
Segmental resection	1 (5%)
Subsegmentectomy	1 (5%)
Left hepatic trisegmentectomy	1 (5%)
Median hospital stays (days)	19 (15-27.3)

ICG, indocyanine green; AFP, α-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist-II

The postoperative clinical course categorized by R0/R1 resection is summarized in Figure 1. Among the 20 patients, 11 patients (55%) achieved R0 resection. After R0 resection, one patient did not have recurrence and died due to infection 61.6 months after surgery. The remaining 10 patients (90.9%) had recurrence. Eight patients had intrahepatic recurrence; three patients underwent trans arterial chemoembolization plus radiation therapy, three patients underwent trans arterial chemoembolization, one patient underwent trans arterial chemoembolization plus sorafenib chemotherapy, one patient received ablation therapy plus sorafenib chemotherapy, and one patient received supportive care. The remaining two patients had lung metastasis; one patient underwent surgical resection and one patient received radiation therapy; these two lung metastasis patients were the only survivors. After R1 resection, two patients (22.2%) had only residual HCC; one patient received radiation therapy and one patient received supportive care. Five patients (55.6%) had lung metastasis; two patients received trans arterial chemoembolization plus sorafenib chemotherapy, one patient received trans arterial chemoembolization plus sorafenib chemotherapy plus radiation therapy, one patient received trans arterial chemoembolization plus sorafenib chemotherapy plus percutaneous intrahepatic perfusion therapy, and one patient received sorafenib chemotherapy. Two patients (22.2%) had brain and lung metastases; one patient received radiation therapy plus sorafenib chemotherapy and one patient received sorafenib chemotherapy.

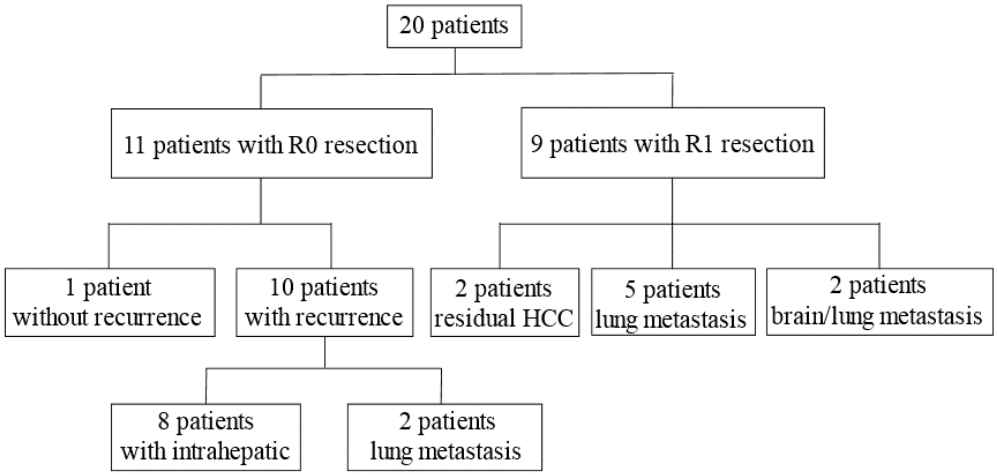

Figure 1. Postoperative treatment flowchart categorized by R0/R1 surgery

Univariate and multivariate analysis for overall survival

Figure 2 shows the cumulative survival rate of all patients. The median survival time was 9.8 months. The 12- and 36-months survival rates were 35% and 12%, respectively. Among the 18 cases of death, 12 cases (66.7%) died of HCC recurrence in the remnant liver. There were three cases of metastasis: two cases of lung metastasis and one case of brain metastasis. The remaining causes of death were two cases of infections and traffic accidents.

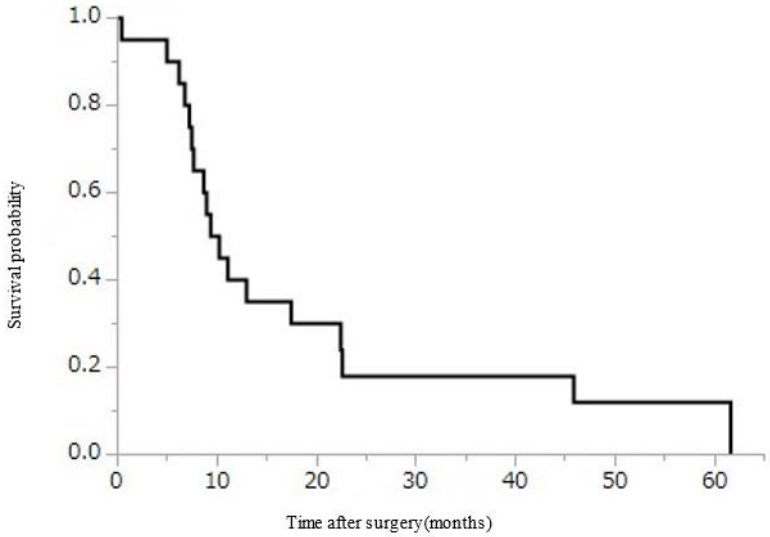

Figure 2. The cumulative survival rate of all the patients.

Table II shows the univariate analysis to identify variables associated with overall survival rates. Number of tumors (solitary vs. multiple; p=0.050) and pathological Vp (pVp0 vs. other; p=0.009) were identified as risk factors for overall survival. In the multivariate analysis, pathological Vp (pVp0 vs. other; p=0.037) was identified as a significant prognostic factor for survival (Table III).

Table II. Univariate analysis of clinicopathological factors for overall survival rates.

Variables	n (%)	HR [95%CI]	P value
Age (<65 years)	7 (35)	1.12 [0.40-2.93]	0.824
Sex (Male)	19 (95)	1.69 [0.33-30.9]	0.590
Child Pugh classification (A)	19 (95)	0.55 [0.10-10.2]	0.600
Hepatitis virus type (NBNC)	8 (40)	0.37 [0.12-1.01]	0.054
ICGR15 (<10 %)	8 (40)	1.53 [0.53-4.36]	0.421
Number of tumors (Solitary)	5 (25)	0.32 [0.07-1.00]	0.050
Maximal tumors size (<10 cm)	10 (50)	0.56 [0.20-1.53]	0.256
Serum AFP (<20 ng/ml)	5 (25)	2.05 [0.64-5.80]	0.214
Serum PIVKAII (<10000 mAU/ml)	11 (55)	0.57 [0.20-1.57]	0.278
Operative time (<600 min)	9 (45)	0.50 [0.17-1.33]	0.164
Blood loss (<1000 ml)	7 (35)	0.48 [0.13-1.43]	0.197
Need thoracotomy (Present)	9 (45)	0.82 [0.30-2.16]	0.697
Need extracorporeal circulation (Present)	3 (15)	0.61 [0.10-2.22]	0.497
Median hospital stays (<20 day)	11 (55)	0.97 [0.37-2.61]	0.953
Clavien-Dindo classification (<III)	16 (80)	0.50 [0.17-1.81]	0.265
Residual tumor (Present)	9 (45)	1.76 [0.67-4.74]	0.248
pVp (pVp0)	4 (20)	0.12 [0.006-0.64]	0.009

ICG, indocyanine green; AFP, α-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist-II
HR, Hazard ratio; CI, Confidence intervals

Table III. Multivariate analysis of clinicopathological factors for overall survival rates.

Variables	HR [95%CI]	P value
Number of tumors (solitary)	0.48[0.10-1.58]	0.242
pVp (pVp0)	0.16[0.008-0.91]	0.037

HR, Hazard ratio; CI, Confidence intervals

Impact of tumor number on survival

As the number of tumors was identified as a risk factor for overall survival in the univariate analysis, Kaplan-Meier analysis was additionally performed. Figure 3 shows the cumulative survival rate of all patients categorized by the number of tumors. Overall survival for the patients with a solitary tumor and multiple tumors was 45.8 months and 8.6 months, respectively. Although survival was superior for patients with solitary tumors compared to patients with multiple tumors throughout the follow-up period, the difference was not statistically significant (p=0.063). Among the five patients with solitary tumors, two patients (40.0%) were categorized as Vp0, while among the 15 patients with multiple tumors, only two patients (13.3%) were categorized as Vp0.

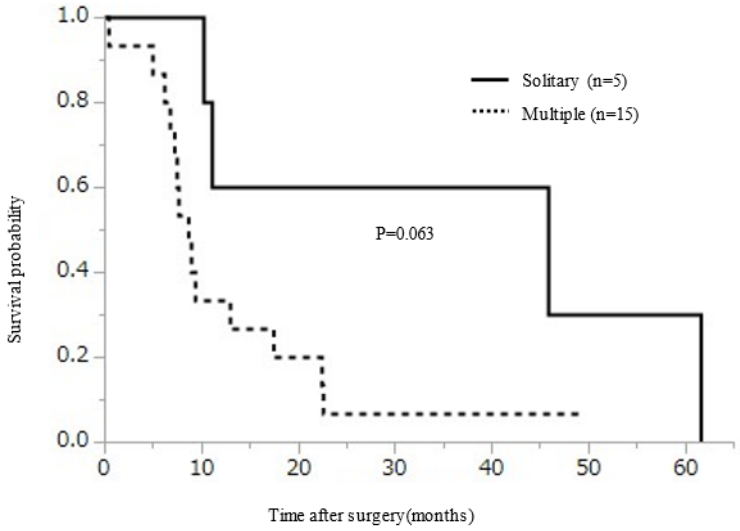

Figure 3. The cumulative survival rate of all the patients categorized by the number of tumors

Impact of portal vein invasion on survival

As portal vein invasion was identified as a risk factor for overall survival in the univariate and multivariate analyses, Kaplan-Meier analysis was additionally performed. Figure 4A shows the cumulative survival rate of all patients categorized by portal vein invasion. Overall survival for the patients with Vp0 and others were 53.7 months and 9.1 months, respectively (p=0.022). Figure 4B shows the cumulative survival rate of each of the patient group divided by pVp0, pVp1, and pVp2-4. The median survival times were 53.7 months with pVp0, 10.2 months with pVp1, and 8.8 months with pVp2-4 (p=0.035). Figure 5 shows the flowchart of all the patients categorized by image Vp (iVp), surgical (sVp) and pVp. iVp (p=0.405) and sVp (p=0.853) were not associated with overall survival.

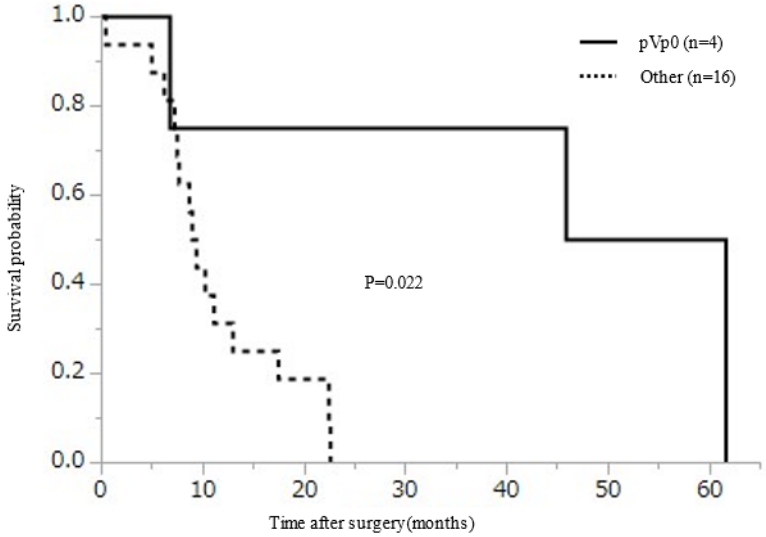

Figure 4A. The cumulative survival rate of all the patients categorized by portal vein invasion

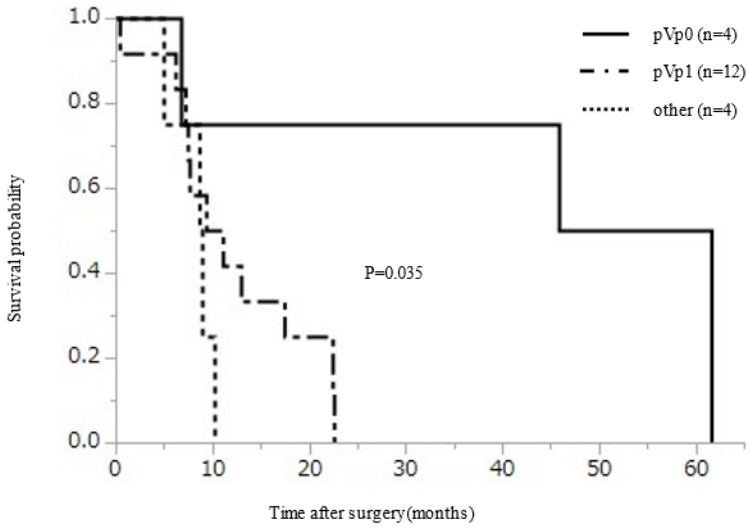

Figure 4B. The cumulative survival rate of all the patient group categorized by pVp0, pVp1, and pVp2-4

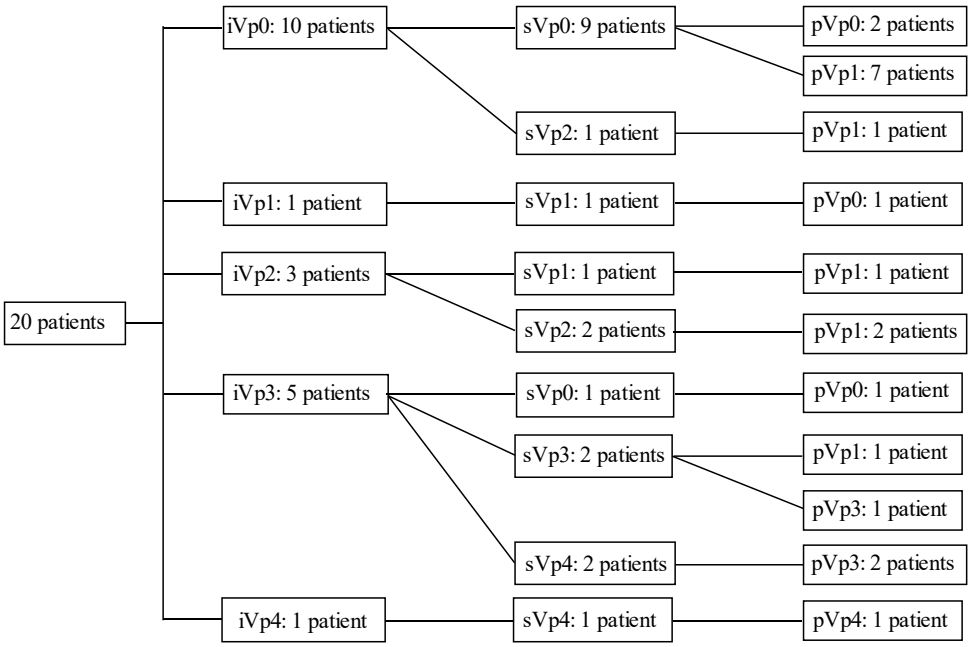

Figure 5. The flowchart of all the patients categorized by iVp, sVp and pVp

DISCUSSION

The current study revealed that the median survival time of IVCTT patients was 9.8 months and the identified risk factor was pVp. pVp affected overall survival even among the patients with IVCTT, and the median survival time was extended with pVp0 in patients by as long as 53.7 months.

There are only a few reports with very small sample sizes from single center experiences investigating the outcome and prognosis of HCC patients with IVCTT (4) (6) (17) (18) (19). The indications for hepatectomy in patients with this type of refractory HCC differ in each of the facilities. In general, patients with poor liver function, multiple extrahepatic metastases, and in cases where R0 resection is judged to be difficult, surgical hepatectomy is considered a contraindication at most facilities. At our facility, we included patients who could not achieve R0 resection because we could perform additional treatment of percutaneous isolated hepatic perfusion to the remaining HCC (7). In fact, we could achieve only 55% R0 resection in our patients. Regarding the patient baseline characteristics, only 40% of our patients had 1–2 HCC tumors and the average tumor size was 100.0 mm, suggesting that our study consisted of more advanced stage HCC patients that may have been excluded from surgical indication at other facilities. The identified risk factor was pVp0. This is the most prominent fact revealed in our study; Vp does affect overall survival even among highly advanced HCC patients with IVCTT, whose survival is expected to be within 1 year.

Based on a Japanese nationwide survey, it was revealed that the presence or absence of portal vein tumor thrombus affected overall survival among patients with major hepatic vein tumor thrombus (9). However, whether the portal vein tumor thrombus could be a prognostic factor among IVCTT patients was not analyzed in the study. Our study provided an answer to this question as even among patients with IVCTT, the presence of portal vein tumor thrombus still affects overall survival.

Among the patients who underwent R0 resection, the average duration from surgery to recurrence was 1571 days with Vp0 patients vs. 162.7 days with others. It might be suggested that for Vp0 patients, recurrence occurs at a much later point compared to the other patients, and accordingly, additional treatment could be successfully completed. Further studies should be performed to reveal the differences in molecular mechanisms between portal vein tumor and hepatic vein tumor invasion. Unfortunately, other Vp factors, such as image Vp and surgical Vp, were not associated with overall survival. We have only two survivors, and both of them underwent R0 resection followed by lung metastasis. Based on our data, it could be suggested that for IVCTT patients, surgical hepatectomy could be recommended only for those who could undergo R0 resection with no portal vein invasion.

A limitation of our data is the scarcity of case numbers and the transition of treatment disciplines. For a decade, the only systematic therapy with a proven survival benefit of 10.7 months vs. 7.9 months in the phase III SHARP trial was the multikinase inhibitor sorafenib, which was approved as the first-line treatment for HCC in the United

States and the European Society (15). After a number of failed trials evaluating other kinase inhibitors, lenvatinib, an oral tyrosine kinase inhibitor, demonstrated improved outcomes for HCC patients in a phase III REFLECT trial in 2017, and it has been available for clinical use in Japan since March 2018 (12). As the follow-up period in our study was until their death or December 31, 2019, we only included one patient who received lenvatinib after surgical hepatectomy. Additional survival benefits might be achieved by a combination of surgical hepatectomy plus postoperative lenvatinib administration. The other treatment option is novel proton radiotherapy. We have previously presented data that particle radiotherapy is potentially preferable in HCC patients with stage IIIB IVCTT with significantly fewer complications in a matched-pair analysis (11). The weakness of the strategy is that proton radiotherapy is not covered by insurance and, accordingly, not all patients could select the treatment option.

In conclusion, the median survival time of IVCTT patients with pVp0 was 53.7 months. For patients who do not have portal vein invasion and could achieve R0 resection, surgical hepatectomy should be indicated. For other IVCTT patients, systematic therapy or proton radiotherapy should be discussed.

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