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ORIGINAL SCIENTIFIC REPORT

Clinical Relevance of Reductive Hepatectomy for Barcelona Clinic Liver Cancer Stages B and C Advanced Hepatocellular Carcinoma: A Single-Center Experience of 102 Patients

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Abstract

Background This study aimed to evaluate the clinical relevance of hepatectomy for Barcelona Clinic Liver Cancer (BCLC) stages B and C advanced hepatocellular carcinoma (HCC).

Methods A total of 314 patients (149 and 165 BCLC stages B and C, respectively) who underwent hepatectomy were included. Complete hepatectomy (without residual tumors after hepatectomy) and reductive hepatectomy (apparent residual tumors after hepatectomy) were performed for 212 and 102 patients, respectively. Short-term operative and postoperative outcomes, as well as long-term outcomes, were evaluated.

Results The median survival times of patients with stage B disease undergoing complete hepatectomy and reductive hepatectomy were 48.9 and 20.1 months, respectively ($p = 0.0075$), whereas those of patients with stage C disease were 19.5 and 17.6 months, respectively ($p = 0.0140$). The 3-year overall survival rates of patients with stage B disease undergoing reductive hepatectomy with and without subsequent local treatments after surgery were 47.5% and 0%, respectively, whereas those of patients with stage C diseases were 18.6% and 0%, respectively.

Conclusions Survival benefits are obvious for both BCLC stages B and C HCC when complete hepatectomy can be performed safely. Reductive hepatectomy is also acceptable for BCLC stages B and C when subsequent local treatment for remnant liver tumors can be performed safely after reductive hepatectomy. Without subsequent local treatment, reductive hepatectomy has little clinical relevance. Thus, a cautious approach to patient selection is required for this aggressive strategy.

Introduction

Several staging systems for hepatocellular carcinoma (HCC) that attempt to predict patient prognosis and guide treatment have been proposed [1-4]. Of these, the Barcelona Clinic Liver Cancer (BCLC) classification is the most widely used staging system because it links staging with treatment indications and prognostic information [3, 5]. Despite its popularity, the main limitation of the BCLC classification is the great prognostic heterogeneity within each stage, especially in stages B and C [6]. Guidelines from the European Association for the Study of Liver Disease and the American Association for the Study of Liver Disease consider patients with very-early- or early-

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stage HCC suitable for curative treatments, while patients with stages B and C disease would only be suitable for palliative treatments such as transcatheter arterial chemoperfusion (TACE), transcatheter arterial infusion (TAI), and/or sorafenib, but the outcomes are not satisfactory [7, 8].

Despite the widespread use of the BCLC classification, several reports have recently demonstrated the feasibility and effectiveness of an expanded surgical indication for patients with stage B and stage C disease [9-13]. Several revisions to surgical treatment in the BCLC guideline have been proposed based on these results. However, even the revised BCLC guidelines only stratify patients with stages B and C who undergo hepatectomy with curative intent. The patients with stage B and stage C disease have several tumor and/or background factors that frequently preclude curative hepatectomy including intra- and/or extra-hepatic metastases, vascular invasion, impaired liver function, and poor performance status. Reductive hepatectomy has been indicated to be effective in overcoming these limitations [14, 15]. However, aggressive strategy for patients with stages B and C disease remains controversial. In this study, we sought to evaluate surgical interventions for patients with HCC and BCLC stages B and C with a special focus on reductive hepatectomy.

Patients and methods

Treatment concept and study design

HCC staging was performed according to the BCLC classification. The treatment strategy for patients with HCC and multiple intrahepatic metastases at our institute consists of treating all tumors in the liver with locoregional treatments for expeditious local control [16, 17]. Hepatectomy was initially performed for large and/or life-threatening tumors which are difficult to treat with other locoregional treatments. Types of resection were defined as either complete or reductive hepatectomies and were clarified based on the operative findings. Complete hepatectomy was defined as surgery in which the entire tumors were resected macroscopically, thus with no apparent residual tumors in the remnant liver. Cases with microscopic positive surgical margin (including portal vein tumor thrombectomy) but without apparent residual tumors were categorized as complete hepatectomy. Reductive hepatectomy was defined as surgery in which residual tumors were obvious in the remnant liver after hepatectomy. Reductive hepatectomy was indicated only when it could eliminate the most pertinent poor prognostic factor by resecting the main tumor, and subsequent treatments of the residual tumors after hepatectomy could be considered. Subsequent local treatments included our original percutaneous isolated hepatic perfusion (PIHP), TACE/TAI, radiofrequency ablation (RFA), and radiotherapy (conventional photon and particle therapy). PIHP was proactively introduced to patients with multiple intrahepatic metastases ($n \geq 4$) in the remnant liver, whereas repeat resection, RFA, and TACE were selected for expeditious local control when the number of residual tumors was ≤ 3, if the situation permitted.

Short- and long-term treatment outcomes were evaluated for all patients with BCLC stage B and stage C disease and sub-analyzed for those who underwent complete and reductive hepatectomy. Medical records were retrospectively reviewed for demographics, clinical presentation, operative results, hospital course, complications, mortality, pathological findings, and long-term follow-up data. Postoperative complications were stratified according to the Clavien-Dindo classification, and complications of grade III or higher were considered severe. This study was conducted following the ethical standards of the Declaration of Helsinki and approved by the ethics committee of Kobe University in 2017 (approval number #170,182). All patients provided written informed consent before the initiation of treatment.

Statistical analyses

Data with a normal distribution are reported as mean (standard deviation). Variables not fitting a normal distribution are presented as median (range). Continuous variables were compared using the Student's t test if normally distributed, otherwise the Mann–Whitney U test was used. Categorical variables were compared using the Chi-square test. Patient overall and disease-free survival rates were estimated using the Kaplan–Meier method and compared with log-rank tests. Data were considered statistically significant at $p < 0.05$. Statistical analyses were conducted using the JMP 13 statistical package (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of all patients with BCLC stage B and stage C disease

Between January 2000 and December 2017, 716 consecutive patients with HCC underwent initial hepatectomy at Kobe University Hospital. Among them, patients who were classified as having BCLC stage B and stage C disease and those who had no lymph nodes and/or distant metastases were included in the present study. A total of 314 patients were included; Table 1 reports the baseline characteristics

Table 1 Patient characteristics

Characteristics	All patients (n = 314)	Complete hepatectomy (n = 212)	Reductive hepatectomy (n = 102)
Age, y, median (range)	68.0 (21–86)	69.0 (21–86)	64.5 (23–86)
Sex, male/female	269/45	181/31	88/14
BCLC classification, ***n*** (%)			
B	149 (47.5)	110 (51.9)	39 (38.2)
C	165 (52.5)	102 (48.1)	63 (61.8)
ICG R15, %, median (range)	13.2 (0.9–56.7)	14.1 (2.1–56.7)	11.8 (0.9–36.9)
Child–Pugh classification, ***n*** (%)			
A	296 (94.3)	205 (96.7)	91 (89.2)
B	18 (5.7)	7 (3.3)	11 (10.8)
HBs-Ag positive / negative	74/240	42/170	32/70
HCV positive/negative	125/189	84/128	41/61
Total bilirubin, μmol/L, median (range)	0.7 (0.1–2.2)	0.7 (0.1–2.1)	0.7 (0.2–2.2)
Serum albumin, g/dL (range)	3.7 (2.2–5.1)	3.8 (2.2–4.8)	3.6 (2.3–5.1)
Prothrombin time, %, median (range)	88.7 (34.1–130)	89.9 (34.1–130)	87.0 (53.9–118.7)
Platelet count $\times 10^9$/L, median (range)	16.4 (2.0–59.7)	16.6 (2.0–38.7)	16.3 (3.0–59.7)
Serum AFP, ng/ml, median (range)	73.5 (1.0–3,960,000)	52 (1.0–608,400)	320 (1.4–3,960,000)
Serum PIVKAII, mAU/ml, median (range)	2704 (13–1,045,500)	2145 (13–1,045,500)	4152.5 (20–194,450)
Preoperative diagnosis			
Maximal tumor size, mm, median (range)	7.0 (1.0–24.0)	6.6 (1.0–24.0)	8.0 (1.0–19.0)
Number of tumors in the liver, *n* (%)			
Solitary	47 (15.0)	47 (22.2)	0 (0)
Within 5	167 (53.2)	136 (64.1)	31 (30.4)
More than 6	100 (31.8)	29 (13.7)	71 (69.6)
Subsequent local treatment to the remnant liver tumors, ***n*** (%)			
Yes	85 (27.1)	0 (0)	85 (83.3)
No	229 (72.9)	212 (100)	17 (16.7)

BCLC Barcelona Liver Clinic, *ICGR15* indocyanine green retention rate at 15 min, *HBs-Ag* hepatitis B surface antigen, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *PIVKAII* protein induced by vitamin K absence or antagonist II

of all patients. One hundred and forty-nine and 165 patients were classified as having BCLC stage B and stage C disease, respectively. The median age was 68 years (range 21–86 years), and 269 patients (87.8%) were male. The median indocyanine green retention rate at 15 min was 13.2% (range 0.9–56.7%), and 296 patients (94.3%) were graded as Child–Pugh classification A, whereas 18 (5.7%) were graded as B. According to the preoperative diagnosis, the median maximal tumor size was 7.0 cm (range 1.0–24.0 cm); 47 patients (15.0%) had a solitary tumor; and 267 (85.0%) had multiple tumors. Two hundred and twelve patients (67.5%) underwent complete hepatectomy, and 102 (32.5%) underwent reductive hepatectomy.

Patients in the reductive hepatectomy group

The characteristics of the 102 patients who underwent reductive hepatectomy are summarized in Table 1. Among the 102 patients, 12 in whom the initial plan was to perform complete hepatectomy were converted to reductive hepatectomy after unexpected operative findings. The median age was 64.5 years (range 23–86 years), and 88 patients (86.3%) were male. Thirty-nine patients (38.2%) had BCLC stage B disease and 63 (61.8%) had BCLC stage C disease. Ninety-one (89.2%) patients were graded as Child–Pugh classification A, and 11 (10.8%) were graded as B. The median serum alpha-fetoprotein level was 320 (range 1.4–3,960,000), and the median protein induced by vitamin K absence or antagonist II level was 4152.5 (range 20–194,450). Preoperative diagnosis showed that the

median maximal tumor size was 8.0 cm (range 1.0–19.0 cm). All patients had multiple tumors, and 71 (69.6%) had more than 6 tumors. Eighty-five (83.3%) patients underwent subsequent local treatments for remnant liver tumors, whereas the remaining 17 (16.7%) could not receive subsequent local treatments. The representative case after reductive hepatectomy and subsequent PIHP is shown in Fig. 1. Preoperative computed tomography revealed multiple tumors with portal vein tumor thrombus in the main portal trunk (Fig. 1a). Multiple residual tumors in the remnant liver can be detected after the left hepatectomy (Fig. 1b). Post-PIHP abdominal computed tomography showed the complete response after PIHP, with no apparent signs of recurrence in the remnant liver (Fig. 1c).

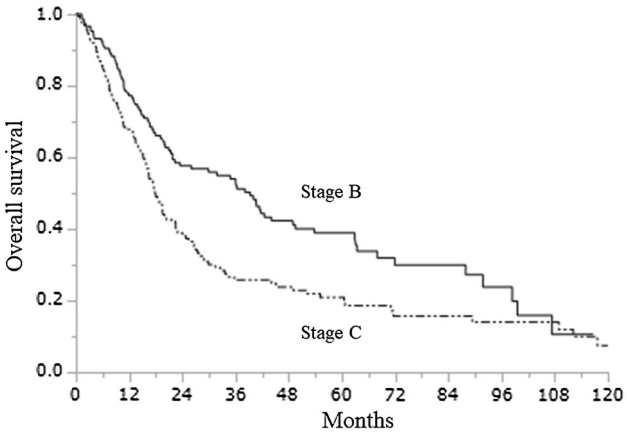

Fig. 2 Survival rates of all 314 patients according to Barcelona Clinic Liver Cancer stages B and C disease

Treatment outcomes of all patients with BCLC stage B and stage C disease

The 3-year overall survival rates of all patients with BCLC stage B (n = 149) and stage C (n = 165) disease were 54.0% and 25.8%, respectively (Fig. 2). The median survival times (MSTs) of stage B and stage C were 39.3 and 18.0 months, respectively (p = 0.0008). Figure 3 shows the survival curves according to complete or reductive hepatectomy in each category. The 3-year overall survival rates of stage B disease with complete and reductive hepatectomy were 60.0% and 38.6%, respectively, and the 3-year overall survival rates of stage C disease with complete and reductive hepatectomy were 34.7% and 13.3%, respectively. The MSTs of stage B disease with complete and reductive hepatectomy were 48.9 and 20.1 months, respectively (p = 0.0075), whereas those of stage C disease were 19.5 and 17.6 months, respectively (p = 0.0140); both differences were statistically significant (Fig. 3).

Complications occurred in 92 patients (43.4%) treated with complete hepatectomy and 50 (49.0%) treated with reductive hepatectomy, without any significant difference in the total frequency of complications (p = 0.3489). Complications of Clavien-Dindo grade III or higher were observed in 37 patients (17.4%) treated with complete hepatectomy and 21 (20.6%) treated with reductive hepatectomy, with no significant difference observed between the two groups (p = 0.5056) (Table 2).

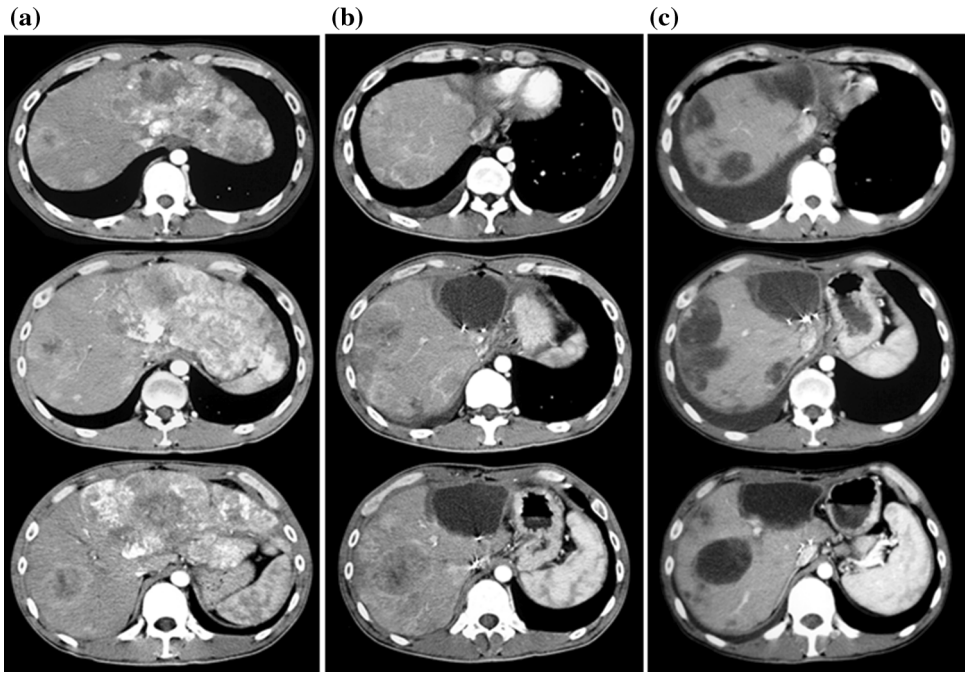

Fig. 1 (a) Preoperative computed tomography revealed multiple tumors with portal vein tumor thrombus in the main portal trunk. (b) Multiple residual tumors can be detected after the left hepatectomy. (c) Post-PIHP abdominal computed tomography shows the complete response after PIHP and no apparent signs of recurrence in the remnant liver. *PIHP*, percutaneous isolated hepatic perfusion

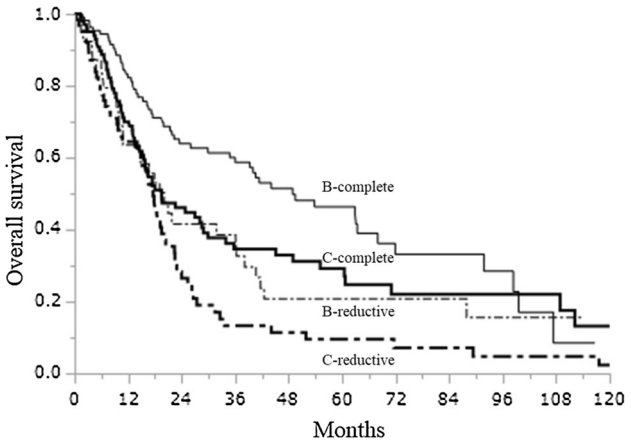

Fig. 3 Survival rates of Barcelona Clinic Liver Cancer stage B and stage C disease according to the operative treatment (complete or reductive hepatectomy)

Table 2 Complications of all patients (n = 314)

Clavien-Dindo grade	Complete hepatectomy (n = 212)	Reductive hepatectomy (n = 102)
0	120 (56.6)	52 (51.0)
I	22 (10.4)	8 (7.8)
II	33 (15.6)	21 (20.6)
IIIa or higher	37 (17.4)	21 (20.6)

Data are presented as n (%)

Treatment outcomes of reductive hepatectomy

Among 102 patients who underwent reductive hepatectomy, 85 (32 with stage B disease and 53 with stage C disease) received subsequent local treatments to the liver, whereas 17 (7 with stage B disease and 10 with stage C disease) could not receive local treatments after reductive hepatectomy. Patients could not receive subsequent local treatments for the remnant liver tumors because of deterioration of their overall condition due to the operation (n = 13; 3 with stage B disease and 10 with stage C disease) and rapid tumor progression not eligible for subsequent local treatments (n = 4; all with stage B disease). The 3-year overall survival rates of all 102 patients treated with reductive hepatectomy with and without subsequent local treatments were 27.5% and 0%, respectively ($p < 0.0001$). When limiting the analysis to stage B or C disease only, the 3-year overall survival rates of patients with stage B disease treated with reductive hepatectomy with or without subsequent local treatments were 47.5% and 0%, respectively ($p < 0.0001$) (Fig. 4a), whereas the values for patients with stage C disease were 15.5% and 0%, respectively ($p < 0.0001$) (Fig. 4b). All differences between patients with or without subsequent local treatments of remnant tumors after hepatectomy were statistically significant.

Details of the treatment courses after reductive hepatectomy are shown in Supplementary Table 1 (online only). Among 32 patients with BCLC stage B disease who underwent subsequent local treatments, 14 underwent PIHP, 16 underwent TACE/TAI, and 2 underwent RFA. Among 53 patients with BCLC stage C disease who underwent subsequent local treatments, 42 underwent PIHP, 6 underwent TACE/TAI, 4 underwent RFA, and 1 underwent re-hepatectomy. Among the 85 patients who received subsequent local treatments to the liver after reductive hepatectomy, there was no significant difference between the 3-year overall survival rates of patients who received PIHP vs those who received other local treatments (TACE/TAI, RFA, and resection) (23.5 vs 35.1%, p = 0.2788) (Supplementary Fig. 1 [online only]).

The surgical and pathological features of reductive hepatectomy with or without subsequent local treatment are summarized in Supplementary Table 2. A significant difference was observed only for the preoperative serum albumin level between the two groups (p = 0.0460). However, there was no significant difference in other background factors between the two groups.

Discussion

In this study, we found that hepatectomy involving complete resection without apparent residual tumors is beneficial for HCC patients with BCLC stage B and stage C disease. In addition, reductive hepatectomy was acceptable in patients with BCLC stage B and stage C disease when appropriate subsequent local treatment was performed.

The BCLC classification recommends palliative treatment in patients with BCLC stage B and stage C, even those with tumors confined to the liver. In patients with HCC and multiple intrahepatic metastases, our strategy consists of treating all hepatic tumors with the most effective locoregional treatments for expeditious local control [16, 17]. We believe that the most effective locoregional treatment is hepatectomy; therefore, we initially resect large and/or life-threatening tumors that are difficult to treat with other locoregional treatments. Consecutive locoregional treatments, including TACE, TAI, and/or our original PIHP, are administered after reductive hepatectomy to treat residual tumors in the remnant liver.

The MSTs of patients who underwent complete hepatectomy for BCLC stage B (n = 110) and stage C (n = 102) are comparable to those reported in patients undergoing hepatectomy for BCLC stage B and stage C (Fig. 3)

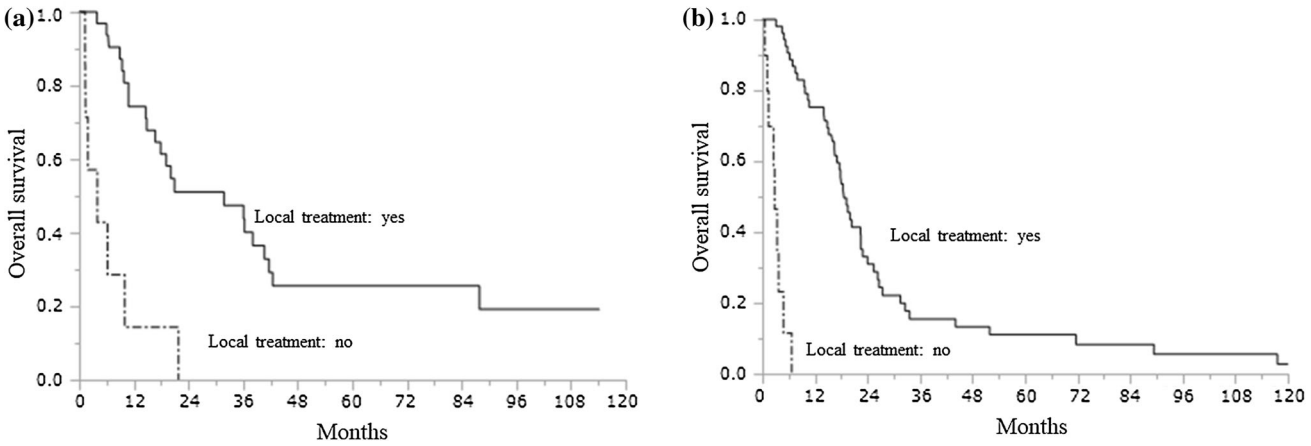

Fig. 4 Survival rates of patients who underwent reductive hepatectomy with and without subsequent local treatments to the liver: (a) stage B and (b) stage C

[13, 18]. In addition, they were significantly better than those reported for non-surgical treatments [7, 8, 10]. These results, in addition to our data, suggest that complete hepatectomy should be the standard therapeutic option for HCC patients with BCLC stage B and stage C disease and that the BCLC classification for stages B and C should be revised.

Meanwhile, in the present study, the MSTs of patients who underwent reductive hepatectomy for BCLC stage B (20.1 months) and stage C (17.6 months) (Fig. 3) were significantly inferior to those of patients who underwent complete hepatectomy and those from previously reported studies [13, 18]. This difference may be because of the considerable heterogeneity in inclusion criteria, definition of reductive hepatectomy, and extent of tumor involvement between studies. In the present study, reductive hepatectomy was reserved to patients with obvious residual tumors in the remnant liver after hepatectomy. Cases with microscopic positive surgical margins, including portal vein tumor thrombectomy, but without apparent residual tumors in the remnant liver, were categorized as complete hepatectomy. Accordingly, the patient population that underwent reductive hepatectomy in the present study included only those with highly advanced HCCs.

However, the MSTs of patients with BCLC stage B who underwent reductive hepatectomy with and without subsequent local treatments were 31.8 and 4.0 months, respectively ($p < 0.0001$) (Fig. 4a). Similarly, the MSTs of patients with BCLC stage C who underwent reductive hepatectomy with and without subsequent local treatments were 18.6 and 2.6 months, respectively, representing significant differences ($p < 0.0001$) (Fig. 4b). Considering the favorable survival with reductive hepatectomy combined with subsequent local treatments for both stages B and C disease, aggressive strategies that include reductive hepatectomy and subsequent local treatments may be justified. In addition, the MST of patients with BCLC stage C who underwent reductive hepatectomy and subsequent local treatments (18.6 months) (Fig. 4b) was comparable to that of patients who underwent complete hepatectomy (19.5 months) (Fig. 3); this was a particularly important finding regarding BCLC stage C treatment. Although the data were insufficient to draw robust conclusions, reductive hepatectomy alone appeared to contribute little toward longer survival in both stages B and C disease (Fig. 4a, b). When the number of residual tumors was ≤ 3, local treatments, including repeat resection, RFA, and TACE, were effective. However, for advanced HCCs associated with multiple intrahepatic metastases, PIHP should be selected after reductive hepatectomy. No significant difference in overall survival was observed according to the subsequent local treatments, as shown in Supplementary Figure 1. The completion of subsequent local treatment according to tumor status is a key component for prolonged patient survival after reductive hepatectomy.

Several investigators have demonstrated the effectiveness of reductive hepatectomy [14, 15, 19, 20]. Wakabayashi et al. [21] reported the treatment outcomes of patients with multiple bilobar HCC and demonstrated significantly better survival rates in patients who underwent reductive hepatectomy plus subsequent local treatments than in those treated with non-surgical treatments such as TACE and TAI. Although their retrospective studies also indicated the clinical relevance of reductive hepatectomy, their small sample sizes have precluded widespread adoption of this strategy. To the best of our knowledge, this is the largest case series, with more than 100 cases, that has

been used to evaluate the efficacy of reductive hepatectomy for advanced HCCs with a focus on BCLC B and C stages.

Among 314 patients, a total of 58 (18.5%) developed serious complications (Clavien-Dindo grade III or higher) after hepatectomy. Patients who developed serious complications after reductive hepatectomy could not receive subsequent treatments for remnant tumors, and this may be the largest reason why the survival rate of patients who underwent reductive hepatectomy without subsequent local treatments was dismal. Although there was no significant difference regarding the proportion of complications between patients treated with complete versus reductive hepatectomy, the proportion of significant complications seemed higher in the present study than previously reported data [22, 23]. This fact suggests that surgical stress can be particularly severe in this patient population (those with stages B and C advanced HCC). A low preoperative serum albumin level can be a possible predictive factor for a failure to complete treatment as shown in Supplementary Table 2. Considering these treatment results and the invasiveness of reductive hepatectomy, this aggressive treatment strategy, which includes reductive hepatectomy and subsequent local treatment, may be justified only in patients with sufficient liver function and performance status to withstand postoperative local treatments.

The limitations of the present study include the retrospective study design and strong selection bias of the patient population. The conclusions drawn from the present study are constrained by a lack of comparative data with other non-surgical treatments. The reported MSTs of BCLC stage B and stage C patients who underwent TACE were 9.2 to 30 months [24-27]. In addition, other modalities, including stereotactic body radiotherapy alone or in combination with TACE, have been recently reported [28, 29]. The patients in the present study had large and/or life-threatening tumors, which were deemed difficult to control with locoregional treatments other than hepatectomy. Thus, they might potentially have advanced-stage disease. Accordingly, the significant heterogeneity in the patients' backgrounds in these stages precludes direct comparison with our data. In addition, deterioration of general condition due to hepatectomy is one of the main reasons for disqualifying patients from further treatments following reductive hepatectomy. This selection bias affects the impact of subsequent local treatments and makes it difficult to assess their efficacy in terms of survival. However, favorable outcomes can certainly be expected with surgical intervention for a specific population of highly advanced HCCs, and future studies will be required to determine its indication preoperatively.

In conclusion, survival benefits are obvious for both BCLC stages B and C disease when complete hepatectomy can be performed safely. In addition, reductive hepatectomy is quite acceptable for both BCLC stages B and C HCC, when subsequent local treatments of remnant liver tumors can be introduced safely after reductive hepatectomy. Meanwhile, reductive hepatectomy itself has little clinical relevance when subsequent local treatments for remnant liver tumors were not performed. Thus, a cautious approach regarding patient selection is mandatory for this aggressive strategy. Although further studies will be necessary to confirm our findings, the present study will serve as an important indicator of the treatment algorithm for advanced HCC in the era of upcoming anti-tumor drugs.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our institutional review board.

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