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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Downstaging with Localized Concurrent Chemoradiotherapy Can Identify Optimal Surgical Candidates in Hepatocellular Carcinoma with Portal Vein Tumor Thrombus

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ABSTRACT

Background. Locally advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) has a poor oncological outcome. This study evaluated the oncological outcomes and prognostic factors of surgical resection after downstaging with localized concurrent chemoradiotherapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC).

Methods. From 2005 to 2014, 354 patients with locally advanced HCC underwent CCRT followed by HAIC. Among these patients, 149 patients with PVTT were analyzed. Exclusion criteria included a total bilirubin $\geq$ 2 mg/dL, platelet count $<$ 100,000/μL, and indocyanine green retention test (ICG R15) $>$ 20%. During the same study period, 18 patients with PVTT underwent surgical resection as the first treatment. Clinicopathological characteristics and oncological outcomes between groups were compared.

Results. Among 98 patients in the CCRT group, 26 patients (26.5%) underwent subsequent curative resection. The median follow-up period was 13 months (range 1–131 months). Disease-specific survival differed significantly between the resection after localized CCRT group and the resection-first group {median 62 months (95% confidence interval [CI] 22.99–101.01) versus 15 months (95% CI 10.84–19.16), respectively; P = 0.006}. Multivariate analyses showed that achievement of radiologic response was an independently good prognostic factor for both disease-specific survival (P = 0.039) and disease-free survival (P = 0.001)

Conclusions. Localized CCRT could be an effective tool for identifying optimal candidates for surgical treatment with favorable tumor biology. Furthermore, with a 26.5% resection rate and 100% response in PVTT for resection after CCRT, our localized CCRT protocol may be ideal for PVTT.

Portal vein tumor thrombosis (PVTT) has been identified in 10–40% of hepatocellular carcinoma (HCC) patients at their initial visit.[1,2] Major vascular invasion is one of the most important factors in recurrence after resection.[3,4] Intrahepatic metastasis by the portal venous system is considered an important mechanism for intrahepatic recurrence.[5] While prognosis is poor, the optimal treatment for HCC with major vascular invasion remains controversial.[6] According to the Barcelona Clinic Liver Cancer (BCLC) classification, portal invasion is categorized as an advanced stage with a median survival of 7.9 months, and only palliative treatment with sorafenib has been recommended.[7]

Several modalities have been attempted in order to increase survival, but overall survival (OS) rarely exceeded 1 year.[1,8] Surgical resection results were found to be superior, with median survival ranging from 8 to 33 months;[9] however, these results were based on varying degrees of PVTT, with the possibility of high selection

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bias. Associated operative mortality percentages were reported to be 0–6%.[1] Further investigations regarding increasing resectability of advanced HCCs using multimodal treatments have also been undertaken.[10–12]

Our institution has implemented localized concurrent chemoradiotherapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC) for HCC with PVTT since 1998.[13] Since then, the indications for CCRT followed by HAIC have widened and have included unresectable or borderline resectable locally advanced HCCs with insufficient functional residual liver volume (FRLV), major vessel invasions, and adjacent organ invasions. Lee et al.[10] reported that localized CCRT followed by HAIC led to curative resection of advanced HCCs in 16.9% of cases by increasing the FRLV and downstaging the tumor; however, their results were based on heterogeneous tumor stages, including T1–T4, according to the 7th American Joint Committee on Cancer (AJCC) staging systems,[14] and underlying liver function was not considered during the comparisons.

In this study, we have limited our analysis to HCC with PVTT, stage IIIB, according to the 7th AJCC staging system. We evaluated the impact of localized CCRT followed by HAIC on subsequent resection, and compared this with resection as the first treatment in an intention-to-treat analysis.

METHODS

Patient Selection

From January 2005 to December 2014, 149 treatment-naive patients received localized CCRT followed by HAIC, for HCC with PVTT, at our institution. A flow diagram of patient selection is shown in electronic supplementary Fig. 1. Concurrently, 18 treatment-naive patients underwent resection for HCC with PVTT. PVTT was defined to include only the first- and second-order branches. Assessment of PVTT was achieved using preoperative dynamic triphasic contrast-enhanced computed tomography (CT) that was completed in all patients. Macroscopic PVTT was determined when portal venous expansion was present with intrathrombus enhancement and the presence of continuity between the tumor mass and the thrombus.[15] To minimize patient selection bias, we excluded patients with decompensated liver function at initial presentation. According to guidelines presented by the European Association for the Study of the Liver (EASL), a very well-preserved liver function was defined as normal bilirubin with a platelet count $\geq$ 100,000/μL.[16] Hence, we excluded patients with initial laboratory results showing total bilirubin $\geq$ 2 mg/dL and platelet counts $<$ 100,000/μL. Patients with bilobar tumors, extrahepatic metastasis, or concurrent malignancies were also excluded as subsequent curative resection was not possible. Furthermore, patients with initial indocyanine green retention test (ICG R15) $>$ 20% were excluded because major liver resections are generally contraindicated in these patients.[17] After exclusions, a retrospective review of 98 patients belonging to the localized CCRT group, and 18 belonging to the resection group, was conducted. The resection criteria were the same as the patient selection criteria, with well-preserved liver function.

Treatment Protocol For treatment planning purposes, each patient in the localized CCRT group underwent three-dimensional (3-D) CT simulation to determine target volumes, dosages, and radiation ports, as previously described.[18] A total of 45 Gy was prescribed in 25 fractions of 1.8 Gy over 5 weeks using a 6 or 10 MV linear accelerator.

The dose and treatment protocols for concurrent HAIC with 5-flurouracil and HAIC following localized CCRT were as previously described.[13] Concurrent HAIC was delivered during the first and fifth weeks of radiotherapy, and HAIC with 5-fluorouracil and cisplatin was administered 1 month after the localized CCRT. The number of cycles ranged from 3 to 12.

Response Evaluation After every three cycles of repeated HAIC, the radiological response was assessed using abdominal pelvis CT according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[19] Radiological responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). If progression was detected during the assessment, the repeated HAIC was stopped. A radiological response was defined as the achievement of CR or PR. Serum α-fetoprotein (AFP) and protein induced by the absence of vitamin K, or antagonist-II (PIVKA-II), were also evaluated at every three cycles of HAIC. Tumor markers were required to be decreased to $<$ 20 ng/mL and 40 mAU/mL for AFP and PIVKA-II, respectively, prior to resection. Tumor resectability was assessed by surgeons prior to localized CCRT, then at every radiological response evaluation. Subsequent resection was considered if CT scans at any HAIC cycle revealed that all gross lesions could be removed with a clear margin. Resection type decisions were based on liver functional reserve and patient performance status. For major hepatectomy, a minimum of 40% of the total liver volume was required as an FRLV. Major resection was defined as resection of three or more adjacent anatomical segments, as described by Couinaud.[20]

The Clavien et al.[21] classification was used to stratify postoperative complications. After the operation, patients were followed up at 1 month and then at 3-month intervals

for early diagnosis of possible disease recurrence using dynamic CT, and AFP and PIVKA-II levels.

Statistical Analysis All statistical analyses were performed using the Statistical Package for Social Sciences, version 20 (IBM Corporation, Armonk, NY, USA). For each quantitative variable, the Shapiro–Wilk test was used as a test of normality. Various tests (the independent *t* test, Mann–Whitney U test, Chi square test, or Fisher's exact test) were applied as warranted for between-group comparisons. Survival parameters were analyzed using the Kaplan–Meier method, and compared using the log-rank test. A Cox proportional hazards model was used for multivariate survival analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Concurrent Chemoradiotherapy (CCRT) Versus Resection Groups

Clinicopathological characteristics between the groups are shown in Table 1. The median follow-up period for both groups was 13 months (range 1–131 months). The results of AFP, PIVKA-II, and ICG R15 were determined prior to any treatment from the time of initial diagnosis, while tumor size was determined from radiological findings. Disease-specific survival (DSS) was measured from the date of initial treatment. Radiological responses in the CCRT group were as following: 62 patients (63.3%) with PD, 13 patients (13.3%) with SD, 18 patients (18.4%) with PR, and five patients (5.1%) with CR. DSS did not significantly differ between the localized CCRT and resection groups {median 13 months (95% confidence interval [CI] 10.10–15.90) versus 15 months (95% CI 10.84–19.16); $P = 0.323$} [Fig. 1].

Resection After CCRT Versus Resection Groups

Among 98 patients in the CCRT group, 26 (26.5%) underwent subsequent curative resection. The median follow-up period for both groups was 26 months (range 2–118 months), median time to resection after CCRT was 7 months (range 3–15 months), and median cycle of HAIC before resection was 3.5 cycles (range 1–9 cycles).

TABLE 1 Patient characteristics of the CCRT versus resection groups

Variables	CCRT [*N* = 98]	Resection [*N* = 18]	*P*-Value
Age, years (± SD)	54.29 ± 11.90	48.67 ± 9.30	0.060
Male sex [*n* (%)]	78 (79.6)	14 (77.8)	> 0.999
Etiology of cirrhosis [*n* (%)]			0.923
HBV	84 (85.7)	15 (83.3)	
HCV	3 (3.1)	1 (5.6)	
Alcoholic	1 (1.0)	0	
Non-B, non-C	10 (10.2)	2 (11.1)	
PVTT location [*n* (%)]			< 0.001
First-order	80 (81.6)	4 (22.2)	
Second-order	18 (18.4)	14 (77.8)	
AFP, ng/mL	1937 (1.39–360,068)	877 (2.44–120,000)	0.973
PIVKA-II, mAU/mL	2000 (19–75,000)	1086 (114–14,230)	0.371
ICG R15, %	10 (3–20)	10 (1–19)	0.247
Tumor size, cm[a]	9.0 (2.5–20.0)	5.9 (3.0–15.0)	0.003
Tumor number [*n* (%)]			0.489
1	70 (71.4)	15 (83.3)	
2	9 (9.2)	1 (5.6)	
3	10 (10.2)	0	
> 4	9 (9.2)	2 (11.1)	
Platelet count, 10^3/uL	188.5 (101–625)	174.5 (101–352)	0.251
Albumin, g/dL	4.1 (2.6–5.0)	4.3 (2.3–5.0)	0.253
Total bilirubin, mg/dL	0.80 (0.30–1.80)	0.60 (0.30–1.95)	0.435

CCRT concurrent chemoradiotherapy, *SD* standard deviation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *PVTT* portal vein tumor thrombus, *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II, *ICG R-15* indocyanine green retention rate at 15 min

[a]Tumor size was measured from initial computed tomography imaging

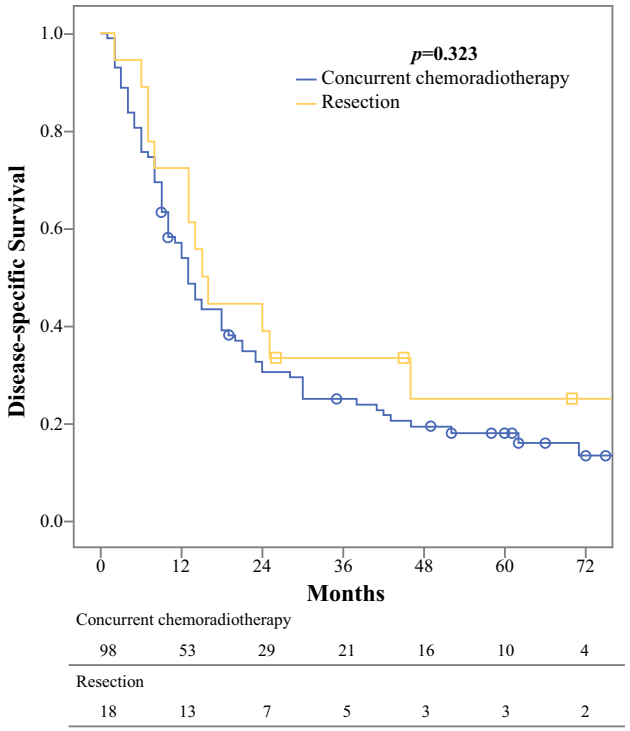

FIG. 1 Disease-specific survival of the concurrent chemoradiotherapy versus resection groups

Clinicopathological characteristics of the two groups are shown in Table 2.

Radiological responses in the resection after CCRT group showed that five patients (19.2%) had CR, 13 (50.0%) had PR, and eight (30.8%) had SD. Five patients (27.8%) with PR were not able to undergo subsequent resection because of hepatic decompensation (three patients) or gastrointestinal bleeding (two patients). Among patients with SD, three (37.5%) underwent resection because further HAIC was not possible because of hepatic arterial catheter migration or obstruction. The remaining patients with SD were determined resectable by surgeons at the response evaluation examination.

Comparisons of DSS between the resection after CCRT and resection groups showed significant differences (median 62 months [95% CI 22.99–101.01] versus 15 months [95% CI 10.84–19.16], respectively; $P = 0.006$). Disease-free survival (DFS) of these groups also revealed significant differences (median 32 months [95% CI 3.47–60.54] versus 3 months [95% CI 2.03–3.97], respectively; $P = 0.002$) [Fig. 2]. Further comparison of DSS after recurrence showed no significant differences between the two groups (median 14 months [95% CI 10.71–17.29] for resection after CCRT, and 12 months [95% CI 5.69–18.31] for resection; $P = 0.511$].

Postoperative Complications

The rate of complications was significantly higher in the resection after CCRT group (Table 2). Four complications in the resection group were all grade I, requiring conservative management for ascites. In the resection after CCRT group, nine cases (56.2%) were grade I, resulting from wound complications or ascites. Two cases (12.5%) were grade II, resulting from biloma and pneumonia and requiring pharmacologic treatment. The remaining five cases (31.3%) were grade IIIA, requiring pigtail insertion for biloma. No mortality was associated with resection in all cases.

Independent Prognostic Factors for Oncological Outcomes After Resection

The prognostic factors were evaluated for all resection patients. The median DFS was 7 months (95% CI 0.636–13.364), and median DSS was 42 months (95% CI 13.581–70.419). In univariate analyses, age, sex, baseline tumor markers, and Edmonson–Steiner grade[22] did not have any significant role in oncological outcomes. The results of multivariate analyses are shown in Table 3. The subgroup analyses of PVTT location, tumor size, and extent of resection were also performed. While PVTT in the first order was an independent poor prognostic factor in oncological outcomes, DFS was significantly longer for the resection after CCRT group (median 11 months [95% CI 0.001–50.256] versus 2 months [95% CI 0.693–3.307], respectively; $P = 0.002$). Patients with tumor size > 5 cm showed better DFS in the resection after CCRT group (median 14 months [95% CI 0.001–36.296] versus 3 months [95% CI 2.265–3.735], respectively; $P = 0.001$). Furthermore, patients with major resection also showed better DFS in the resection after CCRT group (median 31 months [95% CI 0.001–66.274] versus 3 months [95% CI 2.218–3.782], respectively; $P = 0.028$).

DISCUSSION

According to the BCLC staging system, the AJCC 7th edition staging of IIIB is not a candidate for surgical resection; however, several reports have shown that selected patients with advanced HCC may benefit from surgical resection.[9,23–27] Reported 1-year OS and DFS rates were 38.4–52.1% and 13.6–21.1%, respectively, for patients with PVTT in first-order or higher branches.[9] Our study results from the resection group showed that 1-year DSS was 61.1% and 1-year DFS was only 16.7%. Undoubtedly, the presence of PVTT represents aggressive biological features of HCC.[1] In addition, PVTT is also associated with larger tumor size and higher levels of

TABLE 2 Clinicopathologic characteristics between the resection after CCRT versus resection groups

Variables	Resection after CCRT [*N* = 26]	Resection [*N* = 18]	*P*-Value
Mean age, years (± SD)	50.04 ± 10.91	48.67 ± 9.30	0.666
Male sex [*n* (%)]	22 (84.6)	14 (77.8)	0.697
Etiology of cirrhosis [*n* (%)]			0.544
HBV	22 (84.6)	15 (83.3)	
HCV	0	1 (5.6)	
Alcoholic	1 (3.8)	0	
Non-B, non-C	3 (11.5)	2 (11.1)	
Portal vein thrombosis location [*n* (%)]			0.036
First-order	14 (53.8)	4 (22.2)	
Second-order	12 (46.2)	14 (77.8)	
Location of tumor [*n* (%)]			0.742
Right lobe	19 (73.1)	12 (66.7)	
Left lobe	7 (26.9)	6 (33.3)	
Type of resection [*n* (%)]			0.021
Major resection	24 (92.3)	11 (61.1)	
Minor resection	2 (7.7)	7 (38.9)	
Operation time, min	289 (149–630)	232 (173–344)	0.003
Intraoperative bleeding, ml	550 (30–5000)	575 (50–3600)	0.745
Perioperative transfusion [*n* (%)]	9 (34.6)	3 (16.7)	0.303
Postoperative complications [*n* (%)]	16 (61.5)	4 (22.2)	0.010
Preoperative AFP, ng/mL	68 (2–120,000)	877 (2–120,000)	0.052
Preoperative PIVKA-II, mAU/mL	626 (19–38,233)	1086 (114–14,230)	0.274
Preoperative ICG R15, %	12.3 (2.7–20.0)	9.9 (0.8–19.5)	0.042
Pathologic tumor size, cm	4.4 (1.5–14.0)	6.4 (2.5–15.5)	0.096
Microvessel invasion [*n* (%)]	18 (69.2)	18 (100)	< 0.001
Portal vein invasion [*n* (%)]	0	18 (100)	< 0.001
Tumor necrosis, %	100 (0–100)	10 (0–50)	< 0.001
Resection margin, cm	1.2 (0.1–4.5)	1.4 (0.1–6.0)	0.665
Adjuvant therapy [*n* (%)]	6 (23.1)	8 (44.4)	0.135
Recurrence [*n* (%)]	17 (65.4)	15 (83.3)	0.384
Intrahepatic	12 (46.2)	9 (50.0)	
Systemic metastasis	5 (19.2)	6 (33.3)	

CCRT concurrent chemoradiotherapy, *SD* standard deviation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II, *ICG R-15* indocyanine green retention rate at 15 min

AFP.[28] While surgical resection may be the only hope for a cure, reliable patient selection criteria for resection have not yet been reported. Selecting patients based on clinical characteristics for resection has shown limited value, with low curability and high recurrences. Therefore, we need a better tool to help select optimal candidates for surgical treatment in patients with PVTT.

Previous studies have been based on heterogeneous downstaging agents, and tumor characteristics were also heterogeneous, with various reasons for unresectability. In this study, we applied a single standardized downstaging protocol using localized CCRT followed by HAIC, which was reported to have a substantial response.[13] We also included the results of resection as the first treatment for HCC with PVTT. Use of the same anatomical resection principle employed in both treatment groups may reduce bias from surgical techniques.

While discernible advantages were not present in the initial comparison of the CCRT and resection groups, comparisons of the resection after CCRT and resection groups showed significant benefits in oncological outcomes (Fig. 2). Our results of 26 patients (26.5%) undergoing resection following downstaging were higher than the previously reported percentages of 8–18%.[12] The resection rate after CCRT was more pronounced in second-order PVTT, at 50% (9 of 18 patients), whereas the resection rate

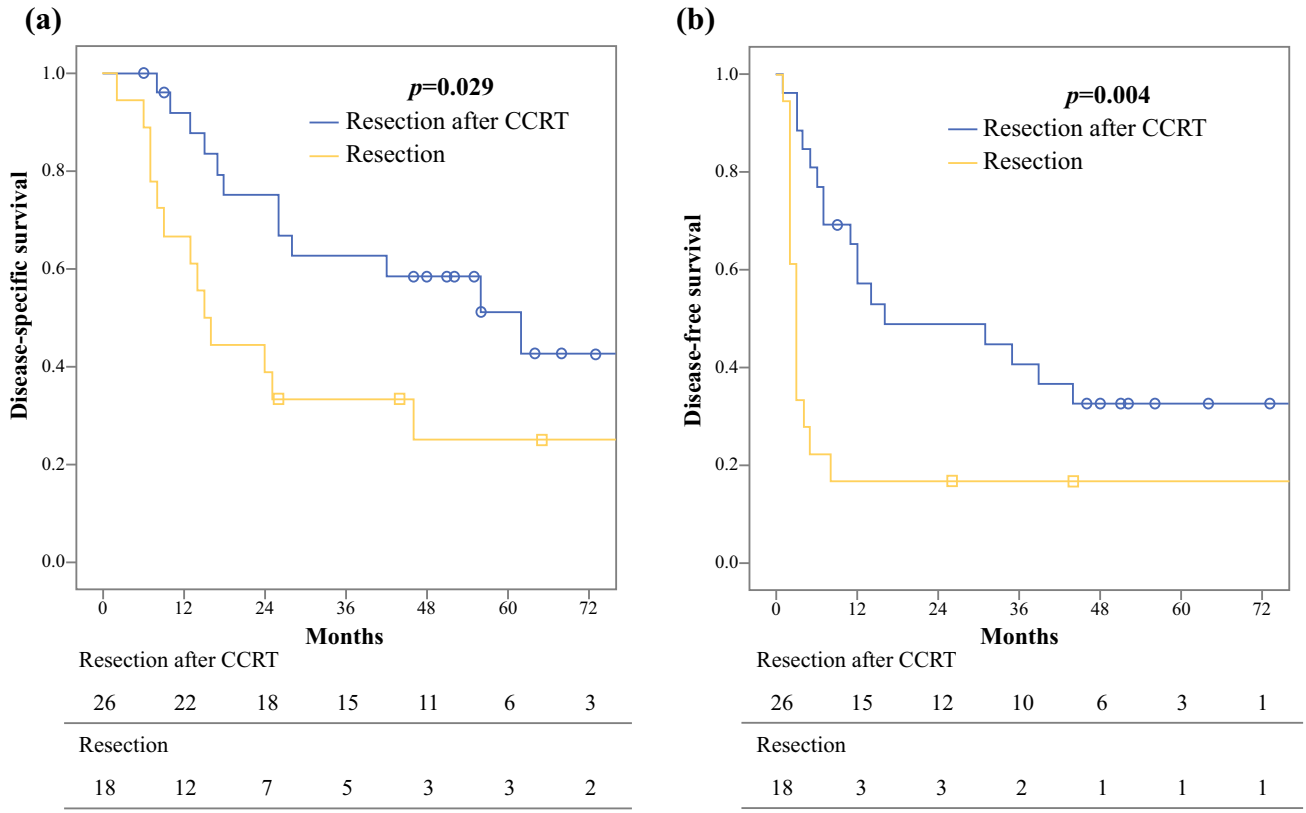

FIG. 2 **a** Disease-specific survival and **b** disease-free survival of the resection after CCRT versus resection groups. *CCRT* concurrent chemoradiotherapy

TABLE 3 Multivariate analysis of factors influencing oncologic outcomes after resection

	Variables	HR	95% CI	*P*-Value
DFS	PVTT in first-order	6.211	2.164–17.857	0.001
	Tumor size (> 5 cm)	3.866	1.022–14.950	0.049
	Minor resection	5.520	1.669–18.257	0.005
	Radiologic response			
	Resection first	Reference		0.006
	SD/PR	0.052	0.006–0.459	0.008
	CR	0.010	0.001–0.169	0.001
DSS	PVTT in first-order	5.236	1.515–18.182	0.009
	Tumor size (> 5 cm)	5.899	1.092–31.879	0.039
	Minor resection	7.013	1.638–30.018	0.049
	Radiologic response			
	Resection first	Reference		0.100
	SD/PR	0.142	0.018–1.131	0.065
	CR	0.040	0.002–0.845	0.039

HR hazard ratio, *CI* confidence interval, *DFS* disease-free survival, *PVTT* portal vein tumor thrombus, *SD* stable disease, *PR* partial response, *CR* complete response, *DSS* disease-specific survival

[a]Tumor size was measured from initial computed tomography imaging

for first-order PVTT was 21% (17 of 80 patients). Three patients were downstaged from first-order PVTT to second-order PVTT at the time of resection. These results could be translated into the following: (1) second-order PVTT has favorable tumor biology with better response; and (2) CCRT may have a role in selecting patients with more favorable tumor biology, even in first-order PVTT with known aggressive tumor biology. In terms of response to PVTT, the resection after CCRT group showed 100% response, with no portal vein invasion in final pathology examinations. The benefits of localized CCRT also included an increased resection rate and/or increased FRLV.[10] These benefits may translate into providing resection under lower-risk conditions during recovery.

PVTT in first-order branches, tumor size > 5 cm, and minor resections were independent poor prognostic factors for both recurrence and OS after resection. Shi et al.[9] have also shown that the proximal location of PVTT was an independent prognostic factor of poor survival after resection. Although PVTT had been completely resolved prior to resection, the risk of poor oncological outcomes associated with PVTT involving the first-order branch was not diminished. Localized CCRT does not alter tumor biology; however, better DFS was shown in the resection after CCRT group, regardless of PVTT location. This

implied that the response to localized CCRT may effectively select for patients with favorable tumor biology among patients with PVTT.

While the biliary complication rate was higher in the resection after CCRT group (43.8% vs. 0%), favorable oncologic outcome justified this finding. Frequent biliary complications may be associated with poor arterial perfusion, causing easier duct ischemia and impaired bile duct healing from fibrosis after radiotherapy.[29]

In an Asian population, 80–90% of HCC cases developed on the background of cirrhotic liver disease.[30] Localized CCRT on a cirrhotic liver always carries a risk of decompensated liver failure as a treatment-related toxicity. In such cases, patients have undergone living donor liver transplantation.[31] However, the current study showed no serious treatment-related toxicities.

The limitations of this study include its retrospective nature and the limited sample size. While patient selection criteria only included patients with well-preserved liver function for an intention-to-treat analysis, resection may not have been possible in some cases due to inadequate FRLV. Furthermore, since the report of favorable outcome with CCRT by Han et al. in 2008, the initial treatment decision may have been biased. These factors could have influenced the results with more favorable baseline disease in the resection group. Furthermore, there were insufficient numbers to evaluate the role of CCRT in resection, therefore we combined all resection cases to evaluate associated prognostic factors. This approach may have a confounding influence on the results due to the effects of CCRT on tumor characteristics. Further prospective studies with more patients undergoing resection after localized CCRT are warranted to correlate the role of localized CCRT with the optimal surgical candidates.

CONCLUSIONS

The role of localized CCRT in aggressive tumor biology of PVTT is uncertain. Downstaging achieved with localized CCRT could be an effective tool for identifying optimal candidates for surgical treatment with favorable tumor biology. Furthermore, with a 26.5% resection rate and 100% response in PVTT for resection after CCRT, our localized CCRT protocol may be ideal for PVTT.

CONFLICTS OF INTEREST Jae Uk Chong, Gi Hong Choi, Dai Hoon Han, Kyung Sik Kim, Jinsil Seong, Kwang-Hyub Han, and Jin Sub Choi have no conflicts of interest to declare.

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