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Feasibility of Reductive Hepatectomy in Patients With BCLC B and C Hepatocellular Carcinoma

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Abstract. *Background/Aim: Few studies have established a definite conclusion regarding the limitation of surgical treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage B and C hepatocellular carcinoma (HCC). Patients and Methods: A retrospective analysis was performed on 717 consecutive patients who underwent initial hepatectomy for HCC. Results: Reductive hepatectomy was performed in 103 patients, with a median survival time (MST) of 18.0 months. Total bilirubin and albumin levels were identified as independent prognostic factors. The predictive score of these factors ranged from 0 to 2. Subsequent local treatment was performed in 91.0, 75.0, and 25.0% of patients who scored 0, 1, and 2, respectively. The MST for patients with a score of 0, 1, and 2 was 20.1, 14.8, and 2.7 months, respectively, with a significant difference. Conclusion: Patients with BCLC stage B and C could be properly treated with reductive hepatectomy and subsequent local treatments.*

The Barcelona Clinic Liver Cancer (BCLC) classification is the most widely accepted staging system because it provides treatment indications and prognostic information of each hepatocellular carcinoma (HCC) stage (1, 2). Based on the BCLC classification, hepatectomy is recommended only for patients with BCLC stage 0 and A HCC, and palliative treatments are recommended for BCLC stage B and C HCC (3, 4). However, some controversies regarding the treatment of patients with BCLC stages B and C exist. Regarding BCLC classification, several studies showed the feasibility and effectiveness of expanding surgical indications to BCLC stage B and C patients (5-7). Although the Barcelona group modified the definition of BCLC stage A considering the results of previous studies, the indication of hepatectomy is still limited to curative treatment (8). Moreover, even when hepatectomy is indicated for patients with BCLC stage B and C, surgery is limited only to those patients that require curative resection.

To overcome this limitation, several investigators have advocated reductive hepatectomy, which is a combination of hepatectomy for the main tumor and local treatment for residual tumors in the remnant liver. We aimed to determine the predictive factors for reductive hepatectomy in patients with BCLC stage B and C to identify the best candidate for the procedure.

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Key Words: Hepatocellular carcinoma, reductive hepatectomy, Barcelona Clinic liver cancer stage, survival, predictive score.

Patients and Methods

Patient population. A total of 717 consecutive patients with HCC who underwent initial hepatectomy at Kobe University from January 2000 to December 2018 were enrolled in this study. HCC was diagnosed by dynamic contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI). As a preoperative check, biochemical tests, viral serological tests, coagulation tests, and serum alpha-fetoprotein (AFP) levels, were performed, and protein induced by vitamin K absence or antagonist II (PIVKA-II) was measured. Preoperative liver function was assessed using the Child–Pugh classification, indocyanine green retention rate at 15 min (ICG R15), and 99mTc-galactosyl human serum albumin scintigraphy.

Hepatectomy. Hepatectomy consisted of two types: complete hepatectomy and reductive hepatectomy. Complete hepatectomy was defined as surgery without macroscopic residual tumor or with microscopic positive surgical margin or as portal vein tumor thrombectomy without apparent residual tumors. Reductive hepatectomy was defined as initial surgery for the main tumor followed by subsequent local treatments of the residual tumors. Postoperative complications were graded based on the Clavien–Dindo classification (9), and grade ≥IIIa complications were regarded as severe.

Criteria for local treatment of residual tumors. Local treatments include re-hepatectomy, radiotherapy (conventional photon or particle beam therapy), transcatheter arterial chemoembolization (TACE)/ transcatheter arterial infusion (TAI), and percutaneous

isolated hepatic perfusion (PIHP), which are generally performed within 1 month after initial hepatectomy. The selection criteria for local treatments were made based on the number of residual tumor and remnant liver function. In patients with tumors ≤3 in the remnant liver, TACE was mainly selected. Re-hepatectomy or radiotherapy was selected in those with a single tumor. In those with tumors ≥4 in the remnant liver, PIHP was proactively performed.

Follow-up. As a postoperative follow-up, liver function and serum tumor markers (AFP and PIVKA-II) were measured at least every 3 months. Radiological examination was performed with enhanced CT or MRI. This study was approved by the Ethics Committee of Kobe University Hospital (approval number: 180330) and was conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration. All patients provided written informed consent prior to the treatment.

Statistical analysis. Survival rate was calculated using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors for overall survival were evaluated by univariate and multivariate analyses using the Cox proportional hazard models. All tests were performed with $p<0.05$ considered statistically significant. Variables with $p<0.1$ in the univariate analysis were included in the multivariate analysis. Analysis was conducted using the JMP software program, version 13 (SAS Institute, Cary, NC, USA).

Results

Clinical difference between complete and reductive hepatectomy. Patient characteristics and the type of hepatectomy are summarized in Table I. The study population included 717 patients (complete hepatectomy group, 614; reductive hepatectomy group, 103). In the complete hepatectomy group, 389 patients were classified as BCLC stage 0 or A and 225 patients as BCLC stage B or C. All 103 patients in the reductive hepatectomy group were classified as BCLC stage B or C. The reductive hepatectomy group had more elderly patients ($p<0.001$) and had more advanced HCC based on tumor size ($p<0.001$), tumor number ($p<0.001$), serum AFP ($p<0.001$), and PIVKA-II ($p<0.001$) than the complete hepatectomy group. Moreover, the number of patients with deteriorated liver function was greater in the reductive hepatectomy group than in the complete hepatectomy group ($p=0.002$).

Figure 1 shows the overall survival of all the patients in the complete and reductive hepatectomy groups. Median survival time (MST) for the complete hepatectomy group was 71.9 months, with 1-, 3-, and 5-year survival rates of 88.9, 68.6, and 56.6%, respectively, while the MST for the reductive hepatectomy group was 18.0 months, with 1-, 3-, and 5-year survival rates of 64.6, 23.3, and 14.0%, respectively.

The reductive hepatectomy group had a higher rate of complications (48.5%; 50/103) than the complete hepatectomy group (32.2%; 198/614) ($p=0.002$). The proportion of severe complications was also significantly higher in the reductive hepatectomy group (20.4%; 21/103) than in the complete hepatectomy group (11.2%; 69/614) ($p=0.012$) (Table II). These data indicate that the reductive hepatectomy group consisted of patients with more advanced HCC, who had major hepatectomy with a higher complication rate and thus lower survival rate.

Table I. *Patient characteristics and type of hepatectomy.*

	Complete hepatectomy (n=614)	Reductive hepatectomy (n=103)	*p*-Value
Age ≥70 years	295 (48.1)	28 (27.2)	<0.001
Gender, male	515 (83.9)	88 (85.4)	0.689
Tumor size ≥5 cm	270 (44.1)	79 (76.7)	<0.001
Tumor number ≥4	58 (9.5)	81 (78.6)	<0.001
Total bilirubin ≥1.0 mg/dl	154 (25.1)	32 (31.1)	0.200
Albumin ≤2.9 g/dl	28 (4.6)	8 (7.8)	0.168
ICG R15 ≥10%	416 (68.1)	65 (63.1)	0.319
Platelet count ≤10×10^4/μl	91 (14.8)	14 (13.6)	0.744
Child–Pugh B	23 (3.8)	11 (10.7)	0.002
AFP ≥40 ng/ml	223 (36.4)	64 (64.7)	<0.001
PIVKA-II ≥200 mAU/ml	340 (55.7)	84 (87.5)	<0.001
Major hepatectomy (two or more segments)	176 (28.7)	74 (71.8)	<0.001
Right lobectomy	109	45	
Extended right lobectomy	4	7	
Left lobectomy	21	10	
Extended left lobectomy	28	6	
Bisegmentectomy	10	2	
Atypical hepatectomy	4	4	
Minor hepatectomy	438 (71.3)	29 (28.2)	<0.001
Segmentectomy	134	15	
Subsegmentectomy	59	1	
Partial hepatectomy	245	13	
Advanced PVTT (Vp3/4)	38 (6.2)	41 (39.8)	<0.001
Vp3	16	12	
Vp4	22	29	

Data are presented as number and (%). ICG R15: Indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; PVTT: portal vein tumor thrombosis.

Prognostic factors for overall survival between the two groups. As the reductive hepatectomy group revealed an inferior overall survival rate compared to the complete hepatectomy group, prognostic factors were further analyzed separately. In the complete hepatectomy group, tumor size ($p<0.001$), tumor number ($p<0.001$), serum albumin ($p=0.037$), ICG R15 ($p=0.020$), serum AFP ($p<0.001$) and PIVKA-II ($p<0.001$) were identified as prognostic factors in the univariate analysis. Multivariate analysis revealed that older age ($p=0.025$), tumor number ($p<0.001$), and serum AFP level ($p=0.025$) were independent prognostic factors. In the reductive hepatectomy group, serum total bilirubin ($p=0.030$), albumin ($p=0.006$), and PIVKA-II ($p=0.025$)

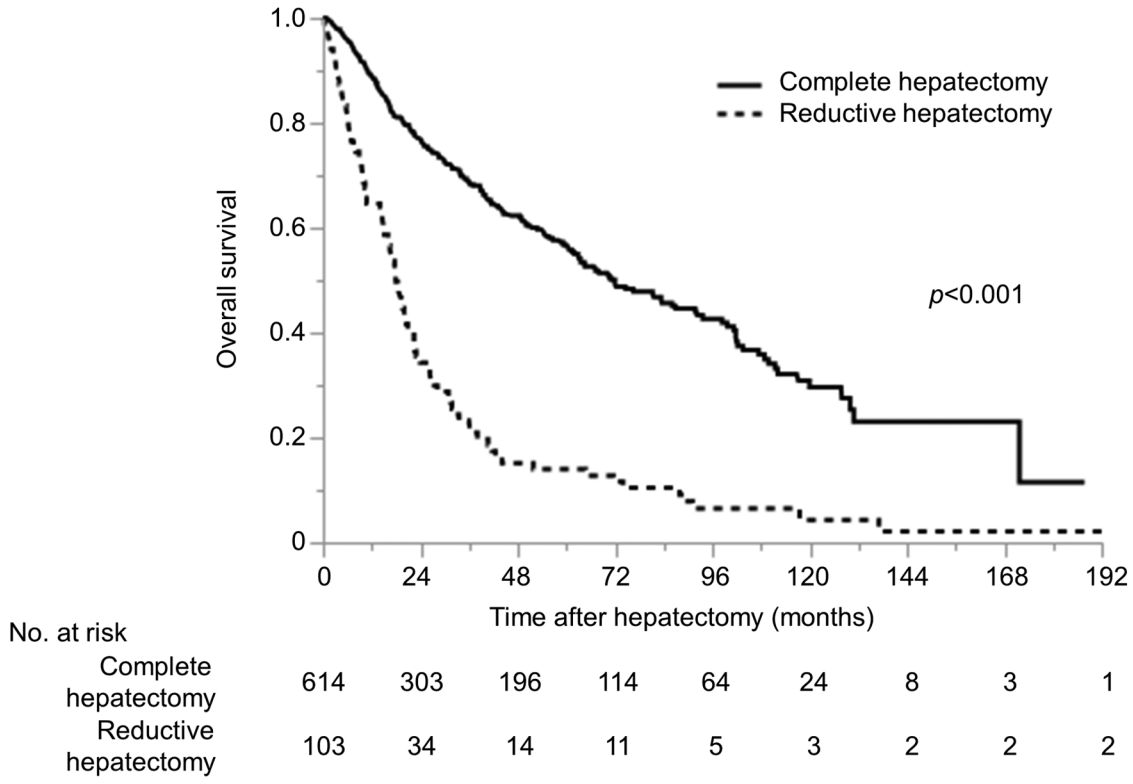

Figure 1. *Overall survival of patients with complete hepatectomy and reductive hepatectomy.*

levels were identified as prognostic factors in the univariate analysis. In the multivariate analysis, serum total bilirubin (p=0.006) and albumin (p=0.006) levels were the independent prognostic factors (Table III).

Subsequent local treatment in the reductive hepatectomy group. In the reductive hepatectomy group, further analysis was performed focusing on the treatment strategy after initial hepatectomy. Of the 103 patients who underwent reductive hepatectomy, 86 (83.5%) received subsequent local treatment: PIHP in 56, TACE/TAI in 23, radiotherapy in six, and re-hepatectomy in one. Patients with liver function deterioration (n=13) and rapid tumor progression (n=4) were not eligible for subsequent local treatments. Of the 86 patients who received subsequent local treatment, 26 had ≤3 tumors and received TACE/TAI, radiotherapy, and re-hepatectomy; the remaining 60 patients had ≥4 tumors in the remnant liver: 56 patients received PIHP and four patients TACE/TAI.

Figure 2 shows the overall survival of the patients with and without subsequent local treatments. The MST for patients with subsequent local treatment was 20.1 months, with 1-, 3-, and 5-year survival rates of 75.5, 27.6, and 16.6%, respectively, while the MST for patients without subsequent local treatment was 3.2 months, with 1-, 3-, 5-year survival rates of 6.4, 0, and 0%, respectively (p<0.001).

Table II. *Complications in all patients*.

Clavien–Dindo grade	Complete hepatectomy (n=614)	Reductive hepatectomy (n=103)
0	399 (65.0)	53 (51.4)
I	50 (8.1)	8 (7.8)
II	79 (12.9)	21 (20.4)
IIIa or higher	69 (11.2)	21 (20.4)
Unknown	17 (2.8)	0 (0)

Data are presented as number and (%).

Figure 3 shows the overall survival of the patients with subsequent treatment according to tumor number. The MST for patients with ≤3 tumors was 31.8 months, with 1-, 3-, and 5-year survival rates of 88.3, 38.9, and 21.6%, respectively, while the MST for patients with ≥4 tumors was 19.2 months, with 1-, 3-, and 5-year survival rates of 70.0, 24.8, and 14.5%, respectively (p=0.192). Figure 4 shows the overall survival of the patients with ≥4 tumors with or without PIHP. The MST for patients with PIHP was 19.8 months, with 1-, 3-, and 5-year survival rates of 69.6, 24.4,

Table III. *Prognostic factors for overall survival.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Complete hepatectomy				
Age ≥70 years	1.28 (0.99-1.66)	0.064	1.37 (1.04-1.80)	0.025
Gender, male	0.84 (0.60-1.20)	0.318		
Tumor size ≥5 cm	1.73 (1.33-2.24)	<0.001	1.30 (0.96-1.78)	0.091
Tumor number ≥4	2.78 (1.95-3.87)	<0.001	2.17 (1.48-3.11)	<0.001
Total bilirubin ≥1.0 mg/dl	1.15 (0.86-1.53)	0.339		
Albumin ≤2.9 g/dl	1.87 (1.04-3.10)	0.037	1.23 (0.50-2.76)	0.641
ICG R15 ≥10%	1.42 (1.06-1.95)	0.020	1.25 (0.92-1.73)	0.159
Platelet count ≤10×10^4/μl	1.12 (0.80-1.55)	0.503		
Child–Pugh B	1.70 (0.90-2.91)	0.097	1.54 (0.59-3.73)	0.370
AFP ≥40 ng/ml	1.67 (1.28-2.16)	<0.001	1.38 (1.04-1.83)	0.025
PIVKA-II ≥200 mAU/ml	1.61 (1.24-2.12)	<0.001	1.25 (0.91-1.71)	0.174
Reductive hepatectomy				
Age ≥70 years	1.27 (0.77-2.02)	0.344		
Gender , male	1.56 (0.85-3.22)	0.161		
Tumor size ≥5 cm	1.08 (0.67-1.83)	0.752		
Tumor number ≥4	1.40 (0.86-2.37)	0.181		
Total bilirubin ≥1.0 mg/dl	1.65 (1.05-2.53)	0.030	2.00 (1.23-3.19)	0.006
Albumin ≤2.9 g/dl	3.34 (1.47-6.58)	0.006	3.48 (1.49-7.13)	0.006
ICG R15 ≥10%	1.16 (0.76-1.79)	0.495		
Platelet count ≤10×10^4/μl	0.84 (0.44-1.47)	0.549		
Child–Pugh B	1.27 (0.64-2.29)	0.474		
AFP ≥40 ng/ml	1.55 (0.99-2.47)	0.055	1.33 (0.81-2.23)	0.266
PIVKA-II ≥200 mAU/ml	2.07 (1.09-4.46)	0.025	1.63 (0.81-3.66)	0.181

ICG R15: Indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

and 15.6%, respectively, while the MST for patients without PIHP was 15.4 months, with 1-, 3-, and 5-year survival rates of 75.0, 0, and 0%, respectively (p=0.057). These data indicate that reductive hepatectomy has benefits on patient survival provided that the subsequent local treatment is successful.

Predictive score for reductive hepatectomy. We developed a predictive score targeting those who could successfully complete reductive hepatectomy. As total bilirubin ≥1.0 mg/dl and albumin ≤2.9 g/dl were identified as independent prognostic factors in the multivariate analysis, the predictive score was defined as follows: score 0, patients with neither total bilirubin ≥1.0 mg/dl nor albumin ≤2.9 g/dl; score 1, those with either total bilirubin ≥1.0 mg/dl or albumin ≤2.9 g/dl; and score 2, those with both total bilirubin ≥1.0 mg/dl and albumin ≤2.9 g/dl (Table IV). Based on the definition, 67 patients (65.0%) scored 0, 32 patients (31.1%) scored 1, and four patients (3.9%) scored 2.

Figure 5 shows the characteristics of all patient: 58.2% of those who scored 0 and 50.0% of those who scored 1 had ≥4 tumors and subsequently treated by PIHP, and 75.0% of those who scored 2 had no subsequent local treatment. Figure 6 shows the overall survival according to the predictive scores. The MST for patients with a score of 0, 1, and 2 was 20.1, 14.8, and 2.7 months, respectively, and a significant difference in MST was observed between scores 0 and 2 (p<0.001) and between scores 1 and 2 (p<0.001). These data indicate that reductive hepatectomy should be aggressively discussed for patients with a score of 0 or 1 with ≤3 tumors. For patients who scored 1 with ≥4 tumors or 2, the indication of reductive hepatectomy should be thoroughly discussed, especially in those without PIHP treatment.

Discussion

In this study, we clarified who among the patients with BCLC stage B and C HCC should undergo reductive hepatectomy. Our results showed that (1) reductive hepatectomy should be a treatment option for those who could complete a subsequent local treatment; (2) patients with ≤3 residual tumors after reductive hepatectomy are good candidates, with MST of 31.8 months; and (3) for those with ≥4 residual tumors, serum bilirubin and albumin are the independent prognostic factors, with MST of 15.4 months, which could be extended up to 19.8 months with PIHP.

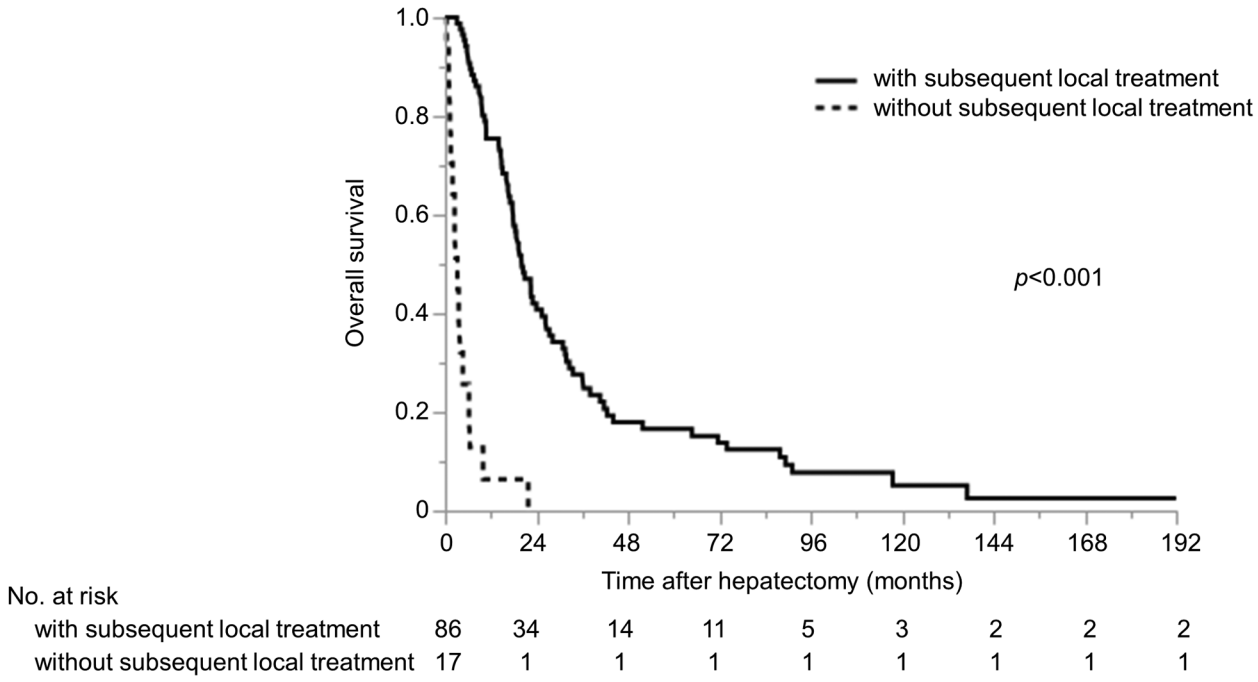

Figure 2. *Overall survival of patients with or without a subsequent local treatment.*

To clarify the demographics of the patients who should receive reductive hepatectomy, we first identified the prognostic factors in all patients who had complete or reductive hepatectomy. In the complete hepatectomy group, the factors include tumor number and tumor marker; this finding is consistent with that in previous reports (10). In the reductive hepatectomy group, liver functional status, such as total bilirubin and albumin, was identified as a prognostic factor. We speculate that liver functional status is an essential factor for a successful reductive hepatectomy. Patients with poor preoperative liver function may survive the first step of surgical insult; however, postoperative remnant liver function was not enough for the subsequent local treatment, which could in turn result in an unfavorable overall survival. In those without subsequent local treatment, the MST was as low as 3.2 months. Hence, patients with poor preoperative liver function should not be considered for reductive hepatectomy, and to assert the feasibility to perform reductive hepatectomy, we should propose inclusion criteria regarding who has sustainable liver function for subsequent local treatment after reductive hepatectomy.

The predictive score for reductive hepatectomy was established using the following prognostic factors: serum total bilirubin and albumin levels. Hypoalbuminemia has been described as a significant prognostic factor in various types of cancer (11, 12) and is generally defined as serum albumin <3.5 g/dl (13, 14). It represents both cancer-related changes and impaired liver function due to an underlying chronic liver disease in patients with HCC (15, 16). In addition, albumin <3.0 g/dl is the lowest category in the liver damage classification according to the Liver Cancer Study Group of Japan (17); thus, a cutoff albumin level of ≥2.9 g/dl is extremely low compared to the previous cutoff albumin level of <3.5 g/dl. We speculate that a lower albumin level is not associated with the underlying chronic liver disease. Patients with HCC who underwent reductive hepatectomy had a huge tumor burden preoperatively, which affected the serum albumin levels irrespective of the liver fibrosis stage.

Table IV. *Predictive score for reductive hepatectomy.*

	Score
Total bilirubin	
<1.0 mg/dl	0
≥1.0 mg/dl	1
Albumin	
>2.9 g/dl	0
≤2.9 g/dl	1

Total score 0: n=67.
Total score 1: n=32.
Total score 2: n=4.

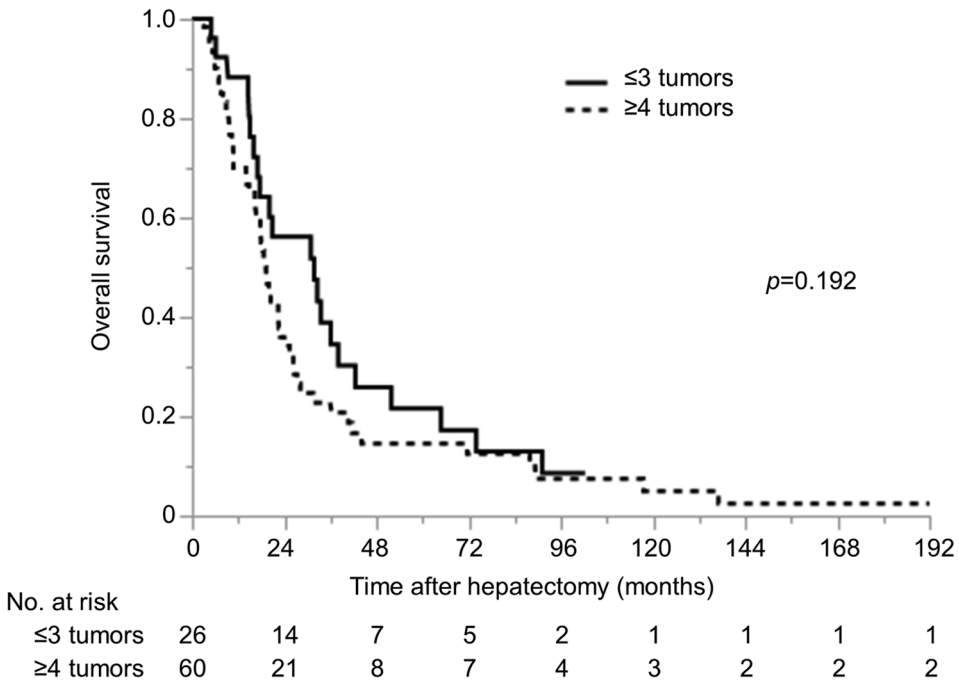

Figure 3. *Overall survival of patients with ≤3 or ≥4 tumors.*

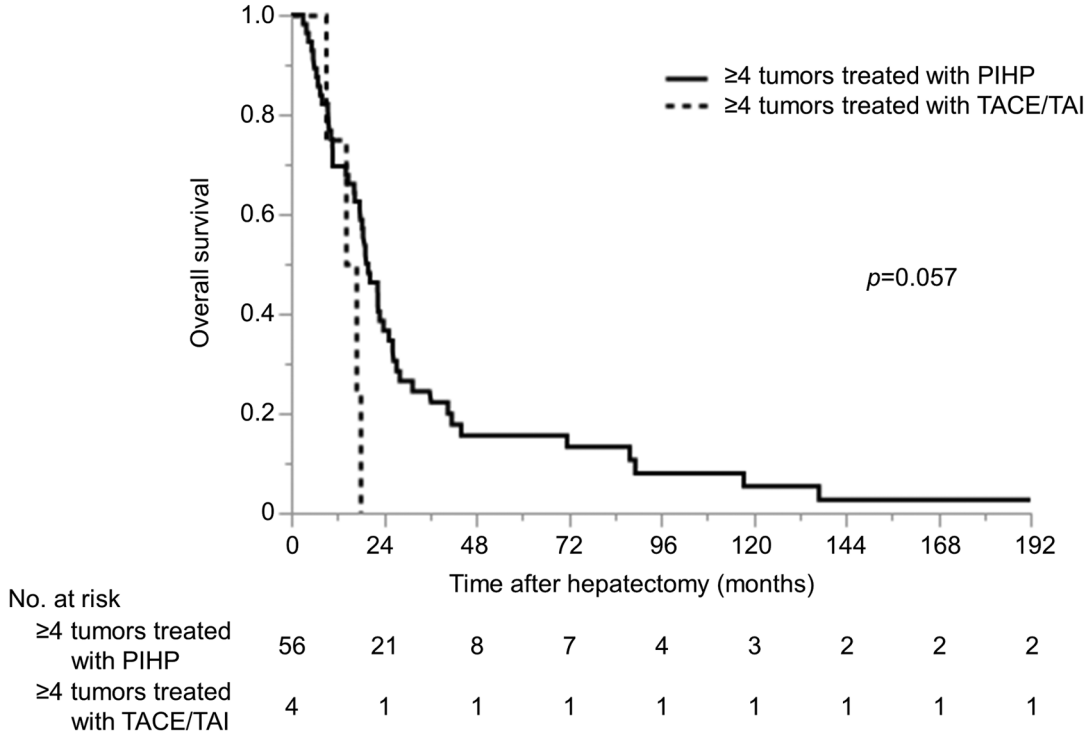

Figure 4. *Overall survival of patients with ≥4 tumors with percutaneous isolated hepatic perfusion or transcatheter arterial chemoembolization/transcatheter arterial infusion treatment. PIHP: Percutaneous isolated hepatic perfusion; TACE: transcatheter arterial chemoembolization; TAI: transcatheter arterial infusion treatment.*

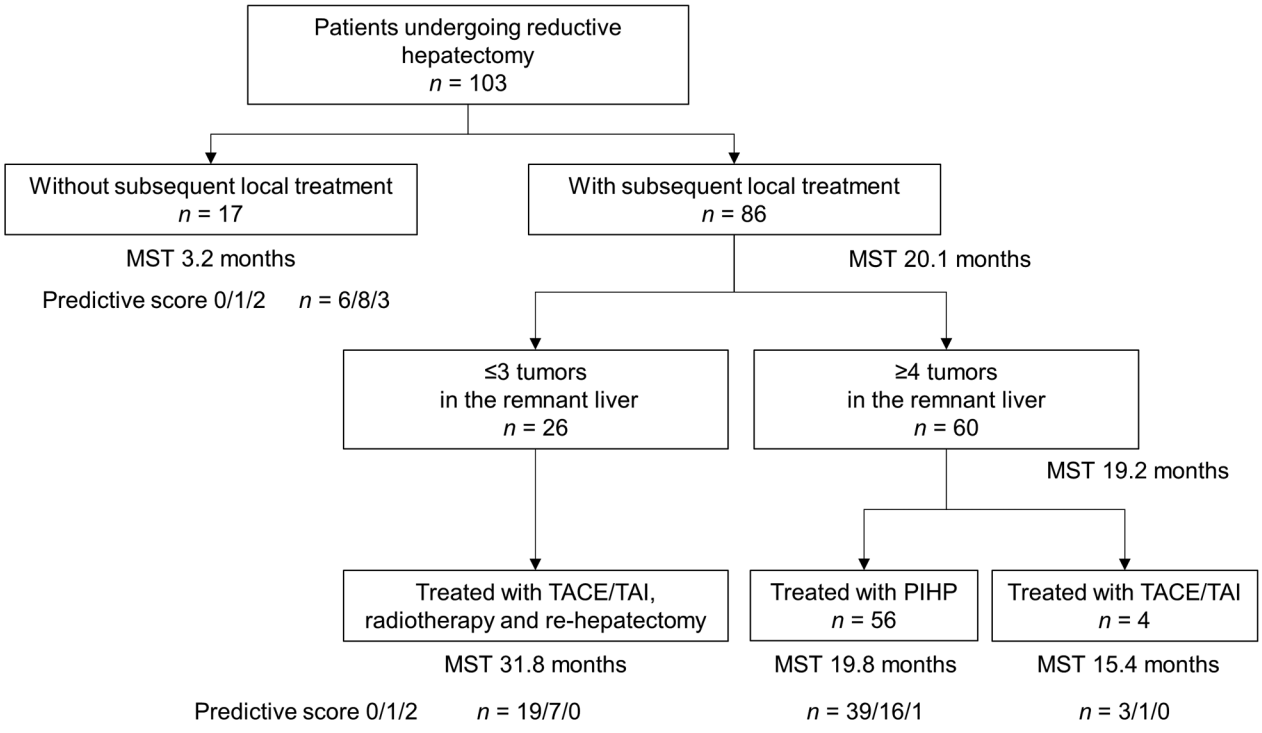

Figure 5. *Flowchart of all the patients and their characteristics. MST: Median survival time; TACE: transcatheter arterial chemoembolization; TAI: transcatheter arterial infusion treatment; PIHP: percutaneous isolated hepatic perfusion.*

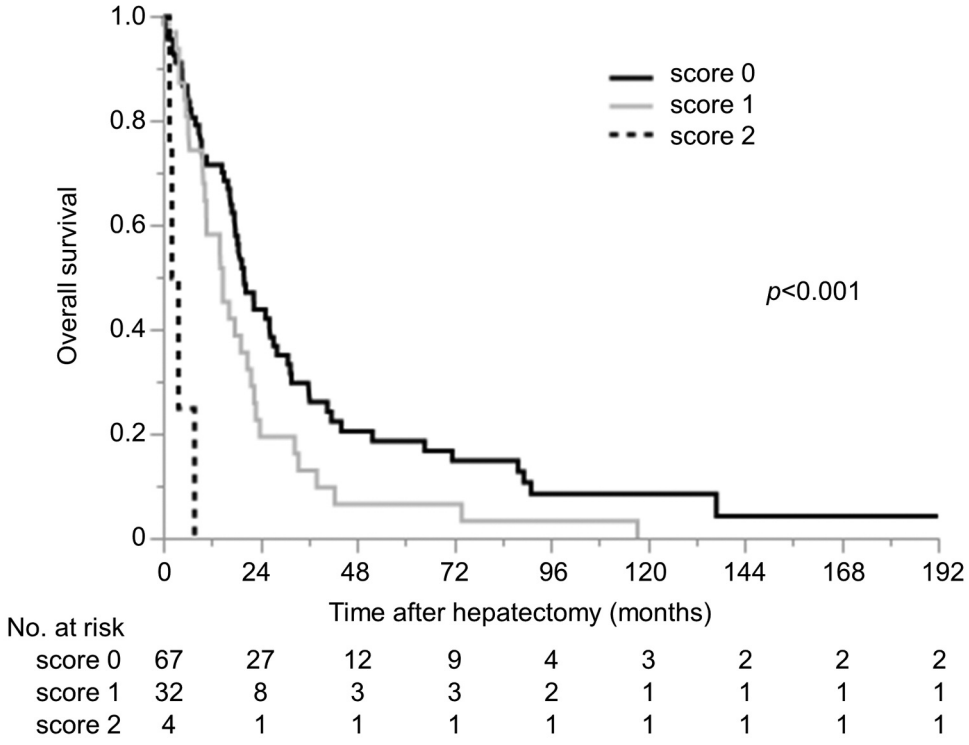

Figure 6. *Overall survival of patients categorized by predictive score: 0, 1, and 2.*

Based on the predictive score, 65% scored 0 (low risk), 31.1% scored 1 (intermediate risk), and 3.9% scored 2 (high risk). Half of the intermediate-risk patients had ≥4 tumors and were treated with PIHP. Although PIHP is associated with a high rate of tumor regression in multiple HCC and a long-term survival, (18-20), facilities where PIHP can be performed are limited. Given that the patients with ≥4 tumors treated with TACE/TAI had an inferior survival compared to those treated with PIHP and considering the particularity of PIHP treatment, reductive hepatectomy for intermediate-risk patients with ≥4 tumors should be thoroughly discussed. Although it is difficult to compare tumor characteristics across several studies, previously reported MST in patients who received sorafenib in the SHARP trial and the subsequent Asia-Pacific trial was 6.5-10.7 months (21, 22). The MST of reductive hepatectomy and subsequent treatment with TACE/TAI for intermediate-risk patients with ≥4 tumors is quite acceptable (15.4 months) compared to the previous report of 6.5-10.7 months, reductive hepatectomy might be a treatment option. The remaining 20% of the intermediate-risk patients had ≤3 tumors and were eligible for a subsequent local treatment, with MST of 31.8 months; thus, reductive hepatectomy should be aggressively discussed. Only four patients were classified as high risk (three had no subsequent local treatment and one had ≥4 tumors and was treated with PIHP). As the MST is as short as 3.2 months in those without a subsequent local treatment and given that only one patient who received PIHP survived for 7.5 months, reductive hepatectomy for high-risk patients should not be considered.

This study has some limitations. This was a retrospective and single-center study. In addition, more than half of the patients who underwent reductive hepatectomy received PIHP as the subsequent local treatment. In fact, reductive hepatectomy may not be initially considered for patients with ≥4 residual tumors in general hospitals where PIHP cannot be performed. Meanwhile, reductive hepatectomy should be aggressively performed for patients with ≤3 residual tumors after reductive hepatectomy.

In conclusion, the present study established the predictive score for reductive hepatectomy and identified the patients with BCLC stage B and C HCC who could obtain survival benefit from reductive hepatectomy. Supported by a subsequent local treatment, reductive hepatectomy could be successfully accomplished, and patients with ≤3 residual tumors after initial hepatectomy are good candidates.

Conflicts of Interest

The Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Authors' Contributions

Study conception and design: Yasuhara Y, Komatsu S. Acquisition of data: Kido M, Tanaka M, Gon H. Analysis and interpretation of data: Kuramitsu K, Yanagimoto H, Toyama H, Ajiki T. Drafting of manuscript: Yasuhara Y, Komatsu S, Fukumoto T.

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