

Salvage Surgery for Initially Unresectable Locally Advanced Hepatocellular Carcinoma Downstaged by Hepatic Arterial Infusion Chemotherapy

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Abstract. *Background/Aim:* Recent studies have demonstrated the efficacy of salvage surgery following downstaging of hepatocellular carcinoma (HCC). The aim was to assess the outcomes of salvage surgery after successful downstaging using hepatic arterial infusion chemotherapy (HAIC). *Patients and Methods:* Patients whose diagnosis was unresectable locally advanced HCC and who were resected after conversion to a resectable status by HAIC were included. The overall survival (OS) rate, and disease-free survival (DFS) rate were analyzed by stratifying patients into those with Vp3/4, Vv2/3, and those without major vascular invasion (MVI). *Results:* Eighteen patients were censored. Among them, six patients had Vp3/4, four patients had Vv2/3, and eight patients had no MVI. The 5-year OS rates of patients with Vp3/4 and those without MVI were 83% and 73%, respectively, whereas those with Vv2/3 had 0% ($p < 0.001$). *Conclusion:* Salvage surgery has the potential to provide excellent outcomes in resectable HCC patients, except for those with Vv2/3.

Among patients with unresectable locally advanced hepatocellular carcinoma (HCC), some patients can be converted to be technically resectable, although no consensus exists regarding the optimal therapeutic strategy for these patients. In clinical practice, downstaging followed by salvage surgery is performed for some of these patients, and some researchers have reported favorable outcomes (1-8). The aim of this study was to analyze the survival benefit of

downstaging with hepatic arterial infusion chemotherapy (HAIC) followed by salvage surgery for initially unresectable locally advanced HCC by stratifying patients according to the presence or not of major vascular invasion (MVI).

Patients and Methods

Study population. Patients who underwent hepatectomy for HCC at our institution between 1999 and 2013 were identified. Among these patients, those whose diagnoses were initially unresectable HCC due to locally advanced disease and were resected after successful downstaging using HAIC were included. We divided patients into three groups by tumor extent at initial diagnosis: tumors with Vp3 (first-order branches of the portal vein)/Vp4 (main trunk or opposite first branch of the portal vein) vascular invasion (Group A), tumors with Vv2 (main trunk of the hepatic vein)/Vv3 [inferior vena cava (IVC) or right atrium (RA)] vascular invasion (Group B), and tumors without MVI (Group C), which includes tumors without Vp3/4 or Vv2/3 vascular invasion. Overall survival (OS) rates, disease-free survival (DFS) rates, and patterns of recurrence were analyzed by reviewing medical record. This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies, and the ethics committee of our institution approved this research (No. 17149).

Hepatic arterial infusion chemotherapy. HAIC was performed after placement of an injection port implanted in a subcutaneous pocket. The tip of the catheter was placed at the common hepatic artery or proper hepatic artery. Low-dose 5-FU/cisplatin (FP) via the injection port was used as the HAIC regimen (9). The first course of chemotherapy consisted of daily administration of cisplatin (7 mg/m²) followed by 5-FU (170 mg/m²) on days 1 to 5, for 1 and 5 h, respectively, by mechanical infusion pump. After cessation of chemotherapy on days 6 and 7, patients received an additional 4 cycles of chemotherapy to complete induction chemotherapy. One or two months after the initial four cycles of induction HAIC, patients received an additional 2 or 4 cycles of low-dose FP based on tumor regression and/or complications; this was repeated continuously until disease progression (9). The response to HAIC was evaluated by CT after 4 cycles of HAIC and every 2 months according to the modified Response Evaluation Criteria in Solid Tumors (10). Senior surgeons assessed resectability during multidisciplinary meetings.

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Key Words: Downstaging, hepatocellular carcinoma, low dose FP, salvage surgery.

Table I. Baseline patient characteristics.

Variables	Pre-chemotherapy	Pre-hepatectomy	p-Value
Age, years, median (range)	68.5 (46-79)		
Gender, male, n (%)	12 (66)		
Etiologies, n (%)			
HCV/HBV/Non-B, -C	9 (50)/5 (28)/4 (22)		
Child-Pugh score 5/6 (%)	18 (100)/0 (0)	16 (89)/2(11)	0.089
ICG-R15 (%), median (range)		20.2 (6.1-49.9)	
AFP (ng/ml), median (range)	3748 (17.8-270,000)	31.8 (2.7-10,452)	0.026
PIVKA-II (mAU/ml), median (range)	3106 (81-32,200)	210 (5-22,456)	0.041
Tumor size, cm, median (range)	71 (15-150)	56 (5-85)	0.012
Tumor size >10 cm, n (%)	5 (28)	0 (0)	0.005
Tumor size reduction rate, n (%)		32.2 (13.3-66.7)	
Tumor number, median (range)	2 (1-5)	1.5 (1-3)	0.328
Single, n (%)	7 (39)	9 (50%)	0.502
Multiple, n (%)	11 (61)	9 (50%)	0.502
T stage*			
T2/T3a/T3b, n (%)	1 (5)/7 (39)/10 (56)	4 (22)/4 (22)/10 (56)	0.252
Macroscopic PVTT, n (%)	9 (50)	9 (50)	
vp2/vp3/vp4, n (%)	3(17)/4(22)/2(11)	3(17)/5(26)/1(5)	0.798
Macroscopic HVT, n (%)	4 (22)	4 (22)	
vv2/vv3, n (%)	1(5)/3(17)	2(11)/2(11)	0.462

HCV: Hepatitis C virus; HBV: hepatitis B virus; ICG-R15: indocyanine green retention rate at 15 min; AFP: α -fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; PVTT: portal vein tumor thrombus; HVT: hepatic vein tumor thrombosis. *According to the American Joint Committee on Cancer 7th TNM classification.

Surgical treatment and technique. The objective of surgery was to resect all detectable lesions with tumor-free margins. In patients with multiple bilateral tumors that could not be resected by a single hepatectomy and for lesions <2 cm, concomitant radiofrequency ablation therapy (RFA) was performed. Thrombectomy was performed in patients with Vp4 vascular invasion under temporary clamping of the main portal vein. Among patients with Vv3 vascular invasion, in case the tumor thrombosis was located in the IVC, a total hepatic venous exclusion procedure (THVE) was applied (11). In case Vv3 vascular invasion extended into the RA, the patient was placed on cardiopulmonary bypass and a longitudinal incision was made from the RA to the IVC under cardiac arrest and THVE, and then the tumor thrombosis was removed under direct view.

Statistical analysis. Continuous variables were expressed as median (range). Student's *t*-test, χ^2 test, or Fisher's exact test was used where appropriate to compare the clinical parameters between the two groups. Survival data were analyzed using the Kaplan-Meier method. Survival curves were compared using the log-rank test. OS was calculated from the date of initial HAIC until death or last follow-up. DFS was calculated from the date of hepatectomy until recurrence or last follow-up. For all tests, $p < 0.05$ was defined as indicating a statistically significant difference. Statistical analysis was performed using the JMP version 13.0 software program (SAS Institute, Cary, NC, USA).

Results

Patients and tumor characteristics before and after HAIC. Between 1999 and 2013, 1,020 patients with HCC underwent hepatic resection at our institution. Among these, 18 patients

underwent resection after successful downstaging using HAIC. Patients were classified as having Vp3/4 (Group A; n=6), Vv2/3 (Group B; n=4), or no MVI (Group C; n=8) at diagnosis. Clinical and pathological patient characteristics are listed in Table I. The median tumor size was 71 mm (range=15-150 mm) and 5 patients (28%) had tumors >100 mm; however, the median tumor size decreased to 56 mm (range=5-85 mm) after HAIC ($p=0.012$). Eleven patients (61%) had multiple tumors before treatment and nine patients (50%) had multiple tumors after HAIC ($p=0.328$). The median levels of both tumor markers, AFP and PIVKA-II, were elevated at 3,748 ng/ml (range=17.8-270,000 ng/ml) and 3,106 mAU/ml (range=81-3,220 mAU/ml), respectively, at diagnosis, but they decreased to 31.8 ng/ml (range=2.7-10,452 ng/ml) and 210 mAU/ml (range=5.0-22,456 mAU/ml), respectively, after HAIC ($p=0.026$ and 0.041 , respectively). All patients in Groups A and B had tumor thrombosis shrinkage, whereas in 2 patients (11%), regression of tumor thrombosis from Vp4 to Vp3 and Vv3 to Vv2, respectively, was observed.

Hepatic arterial infusion chemotherapy. The modality, duration, and efficacy of HAIC are summarized in Table II. All patients received low-dose FP, and 8 of 18 patients (44%) underwent additional TACE. The mean period of chemotherapy was 5.1 months (range=1.0-25.4 months). Fifteen patients (83%) achieved a PR and were converted to

Table II. Downstaging chemotherapy and operative findings.

Variables	Median (range)	Number of patients (%)
Additional TACE		8 (44)
Duration of chemotherapy, months	5.2 (1-25)	
Objective response PR/SD		15 (83)/3(17)
Type of resection		
Right tri sectionectomy		1 (5)
Extended right hepatectomy		1 (5)
Right hepatectomy		6 (33)
Left tri sectionectomy		1 (5)
Extended left hepatectomy		3 (17)
Left hepatectomy		2 (10)
Extended posterior sectionectomy		1 (5)
Anterior sectionectomy		1 (5)
Segmentectomy		2 (10)
Resection margin, mm	12.7 (1-25)	
Operation time, min	500 (380-1,080)	
Amount of bleeding, ml	1,240 (230-9,115)	

**p*-Value: pre-downstaging chemotherapy vs. post-downstaging chemotherapy.

resectable status. In addition, 3 patients with stable disease (SD), even after HAIC, experienced some degree of tumor shrinkage and were also converted to resectable status.

Surgical procedures. Overall, 14 of 18 patients underwent major hepatectomy. Concomitant RFA was performed in 1 patient. In 9 patients, tumor thrombectomy was necessary. Extracorporeal circulation was required in 1 case with RA tumor thrombosis and THVE was necessary in 1 case with IVC tumor thrombosis. The median operation time was 500 min (range=380-1,080 min) with a median amount of bleeding of 1,240 ml (range=230-9,115 ml). All patients achieved macroscopic R0 resection (Table II).

Short- and long-term outcomes. All patients were discharged without in-hospital mortality. OS and DFS of patients are shown in Figure 1. The median observation time was 58.5 months (range=9.5-122.6 months). The 1-, 3-, and 5-year OS rates were 94.4%, 83.3%, and 58.7%, respectively. The 1-, 3-, and 5-year DFS rates were 61.1%, 33.3%, and 33.3%, respectively. OS by different patient groups is shown in Figure 2. The 1-, 3-, and 5-year OS rates in Group A were 100%, 100%, and 83%, respectively, and those in Group C were 100%, 100%, and 73%, respectively. The 1-, 3-, and 5-year OS rates in Group B were 75%, 50%, and 0%, respectively. DFS of downstaged patients by group are shown in Figure 3. The 1-, 2-, and 3-year DFS rates in Group A were 100%, 33%, and 33%, respectively and those in Group C were 62%, 50%, and 50%, respectively. With respect to DFS in Group B, all patients experienced recurrences within 1 year. The OS and DFS rates in Group B were worse

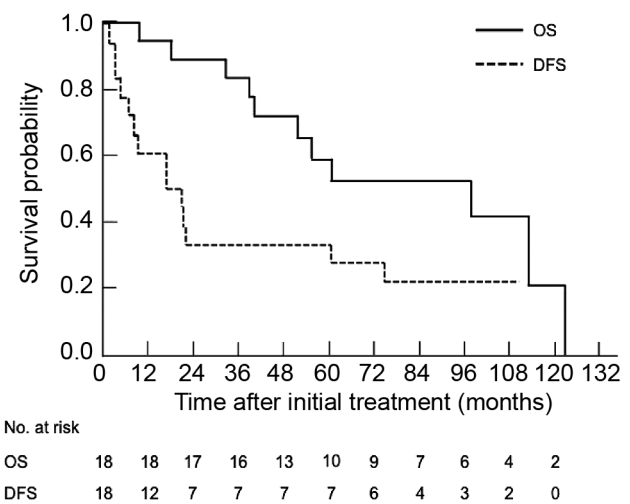


Figure 1. Overall survival and disease-free survival of downstaged patients (n=18).

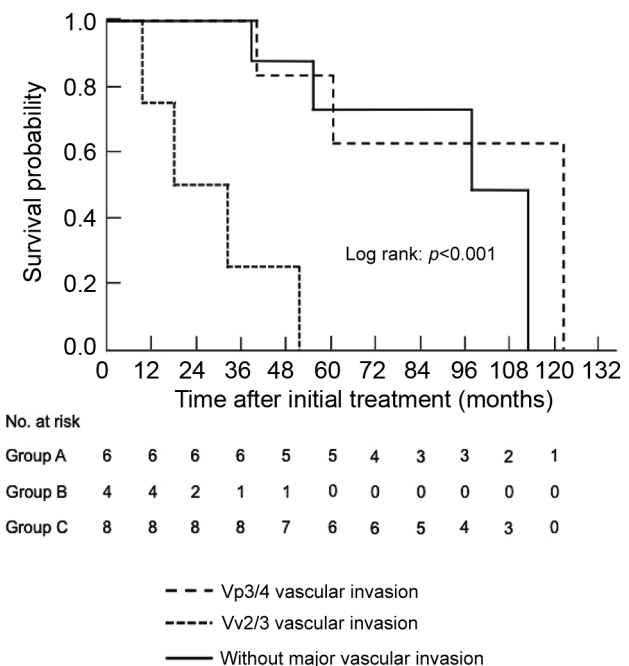


Figure 2. Overall survival rate by stratifying patients into those with Vp3/4, Vv2/3, and those without major vascular invasion. $p<0.001$ by log-rank test.

compared to those in Groups A and C ($p<0.001$ and $p<0.001$, respectively). Overall, 14 of 18 patients (78%) experienced postoperative recurrences. In Group A, 1 patient had metastasis to the bone and 4 patients had a single intrahepatic recurrence.

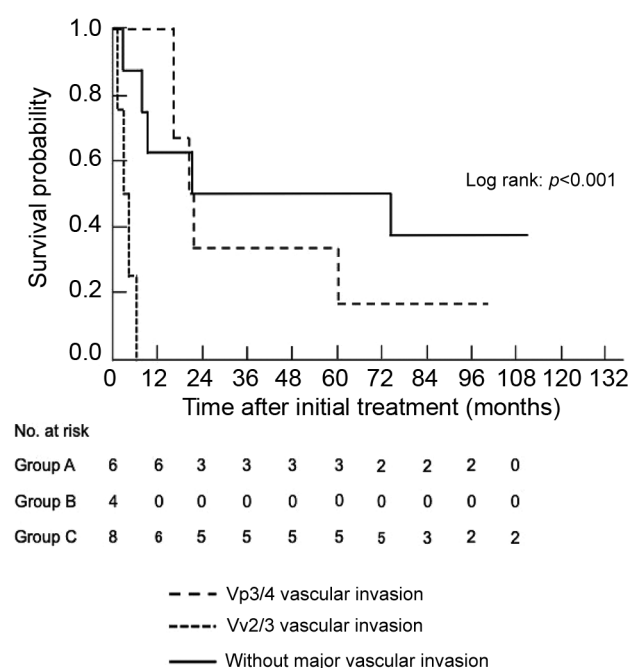


Figure 3. Disease-free survival rate by stratifying patients into those with Vp3/4, Vv2/3, and those without major vascular invasion. $p<0.001$ by log-rank test.

In Group B, 2 patients had metastasis to the lung, 1 patient had lung metastases accompanying by relapsed RA tumor thrombosis, and 1 patient had multiple intrahepatic recurrences. In Group C, 2 patients had metastasis to the lung and 3 patients had intrahepatic recurrences (Table III).

Discussion

We assessed the outcomes of salvage surgery in 18 patients who were successfully converted from unresectable to resectable status with HAIC using a low-dose FP regimen. Patients had different degrees of tumor extent, including Vp3/4, Vv2/3, and no MVI. Analysis of patients with different tumor characteristics demonstrated excellent outcomes especially in patients with Vp3/4 and those without MVI. There is no consensus about how to treat locally advanced HCC patients who respond well to chemotherapy and who have been converted technically from unresectable to resectable. In clinical practice, it is always difficult to decide whether these patients should be resected or not resected. However, our series of patients achieved a 5-year OS of 58.7% even though these patients were highly selected during chemotherapy. What is also interesting is that the OS and DFS rates of these two groups were almost the same even though their oncological malignant potential would be different. These results suggest that salvage surgery has the potential to provide excellent outcomes and a chance of cure by selecting

Table III. Site of recurrence after surgery and tumor characteristics.

Site of recurrence	Total number	Group A	Group B	Group C
Intrahepatic	8	4	1	3
Single	7	4	0	3
Multiple	1	0	1	0
Extrahepatic	7	1	4	2
Lung	5	0	3	2
Bone	1	1	0	0
RA tumor thrombus	1	0	1	0

RA: Right atrium.

patients during the chemotherapy period even if they were accompanied by major portal invasion or not. In contrast, OS and DFS of patients with Vv2/3 were dismal compared to those of other patients even after effective downstaging using HAIC. These patients had a high incidence of extrahepatic recurrence during the very early postoperative period, within 12 months after surgery, which affected OS. The existence of Vv2/3 is reported to be one of the poorest prognostic factors, with no established therapeutic strategies (12, 13). The reported median survival time (MST) of these patients who did not undergo surgical intervention has been reported to range from 5.5 to 9.5 months (12, 13). These patients have also a risk of sudden death caused by pulmonary embolism from the tumor thrombosis, especially patients with tumor thrombosis in the RA (12). These risks may justify surgical intervention even in patients with Vv2/3.

In the recent literature, downstaging followed by salvage surgery has been performed after multidisciplinary therapy including transarterial chemoembolization (TACE) (6, 7), HAIC (1, 2), immunotherapy (14), chemoradiotherapy (3, 4), and systemic chemotherapy (5, 8). The reported conversion rate of unresectable to resectable disease is 15-20%, with a 5-year OS rate of roughly 50%. No definitive evidence has been published in the medical literature to indicate which modality is the best for downstaging tumors in patients with unresectable HCC. We used HAIC as the downstaging modality because HAIC can deliver high concentrations of anti-cancer agents directly to the tumor and it also minimizes systemic toxicities due to first-pass effect (9). It has also been reported that HAIC is effective against HCCs with macroscopic portal vein tumor thrombosis and intrahepatic multiple tumors who had responded well to HAIC, with a MST of 31.6 months (9, 15). Additionally, we preferred HAIC, because TACE or yttrium-90 micro-spheres are contraindicated in patients with major portal vein tumor thrombosis, because of their potential risk of hepatic infarction caused by arterial complication (8). One problem of downstaging chemotherapy is that we cannot predict which patients will respond. However, an important role of downstaging chemotherapy might be the selection of patients who do not progress during chemotherapy, including those who

do not develop distant metastasis. These patients are ideal candidates for surgery due to having tumors with a lower malignant potential.

Conclusion

Salvage surgery after successful downstaging using HAIC can provide excellent outcomes, after selecting patients that are ideal surgical candidates, especially in patients with Vp3/4 and those without MVI.

Conflicts of Interest

All Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Yuichi Goto designed the study, and wrote the initial draft of the manuscript. Yuichi Goto and Toru Hisaka contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript.

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