Impact on Prognosis Following Nonanatomical Resection of Hepatocellular Carcinoma Postoperatively Proven as Micro Portal Vein Tumor Thrombus on Histology

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Objective: The prognostic impact of intrahepatic recurrence pattern and/or operative procedure (anatomical resection [AR] and nonanatomical resection [NAR]) for hepatocellular carcinoma (HCC) in patients with postoperatively proven portal vein tumor thrombus on histology has not yet been clearly examined.

Summary of background data: A total of 52 HCC patients who had no visible macroscopic vascular invasion preoperatively and histologically proven portal vein tumor thrombus distal to second-order portal branches after surgery were analyzed.

Methods: The overall survival and disease-free survival rates were analyzed using the Kaplan-Meier method. The risk factors for intrahepatic recurrence and distant metastasis were analyzed using the log-rank test.

Results: There was no significant difference in the overall survival rates at 5 years, based on the operative procedure. The disease-free survival rates at 3 years were 59.2% (AR group) and 30.1% (NAR group), respectively, and were statistically significant. Intrahepatic recurrence in the same remnant segment was seen in 5 patients undergoing NAR. These cases developed multiple bilobar recurrences simultaneously, including the same segment,

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and recurrence only in the same remnant segment was not seen in any case, irrespective of solitary or multiple recurrence.

Conclusions: Intrahepatic recurrence in the same remnant segment does not influence the disease-free survival rate in patients after NAR. Although AR would be an ideal procedure, the current study suggests NAR can achieve identical outcomes for patients who cannot be considered for AR.

Key words: Hepatocellular carcinoma – Tumor thrombus – Anatomical resection – Nonanatomical resection – Intrahepatic recurrence

Hepatocellular carcinoma (HCC) has received major clinical attention because of its increasing incidence worldwide.[1] Although liver transplantation has provided an alternative to surgical management of HCC,[2] liver resection remains the mainstay of treatment, offering hope of a cure. However, the long-term outcome remains unsatisfactory because of the high incidence of tumor recurrence, and intrahepatic recurrence is the most common form of recurrence.[3,4] Intrahepatic embolism secondary to vascular invasion is one of the most common causes for recurrence of HCC. HCC has a propensity to invade the portal vein, resulting in intrahepatic spread as a macroscopic or microscopic portal vein tumor thrombus (PVTT).[4,5] The grade of PVTT (Vp) detected on preoperative imaging is classified into 4 categories by the Liver Cancer Study Group of Japan[6]; Vp0, no PVTT; Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branches of the portal vein; and Vp4, tumor thrombus in the main trunk.

Macroscopic vascular invasion (Vp2 or more) has an important influence on treatment selection and can be detected on imaging examinations preoperatively, but identification of microvascular invasion (Vp0 or 1) requires histologic examination, which limits the preoperative assessment of prognosis.[7,8] When macroscopic vascular invasion (Vp2 or more) is detected during the pretreatment clinical diagnosis, anatomical resection (AR) of no less than 1 segment is indispensable, because the first or second portal branch must be excised to eliminate tumor thrombus. However, when no macroscopic vascular invasion (Vp0 or 1) is observed preoperatively, both AR and nonanatomical resection (NAR: partial hepatic resection) can theoretically be considered. AR is preferable, because it can eliminate the spread of cancer.[9] On the other hand, NAR is performed in patients with considerably impaired liver function

and in those with a minimal tumor located at the junction between different liver segments. In fact, NAR can only be performed for tumors diagnosed without PVTT (Vp0 and Vp1).

To understand metastasis via the portal venous system, we focused on tumors histologically proven as micro PVTT (Vp1) postoperatively. The purpose of this study was to examine the influence of intrahepatic recurrence based on the operative procedure, and the intrahepatic recurrence pattern in patients undergoing liver resection, and to assess the outcomes of NAR for tumors with absence of macroscopic PVTT during the pretreatment imaging.

Patients and Methods

Patient characteristics

The subject pool consisted of patients who underwent open liver resection for HCC between January 2006 and December 2012 at Kobe University School of Medicine and Hyogo Cancer Center. Patients who met the following criteria were included in this study: (1) no macroscopic vascular invasion seen on pretreatment imaging; (2) no extrahepatic metastasis; (3) potentially curative resection defined as complete removal of all detectable tumor; (4) no preoperative anti-HCC therapy; and (5) histologically proven PVTT in distal to second-order portal branches (Vp1). A total of 52 patients were enrolled, and the baseline clinical characteristics of patients are shown in Table 1. The median age was 69 years old, ranging from 33 to 81 years. Among them, 49 and 3 patients had Child-Pugh score class A and B, respectively. Twenty-two and 35 patients revealed a serum alpha-fetoprotein (AFP) level of ≥100 ng/mL and serum protein induced by vitamin K absence or antagonist II (PIVKAII) level of ≥100 mAU/mL. The present study was conducted according to the Helsinki Declaration, and written informed consent was obtained from all patients. This study was

Table 1   Patient characteristics

Variables	No. of patients (%)
Age, yr	
≤70	20 (38)
>70	32 (62)
Sex	
Male	43 (83)
Female	9 (17)
Positive viral marker	
Hepatitis B virus	8 (16)
Hepatitis C virus	21 (40)
None	23 (44)
Child-Pugh classification	
A	49 (83)
B	3 (17)
ICG R15, %	
<20	36 (69)
≥20	16 (31)
Serum AFP, ng/mL	
<100	31 (60)
≥100	21 (40)
Serum PIVKAII, mAU/mL	
<100	18 (35)
≥100	34 (65)

AFP, alpha-fetoprotein; ICG R15, indocyanine green retention rate at 15 minutes; PIVKAII, prothrombin induced by vitamin K absence or antagonist II.

Table 2   Baseline clinical characteristics

Variables	No. of tumors (%)
Tumor size (mm)	
≤30	9 (17)
>30, ≤100	30 (58)
>100	13 (25)
Differentiation	
Well	4 (8)
Moderate	41 (79)
Poorly	6 (12)
Undifferentiated	1 (1)
Capsule formation	
Yes	48 (92)
No	4 (8)
Surgical margin	
Negative	49 (94)
Positive	3 (6)
Fibrosis of background liver	
F0-F2	25 (48)
F3-F4	23 (44)
Unknown	4 (8)
Existence of pathologic vv and/or va and/or b	
No	48 (92)
Yes	4 (8)
Operative procedure	
Nonanatomical resection	19 (37)
Anatomical resection	33 (63)

approved by the institutional review board at Kobe University in 2017 (approval 170219).

Tumor characteristics and operative procedure

All patients enrolled in the present study had tumors with microvascular invasion, which was defined as invasion of HCC through the vascular endothelium, visible only on microscopy, but not detected on pretreatment imaging. The clinicopathologic characteristics of the tumors are summarized in Table 2. The tumor size and width of the surgical margin were recorded before the specimens were fixed. The histologic grade of differentiation of the tumor, the degree of fibrosis in the liver tissue, and the presence/absence of vascular invasion were also assessed microscopically, based on the classification system proposed by the Liver Cancer Study Group of Japan.[6] AR is defined as a resection in which lesions are completely excised anatomically, based on Couinaud's classification (segmentectomy, sectionectomy, and hemihepatectomy or more). In a NAR, a surgical margin of at least 5 mm from the tumor edge was secured whenever possible. When it was not possible, liver parenchymal transection was performed without exposing the tumor surface, allowing enucleation of the tumor.

Follow-up and evaluation criteria

Patients underwent follow-up investigations every 3 months for 3 years and every 6 months thereafter. Investigations included tumor markers serum AFP, PIVKAII levels, and abdominal imaging studies (computed tomography or magnetic resonance imaging). Hepatic angiography was performed when intrahepatic recurrence was suspected. If tumor recurrence was detected, second liver resection, transcatheter arterial chemoembolization, or locoregional ablation such as radiofrequency ablation was recommended depending on liver function, liver volume, tumor size, and tumor location.

Statistical analysis

The overall survival and disease-free survival rates were analyzed using the Kaplan-Meier method. The risk factors for intrahepatic recurrence and distant metastasis were analyzed using the log-rank test. A Cox proportional hazards regression model was used to analyze independent risk factors. $P < 0.05$ was considered significant. All statistical analyses were performed using the JMP 10 statistical package.
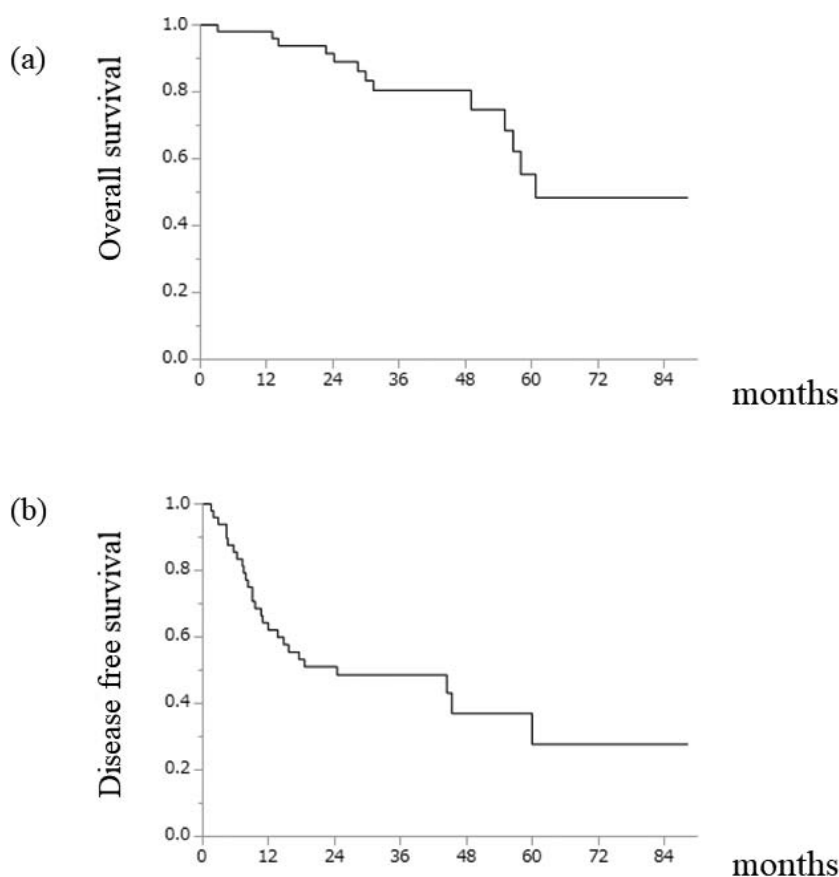
Fig. 1 (a) Overall survival rate of all patients. (b) Disease-free survival rate of all patients.

Results

Overview

The overall survival rates of 52 patients at 3 and 5 years were 80.5% and 55.4%, respectively, with a median follow-up period of 43 months (Fig. 1a). Among the 52 patients, 25 had an intrahepatic recurrence and 15 had distant metastasis at the last follow-up. The disease-free survival rates of all cases at 3 and 5 years were 48.6% and 27.8%, respectively, and the median time to recurrence was 13.9 months (Fig. 1b). The overall survival rates at 5 years according to the operative procedure were 53.4% (AR group) and 59.0% (NAR group), respectively, and there was no significant difference between the 2 groups (Fig. 2a).

Risk factors for postoperative recurrence

To identify the risk factors for postoperative recurrence, the cumulative recurrence rates were compared for 13 clinically plausible factors (Table 3). Among the risk factors for recurrence examined, the operative procedure was the only independent factor that significantly affected the disease-free survival rate in univariate analysis ($P < 0.05$; Table 4; Fig. 2b). Furthermore, a subgroup analysis of patients whose tumor size was <5 cm revealed a similar outcome (data not shown). There was no significant difference in overall survival rates according to the operative procedure (Fig. 2a).

Patterns of intrahepatic and distant recurrence

Of the 15 patients with distant metastasis, the sites included the lungs (n = 12), bones (n = 3), lymph nodes (n = 3), and peritoneal dissemination (n = 1). Of these, the appearance of distant metastasis preceded intrahepatic recurrence in 6 patients. Table 5 shows the first intrahepatic recurrence site after liver resection of both groups. In the NAR group, intrahepatic recurrence in the same remnant segment was seen in 5 patients. However, all these patients developed multiple bilobar recurrences simultaneously, including the same remnant segment. No patient developed recurrence only in the same remnant segment, whether the type of recurrence was solitary or multiple.
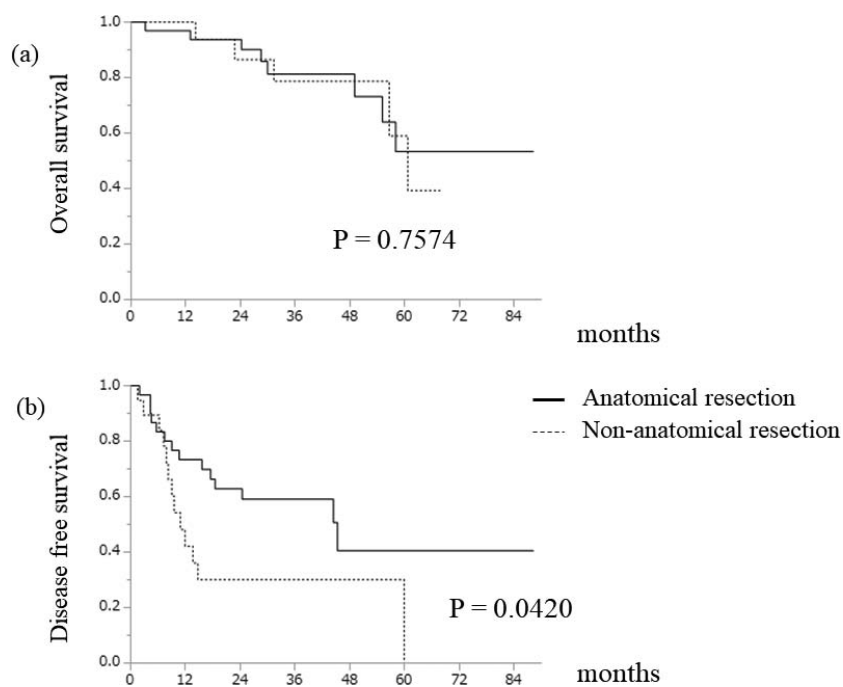
Fig. 2 (a) Overall survival rates according to the operative procedure. (b) Disease-free survival rates according to the operative procedure.

Table 3 Univariate analysis of factors related to patient characteristics

Factors	No. of patients (%)	Disease-free survival	
		Rate at 3 years (%)[a]	Univariable P[b]
Age, yr			0.8306
$\leq$70	20 (38)	45.0	
>70	32 (62)	51.1	
Sex			0.2642
Male	43 (83)	52.1	
Female	9 (17)	33.3	
Positive viral marker			0.4017
Hepatitis B virus	8 (16)	37.5	
Hepatitis C virus	21 (40)	42.2	
None	23 (44)	59.7	
Child-Pugh classification			0.7732
A	49 (83)	50.1	
B	3 (17)	33.3	
ICG R15, %			0.7054
<20	36 (69)	50.1	
$\geq$20	16 (31)	45.7	
Serum AFP, ng/mL			0.1396
<100	31 (60)	57.7	
$\geq$100	21 (40)	36.4	
Serum PIVKAII, mAU/mL			0.1037
<100	18 (35)	70.8	
$\geq$100	34 (65)	36.8	

AFP, alpha-fetoprotein; ICG R15, indocyanine green retention rate at 15 minutes; PIVKAII, prothrombin induced by vitamin K absence or antagonist II.

[a]Kaplan-Meier analysis.

[b]Log rank test.

Table 4   Univariate analysis of factors related to patient characteristics

Factors	No. of tumors (%)	Disease-free survival	
		Rate at 3 years (%)[a]	Univariable P[b]
Tumor size (mm)			0.2971
≤50	16 (31)	57.1	
>50	36 (69)	45.3	
Differentiation			0.8835
Well-moderate	45 (87)	45.8	
Poorly undifferentiated	7 (13)	66.7	
Capsule formation			0.5946
Yes	48 (92)	47.2	
No	4 (8)	75.0	
Fibrosis of background liver			0.9454
F0-F2	25 (48)	57.5	
F3-F4	23 (44)	40.9	
Unknown	4 (8)	-	
Existence of pathologic vv and/or va and/or b			0.3063
No	48 (92)	49.5	
Yes	4 (8)	40.0	
Operative procedure			0.0420
Nonanatomical resection	19 (37)	30.1	
Anatomical resection	33 (63)	59.2	

[a]Kaplan-Meier analysis.

[b]Log rank test.

Discussion

Until now, various factors influencing the risk of recurrence of HCC have been reported, including tumor size, tumor number, vascular invasion, the presence of satellite nodules, histopathologic grade, underlying cirrhosis, and type of surgery.[9–12] Nevertheless, it is still debatable as to what extent the surgical strategy might contribute to reducing the risk of intrahepatic tumor recurrence. Several retrospective studies compared the survival benefits of AR and NAR for the treatment of HCC, and several authors have described the survival benefits of AR in select patients compared with NAR.[9,13–18]

However, these retrospective analyses might reflect selection bias in that NAR may have been preferred to AR in patients with poor liver function, which strongly affects the incidence of postoperative recurrence of HCC based on the nature of multicentric carcinogenesis.[15,19,20] Moreover, because the resection volume is generally larger in AR than in NAR, the lesser remnant liver volume is potentially less likely to cause intrahepatic recurrence after liver

Table 5   Site of initial intrahepatic recurrences after hepatectomy

Recurrence site	No. of patients	
	Nonanatomical resection (n = 12)	Anatomical resection (n = 13)
Recurrence in the same segment (SS)		—
Solitary recurrence only in the SS	0	—
Multiple recurrences only in the SS	0	—
Bilobar recurrences including the SS	5	—
Recurrence in the distal segment		
Solitary recurrence only in the same lobe	1	0
Solitary recurrence only in the distal lobe	4	3
Multiple recurrences only in the same lobe	0	2
Multiple recurrences only in the distal lobe	0	6
Multiple bilobar recurrences	1	1
Recurrence at the resection stump	1	1

resection. This difference was quite evident in the retrospectively designed studies, which could be caused by the selection bias of patients undergoing AR. Considered together, the aforementioned findings suggest that the previously reported superiority of AR to NAR is potentially because of the differences in liver function and HCC stage. Therefore, the previous studies are not clinically helpful in decision making for the preoperative selection of AR or NAR.[19,21] AR is preferred over NAR in liver resection performed with curative intent, because micrometastases disseminate via portal venous branches.[9,13] However, clinically, we are often faced with a decision to perform limited resection in patients with considerably impaired liver function, because tumors without PVTT in the pretreatment imaging (Vp0 and Vp1) are theoretically resected by NAR.[22]

In this study, as well as in previous reports, the disease-free survival rate of NAR was significantly lower than that of AR (Fig. 2b). However, no intrahepatic recurrence occurred in the same remnant segment alone after NAR. Among 12 patients who developed intrahepatic recurrence after NAR, 5 patients had recurrence in the same segment. Nonetheless, all these cases developed bilobar recurrences at the first recurrence after liver resection, at the same time including the same remnant segment. It indicates that intrahepatic recurrence does not influence the disease-free survival rate in patients after NAR. It appears that the disease-free survival rates would have been the same, even if the NAR patients had undergone AR, although more data confirming the same is required. There have been no reports describing the treatment outcomes with special focus on the site of intrahepatic recurrence pattern and its influence on prognosis after liver resection.

Our study has some limitations. The sample size was small, and therefore, comparisons between the results obtained for the 2 groups might be of limited value. Many uncertainties remain regarding our concept, which is a limitation in direct acceptance of the outcomes. We considered the disease-free survival of patients after NAR, based on the supposition that if he/she had undergone the AR. Previous studies compared the patients having a completely different background, whereas we assessed patients focusing only on intrahepatic recurrence pattern after the surgery. This is totally a new concept and includes some clinically relevant evidence.

Conclusion

For the surgical treatment of HCCs, the balance between curability and preservation of hepatic function is important. Considering that intrahepatic recurrence can occur via the portal venous system, it seems that AR, that is, resection of the tumor with the surrounding portal territory, would be an ideal treatment for HCC. However, the current study indicates that NAR can be performed for patients unsuitable to undergo AR without affecting prognosis.

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