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Conversion Surgery after Immune Checkpoint Inhibitor-Based Combination Therapy for Initially Unresectable Hepatocellular Carcinoma: A Retrospective Cohort Study

Mingjian Piao Chengjie Li Ziyue Huang Nan Zhang Jiongyuan Li Xu Yang Shuofeng Li Shanshan Wang Ziyu Xun Longhao Zhang Boyu Sun Ting Zhang Xiaobo Yang Haitao Zhao

Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Keywords
Conversion surgery · Immune checkpoint inhibitors · Unresectable hepatocellular carcinoma · Survival outcomes

Abstract

Introduction: Hepatocellular carcinoma (HCC) has a high incidence rate and is often asymptomatic in its early stages. Combination therapies using immune checkpoint inhibitors (ICIs) have demonstrated survival benefits and high objective response rates, offering hope for conversion surgery in patients with initially unresectable HCC. We aimed to investigate the oncological outcomes of conversion surgery compared to those with continuing systemic treatment alone in patients who responded well to ICI-based therapy, as well as the surgical outcomes associated with conversion surgery. ***Methods:*** We consecutively enrolled patients diagnosed with HCC between January 1, 2019, and February 1, 2024. These patients received treatment with ICIs combined with either anti-vascular endothelial growth factor antibodies or tyrosine kinase inhibitors. Tumor response and resectability were assessed every 2 months. Patients who responded positively and met the criteria for conversion surgery were included. ***Results:*** Among 613 patients with initially unresectable HCC, 128 achieved conversion and met the surgical resection criteria during combination therapy. Of these, 54 continued nonsurgical comprehensive treatment, 74 underwent conversion surgery, and 57 continued their original treatment post-surgery. The median follow-up time was 24.1 and 42.5 months for the surgery and non-surgery groups, respectively. The median progression-free survival (PFS) was 29.4 months in the surgery group versus 11.2 months in the non-surgery group ($p < 0.0001$, hazard ratio [HR] = 0.39 [0.24–0.63]). The median OS was not reached in the surgery group, compared to 25.4 months in the non-surgery group ($p < 0.0001$, HR = 0.26 [0.14–0.46]). Multivariate Cox regression analysis indicated that conversion surgery was independently associated with improved OS and PFS ($p < 0.001$), and continuing the original treatment post-surgery significantly influenced OS and recurrence-free survival. ***Conclusion:*** Conversion surgery after meeting the surgical criteria during immunotherapy provides significant prognostic benefits for

Mingjian Piao, Chengjie Li, Ziyue Huang, Nan Zhang and Jiongyuan Li contributed equally to this work.
Trial registration number: NCT03892577.

karger@karger.com
www.karger.com/lic

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Correspondence to:
Xiaobo Yang, yangxiaobo67@pumch.cn
Haitao Zhao, zhaoht@pumch.cn

patients with initially unresectable HCC, demonstrating high safety and R0 resection rates. For those undergoing conversion surgery, promptly resuming the original treatment after surgery is necessary.
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Introduction

Primary liver cancer is one of the most common malignant tumors worldwide, with its mortality rate increasing annually [1, 2]. Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer [3]. Surgical resection remains the only curative option for HCC and offers the potential for long-term survival. However, most patients are diagnosed at advanced stages, and approximately 30% are eligible for immediate surgical intervention at the time of diagnosis [4, 5]. Despite recent advances in immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs), which have extended survival for some patients with advanced HCC, the objective response rate for most treatment regimens remains low, and the proportion of benefiting patients is still limited [6–8]. Therefore, improving survival and prognosis in advanced HCC remains a significant clinical challenge.

Conversion therapy, which aims to render unresectable tumors resectable, has emerged as a promising treatment approach. Before the advent of ICIs, the primary modalities for conversion therapy in advanced, unresectable HCC included transcatheter arterial chemoembolization (TACE) [9], hepatic arterial infusion chemotherapy (HAIC) [10, 11], selective internal radiation therapy and external beam radiation therapy [9, 12]. Since 2018, TKIs and ICIs have made significant progress in the treatment of advanced HCC, and their potential role in conversion therapy has gained increasing attention [13]. However, the optimal post-conversion treatment strategy remains unclear. Whether to proceed with aggressive surgery following successful conversion or continue with the original systemic treatment regimen is still debated, and the efficacy and safety of conversion surgery have not yet been well established.

We aimed to explore whether surgical resection would delay tumor progression and prolong survival in patients with initially unresectable HCC who responded to ICI-based combination therapy and met surgical criteria. In this study, we investigated the oncological outcomes of conversion surgery compared to those of continuing systemic treatment alone in patients who responded well to ICI-based therapy, as well as the surgical outcomes associated with conversion surgery.

Methods

From January 1, 2019, to February 1, 2024, patients with unresectable HCC who received at least two cycles of ICI-based combination therapy at Peking Union Medical College Hospital (PUMCH) were enrolled in this study. The diagnosis of HCC was made based on multiphase computed tomography (CT), magnetic resonance imaging (MRI), or fine-needle aspiration pathology in accordance with established HCC guidelines. Unresectability was determined by a multidisciplinary team (MDT) and was defined as the inability to achieve R0 resection, even with aggressive surgical procedures such as combined vascular resection, due to distant metastases, or the inability to tolerate curative liver resection (e.g., due to insufficient remaining liver volume).

Patients who met the criteria for conversion surgery after receiving ICI-based combination therapy were included. We compared survival outcomes between patients who underwent conversion surgery and those who opted not to. The exclusion criteria for this study were (1) residual or recurrent HCC and (2) the presence of other malignancies.

This study was registered at ClinicalTrials.gov (identifier: NCT03892577) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board and the Ethics Committee of PUMCH.

Treatment and Data Collection

All eligible patients received intravenous programmed cell death protein 1 (PD-1)/programmed death ligand-1 inhibitor on day 1 of a 21-day treatment cycle. The drugs included pembrolizumab [6], camrelizumab [14], sintilimab [15], tislelizumab (200 mg) [16], toripalimab (240 mg) [17], atezolizumab (1,200 mg) [8], nivolumab, or cadonilimab (anti-PD-1 and CTLA-4 bispecific antibody, 15 mg/kg) [18, 19]. Patients also received either a TKI or an anti-vascular endothelial growth factor agent, such as lenvatinib (12 mg/day for body weight ≥60 kg or 8 mg/day for body weight <60 kg), apatinib (250 mg orally once daily) [6, 14], regorafenib (160 mg orally for the first 3 weeks of each 4-week cycle), or bevacizumab (15 mg/kg intravenously on day 1 of a 21-day treatment cycle) [8, 15, 20]. The choice of ICIs was at the patient's discretion, and decisions to proceed with local therapy (e.g., TACE, HAIC, or radiotherapy) were based on MDT recommendations. Patient demographics, laboratory results, surgical and pathological outcomes, stereotactic therapy regimens, safety assessments, grading, and clinical outcomes were recorded.

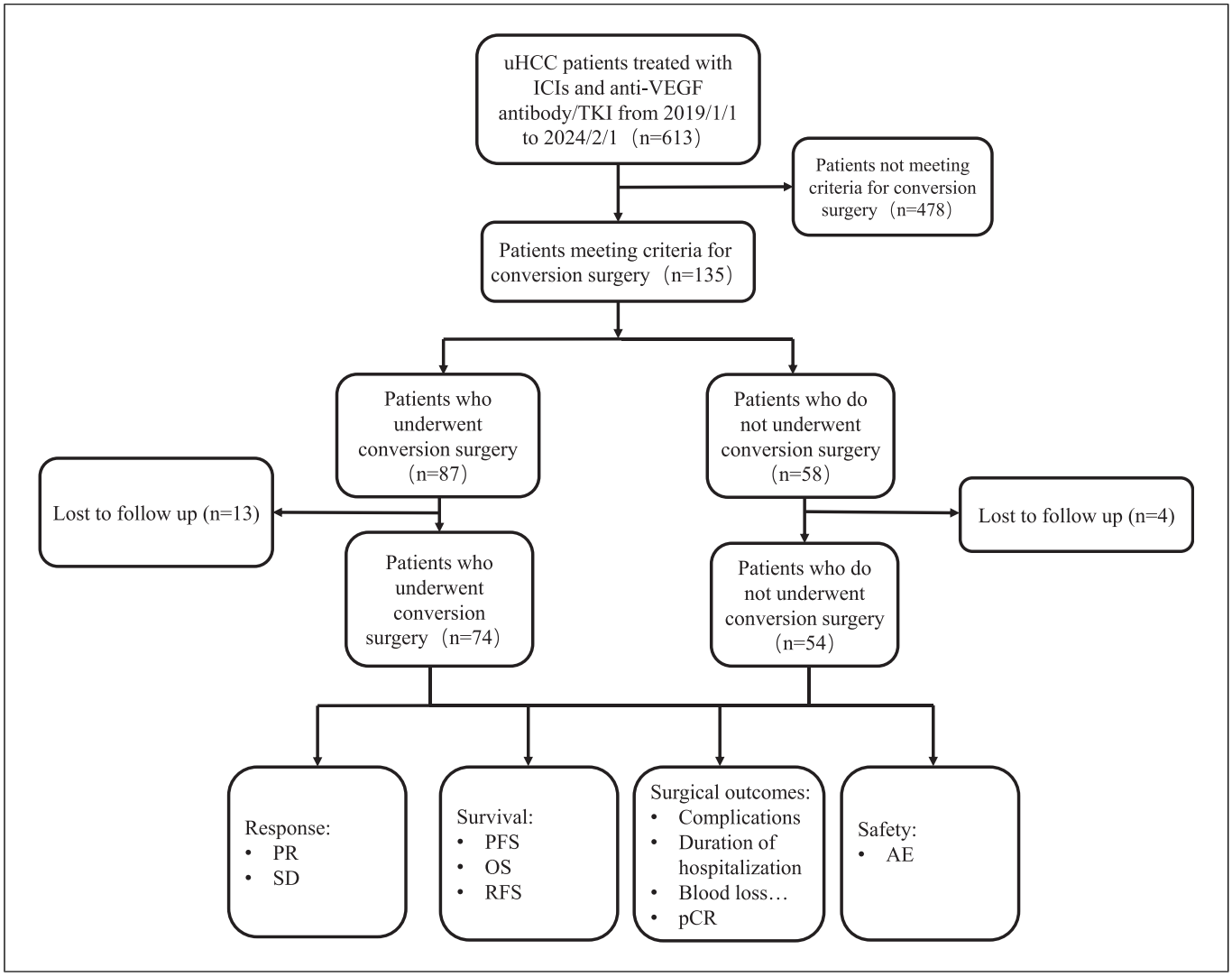


Fig. 1. Patient flowchart. AE, adverse event; HCC, hepatocellular carcinoma. OS, overall survival; PFS, progression-free survival; pCR, pathological complete response; RFS, recurrence-free survival; ICIs, immune checkpoint inhibitors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Assessments and Endpoints

Complete blood counts; liver, renal, thyroid, adrenal, and cardiac functions; and tumor markers were monitored every 2–3 weeks before each anti-PD-1 antibody treatment cycle. Clinical objective responses were evaluated by independent imaging, using the Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 and modified RECIST (mRECIST). Evaluations were performed by professional radiologists at PUMCH who were blinded to therapeutic outcomes and clinicopathological features. Resectability was assessed by the investigator every 6–8 weeks (the first assessment before the fourth cycle). The resectability criteria were defined based on the "Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition)" and our previous studies [21, 22]. Patients who successfully converted and underwent curative-intent surgery received adjuvant therapy based on postoperative pathology or willingness. Follow-up visits occurred 4 weeks after surgery and then every 12 weeks.

Safety was continuously monitored through vital signs, clinical laboratory test results, and assessment of adverse events (AEs), which were evaluated based on incidence and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The primary study endpoint included overall survival (OS), defined as the time from the initiation of

Table 1. Patient demographics and baseline characteristics

Characteristic	Surgery, *n* (%)			*p* value[1]
	overall, *N* = 128	yes, *N* = 74 (57.8)	no, *N* = 54 (42.2)	
Sex				0.774
Male	115 (89.8)	66 (89.2)	49 (90.7)	
Female	13 (10.2)	8 (10.8)	5 (9.3)	
Age				0.180
≥60 years	46 (35.9)	23 (31.1)	23 (42.6)	
<60 years	82 (64.1)	51 (68.9)	31 (57.4)	
HBV infection				0.141
Yes	115 (89.8)	64 (86.5)	51 (94.4)	
No	13 (10.2)	10 (13.5)	3 (5.6)	
Cirrhosis				0.535
Yes	96 (75.0)	54 (73.0)	42 (77.8)	
No	32 (25.0)	20 (27.0)	12 (22.2)	
BCLC stage				0.096
B	36 (28.1)	25 (33.8)	11 (20.4)	
C	92 (71.9)	49 (66.2)	43 (79.6)	
Child-Pugh				>0.999
A	117 (91.4)	68 (91.9)	49 (90.7)	
B	11 (8.6)	6 (8.1)	5 (9.3)	
ECOG				0.935
0	100 (78.1)	58 (78.4)	42 (77.8)	
1	28 (21.9)	16 (21.6)	12 (22.2)	
Macrovascular invasion				0.093
Yes	60 (46.9)	30 (40.5)	30 (55.6)	
No	68 (53.1)	44 (59.5)	24 (44.4)	
PVTT				0.066
Yes	43 (33.6)	20 (27.0)	23 (42.6)	
No	85 (66.4)	54 (73.0)	31 (57.4)	
Extrahepatic metastasis				0.333
Yes	46 (35.9)	24 (32.4)	22 (40.7)	
No	82 (64.1)	50 (67.6)	32 (59.3)	
Pulmonary metastasis				0.281
Yes	8 (6.2)	3 (4.0)	5 (9.3)	
No	120 (93.8)	71 (96.0)	49 (90.7)	
Lymph node metastasis				0.395
Yes	33 (25.8)	17 (23.0)	16 (29.6)	
No	95 (74.2)	57 (77.0)	38 (70.4)	
Abdominal cavity metastasis				0.698
Yes	7 (5.5)	5 (6.8)	2 (3.7)	
No	121 (94.5)	69 (93.2)	52 (96.3)	
Adrenal gland metastasis				>0.999
Yes	3 (2.3)	2 (2.7)	1 (1.9)	
No	125 (97.7)	72 (97.3)	53 (98.1)	
Baseline AFP (ng/mL)				0.668
Median (IQR)	415.3 (19.7, 4,281.8)	370.5 (17.3, 3,448.6)	415.3 (45.6, 5,662.5)	
Unknown	16	10	6	

HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; IQR, interquartile range; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein. [1]Pearson's chi-squared test, Fisher's exact test, Wilcoxon rank sum test.

Table 2. Summary of treatment of two groups of patients

Characteristic	Surgery, *n* (%)	
	no, *N* = 54	yes, *N* = 74
Treatment		
PD-1 inhibitors + TKI	52 (96.3)	69 (93.2)
Atezolizumab + bevacizumab	2 (3.7)	4 (5.4)
Cadonilimab + TKI	0 (0.0)	1 (1.4)
Prior local therapy		
No	15 (27.8)	8 (10.8)
Yes	39 (72.2)	66 (89.2)
Tumor response, by RECIST 1.1		
PR	45 (83.3)	44 (59.5)
SD	9 (16.7)	30 (40.5)
Tumor response, by mRECIST		
PR	45 (83.3)	63 (85.1)
SD	9 (16.7)	11 (14.9)
Treatment line		
1	48 (88.9)	60 (81.1)
2	4 (7.4)	12 (16.2)
≥3	2 (3.7)	2 (2.7)

ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease.

ICI treatment to death or the last follow-up. Secondary endpoints included OS from surgery (time from surgery to death or the last follow-up), progression-free survival (PFS; time from ICI initiation to disease progression, recurrence, last follow-up, or death), and recurrence-free survival (RFS; time from surgery to first recurrence, last follow-up, or death). Safety, postoperative hospital stay, and surgical complications (classified according to the Clavien-Dindo classification) were also evaluated. The time from ICI initiation to surgery was analyzed as well.

Indication and Procedure for Conversion Surgery

Patients considered for conversion surgery were required to show a confirmed positive response, classified as partial response or shrinkage-stable disease, as assessed via CT or MRI of the chest, abdomen, and pelvis. Positron emission tomography-CT (PET-CT) was also used for evaluation when necessary.

The indications for surgery included (1) hepatic lesions: radiographically favorable response lasting ≥1 month, (2) metastatic activity: no distant metastases or metabolic activity on PET-CT for ≥1 month, (3) tumor marker stabilization, (4) technically resectable vascular tumor thrombus, (5) liver volume: expected remnant liver volume ≥35% in patients without chronic liver disease and ≥45% in patients with chronic liver disease, (6) absence of contraindications for hepatectomy. R0 resectability was assessed by an experienced MDT. Subsequent resection was performed after consultation, and informed consent was obtained from all patients. The risks and benefits of surgery were clearly explained to all patients.

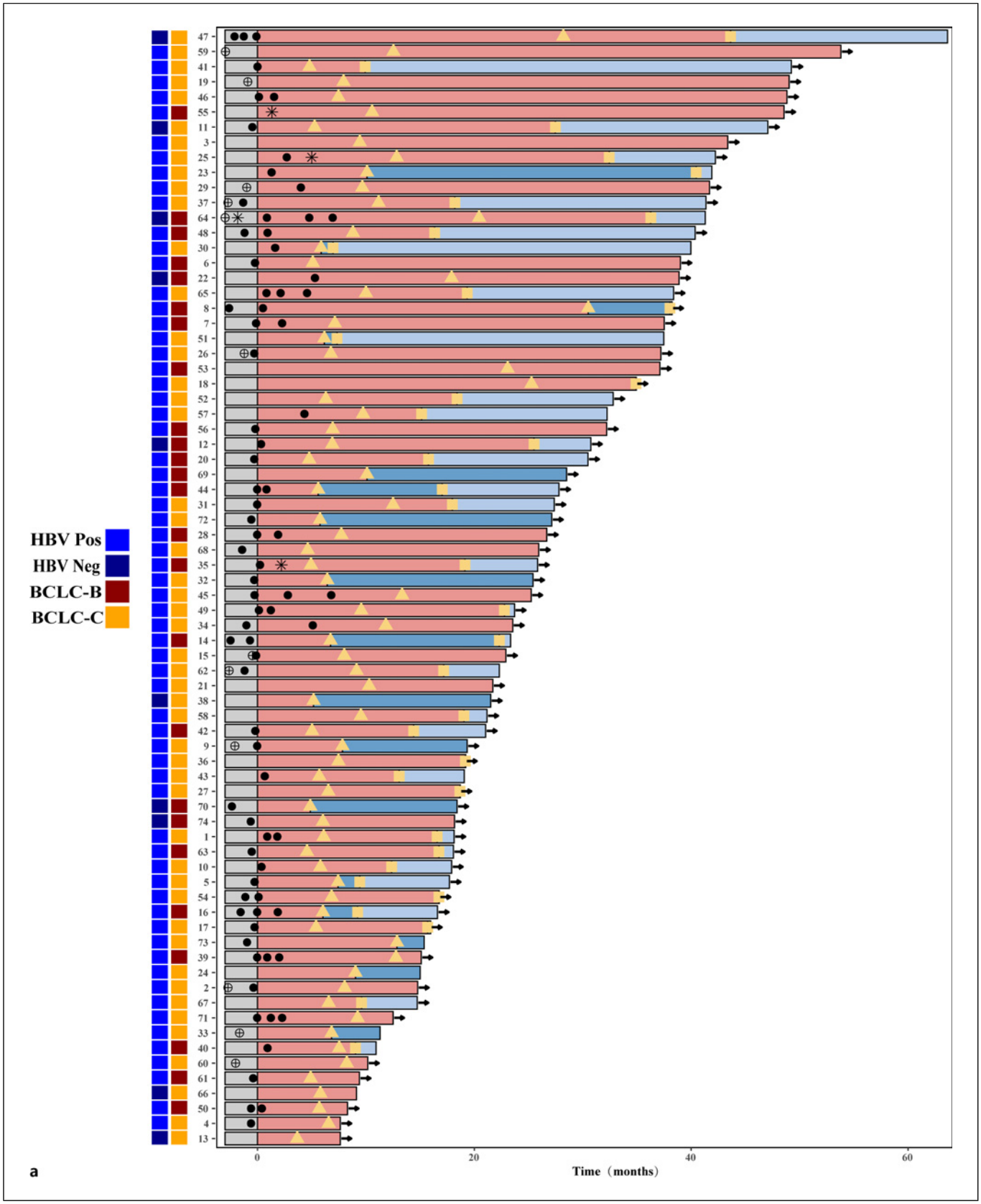
The decision to proceed with conversion surgery was based on patient autonomy. The resection approach was selected on a case-by-case basis. A laparoscopy or laparotomy approach was adopted based on the extent and complexity of the cases. Suspicious metastatic lesions were excluded from frozen section evaluation. A single experienced surgical team performed all surgeries. Before conversion surgery, TKIs and ICIs were discontinued for at least 1 week. A pathological complete response (pCR) was defined as the absence of residual viable tumor cells on hematoxylin and eosin staining of slide sections from completely resected primary tumors or metastatic lesions.

Postoperative Management and Follow-Up

Postsurgical therapy resumed once the patients recovered from surgery, typically 3–4 weeks after the surgery. The MDT determined the choice and duration of postoperative systemic therapy, typically for 2 years, based on the patient's original response, postoperative clinical conditions, and preference. Upon the diagnosis of tumor recurrence, subsequent treatment was based on the recurrence pattern, clinical conditions, and other relevant factors. Patients who did not undergo surgery were advised to continue the initial effective therapy. Tumors were assessed 4 weeks after surgery and every 12 weeks thereafter using serum alpha-fetoprotein levels and imaging examinations. Enhanced MRI/CT scans were conducted every 2–3 months or when recurrence was suspected based on elevated serum tumor biomarkers. PET-CT was performed if clinically indicated. The endpoint of the follow-up was June 29, 2024.

Statistical Analysis

Continuous variables were presented as medians with ranges or interquartile ranges (IQRs) and compared using the unpaired *t* test or Mann-Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages and compared using a Fisher's exact test. Survival analyses were conducted using the Kaplan-Meier method and compared using the log-rank test. A Cox regression model was used for multivariate analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software (version 4.2.2) and GraphPad Prism software (version 9).



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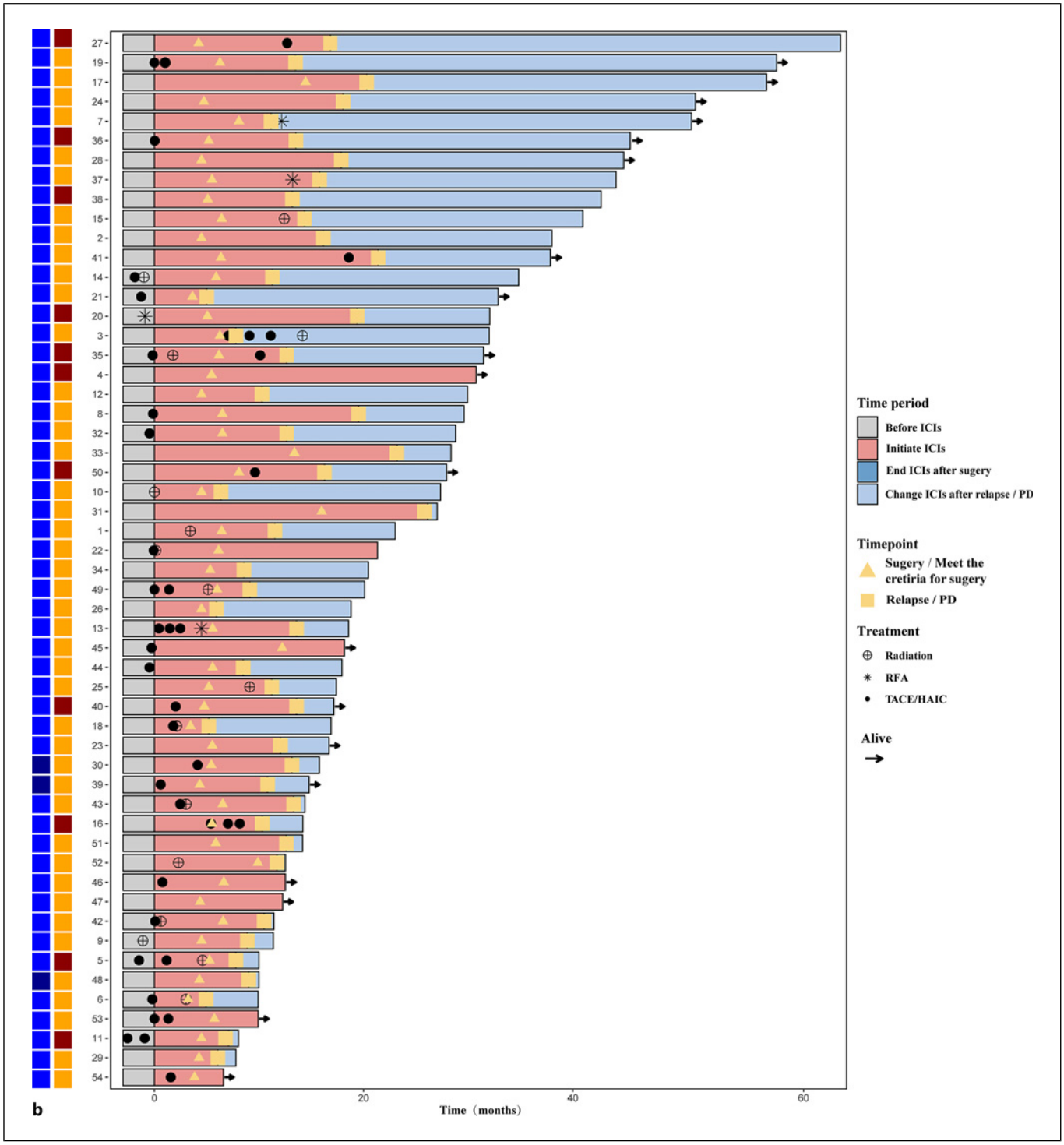


Fig. 2. Swimming chart showing duration of treatment in two groups. **a** Surgery group. **b** Non-surgery group. BCLC, Barcelona Clinic Liver Cancer; ICIs, immune checkpoint inhibitors; PD, progressive disease; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

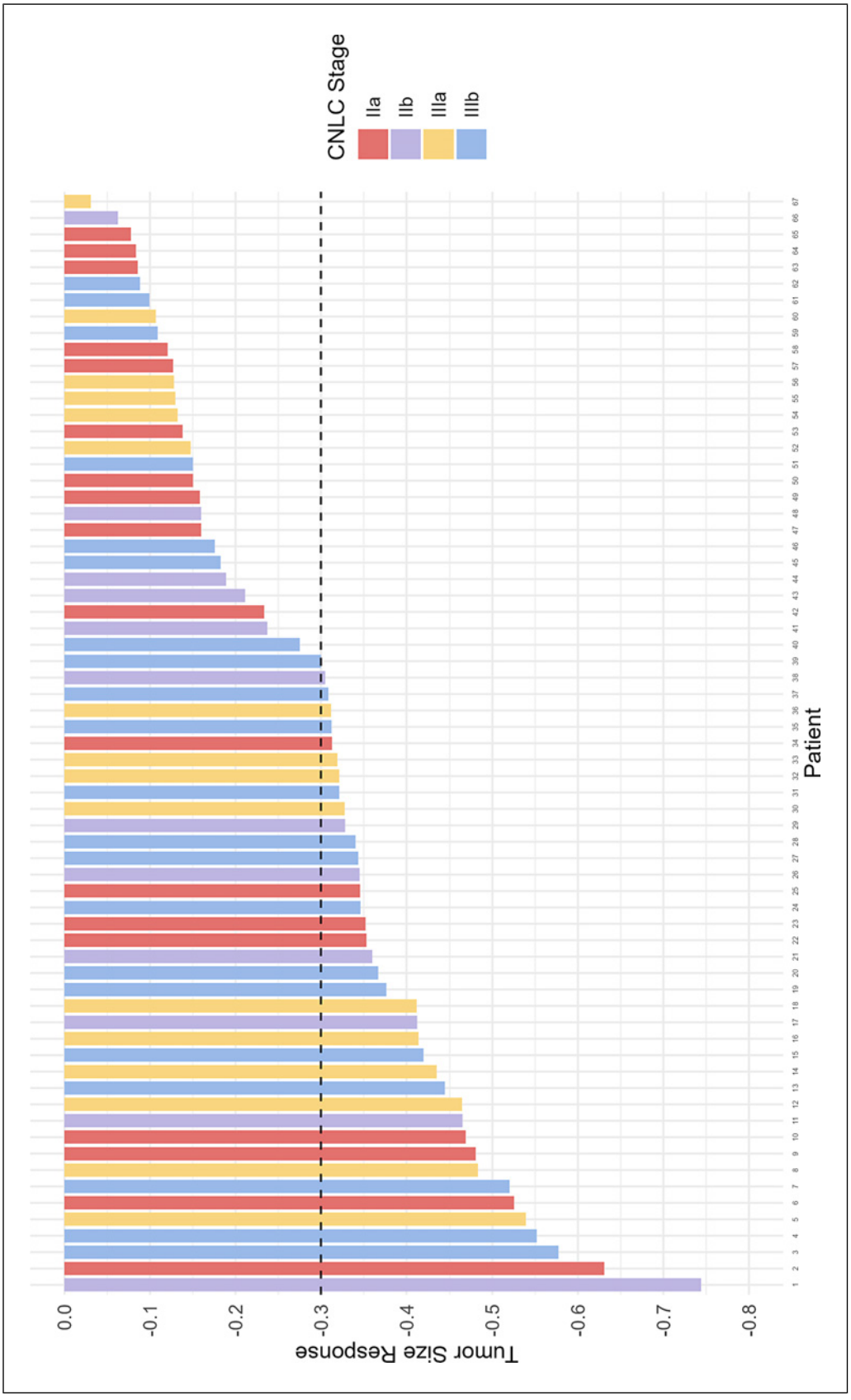


Fig. 3. Response of 74 patients with HCC to conversion therapy. Waterfall plot of the optimal percentage change in target lesion size from baseline according to RECIST 1.1. Seven patients in the surgical group were not included in the presentation due to the absence of specific tumor size information, with only their tumor response information available. Consequently, their data could not be represented in the analysis. CNLC, China Liver Cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version.1.1.

Table 3. Surgical and oncological outcomes of surgery group (N = 74)

Characteristic	
ICI cycles	
Median (IQR)	4 (3, 6)
Unknown	6 (8.1)
Interval from initial treatment to operation, months	
Median (IQR)	4.5 (2.8, 6.9)
Pre-operation AFP, *n* (%)	
<400 ng/mL	60 (81.1)
≥400 ng/mL	14 (18.9)
Surgical type, *n* (%)	
Laparoscopic	40 (54.1)
Open	34 (45.9)
R0 resection, *n* (%)	
No	6 (8.1)
Yes	68 (91.9)
Pathological differentiation[1], *n* (%)	
Moderate	31 (41.9)
Moderate-high	9 (12.2)
Moderate-poor	8 (10.8)
Poor	5 (6.8)
pCR	17 (22.0)
Unknown	4 (5.4)
MVI, *n* (%)	
M0	25 (33.8)
M1	10 (13.5)
M2	7 (9.5)
M3	1 (1.3)
Unknown	31 (41.9)
pCR, *n* (%)	
No	51 (68.9)
Yes	23 (31.1)
Blood loss, mL, *n* (%)	
Median (IQR)	200 (100, 400)
Blood transfusion, *n* (%)	
No	47 (63.5)
Yes	27 (36.5)
Grading of postoperative complications (Clavien-Dindo), *n* (%)	
I	44 (59.5)
II	27 (36.5)
IIIa	2 (2.7)
IIIb	1 (1.3)
Hospital stays, days	
Median (IQR)	11.0 (9.0, 14.0)
Continue the original treatment after surgery, *n* (%)	
No	13 (17.6)
Yes	57 (77.0)
Unknown	4 (5.4)

IQR, interquartile range; AFP, alpha-fetoprotein; pCR, pathological complete response; MVI, microvascular invasion; ICIs, immune checkpoint inhibitors. [1]Some patients who underwent puncture pathology biopsy prior to conversion therapy had the type of pathologic differentiation based on the pretreatment period. pCR refers to pathology results suggesting complete necrosis of tumor cells, which could not be determined. Unknown indicates that the pathology results did not report the type of differentiation, but residual tumor cells remained.

Results

Patient Characteristics

Between January 1, 2019, and February 1, 2024, 613 patients receiving ICI-based combination therapy were screened for inclusion in this study. Of these, 135 patients met the criteria for conversion surgery after treatment. Following the exclusion of patients with incomplete information or those lost to follow-up, 128 patients were included in the final analysis. Among them, 74 (57.8%) opted for conversion surgery after receiving a thorough explanation of the potential benefits and risks, whereas 54 patients declined surgery, citing concerns over surgical risks and uncertain benefits, and continued with their initial systemic therapy. We conducted separate analyses of survival outcomes, ICI treatment, surgical procedures, and safety of ICI treatment in both groups, as shown in Figure 1.

Table 1 outlines the baseline characteristics of patients in the surgery and non-surgery groups. Baseline demographics and disease characteristics were generally balanced between the two groups. Most patients in both groups were male, with no significant difference in sex distribution (p = 0.774). The age distribution indicated a higher proportion of patients aged <60 years across the entire cohort, with a similar trend in both groups. Notably, 49 of the 74 patients (66.2%) in the surgery group were classified as stage C according to the Barcelona Clinic Liver Cancer (BCLC) staging system, a trend similar to the non-surgery group (p = 0.096). There were no significant differences in macrovascular invasion and extrahepatic metastasis between the groups (Table 1). Additionally, the median baseline alpha-fetoprotein levels, indicative of tumor burden, were comparable between the surgery and non-surgery groups, with no significant difference [23].

Treatment and Efficacy

All 128 patients in both groups received at least two cycles of various ICIs, TKIs, or anti-vascular endothelial growth factor antibodies. Most patients received lenvatinib as TKI therapy. Specific treatment regimens are listed in Table 2 and online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000543994). Local therapies, such as TACE, HAIC or radiotherapy, were chosen based on individual tumor characteristics and patient preferences. In the surgery group, 66 patients (89.2%) received local therapy, compared to 39 patients (72.2%) in the non-surgery group. Detailed information on the 128 patients who underwent conversion therapy is shown in Figure 2.

All 128 patients who met the criteria for resectability achieved PR or stable disease according to RECIST 1.1 and

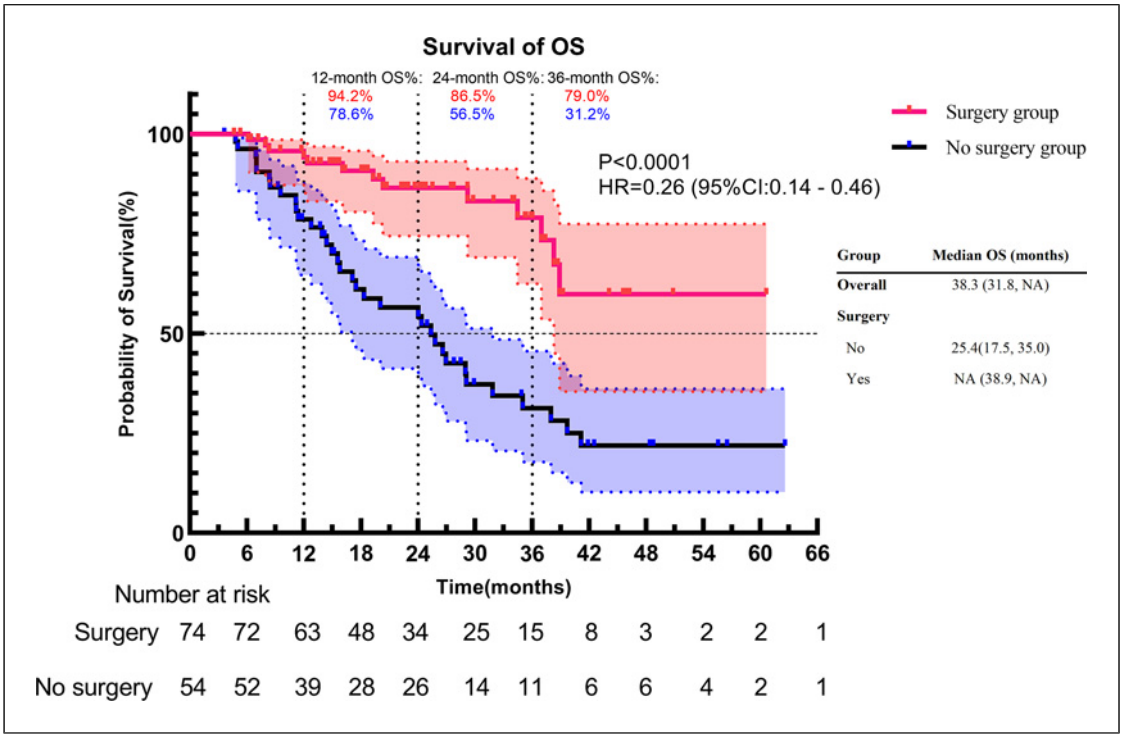


Fig. 4. Kaplan-Meier analysis of OS of surgery group and non-surgery group. OS, overall survival; HR, hazard ratio.

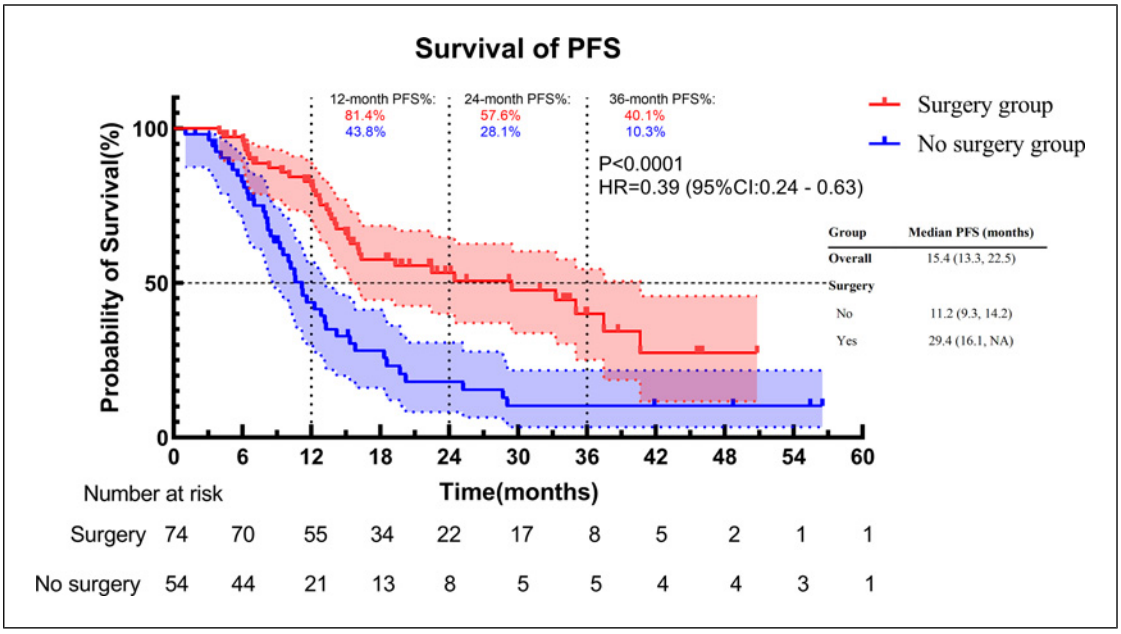


Fig. 5. Kaplan-Meier analysis of PFS of surgery group and non-surgery group. PFS, progression-free survival; HR, hazard ratio.

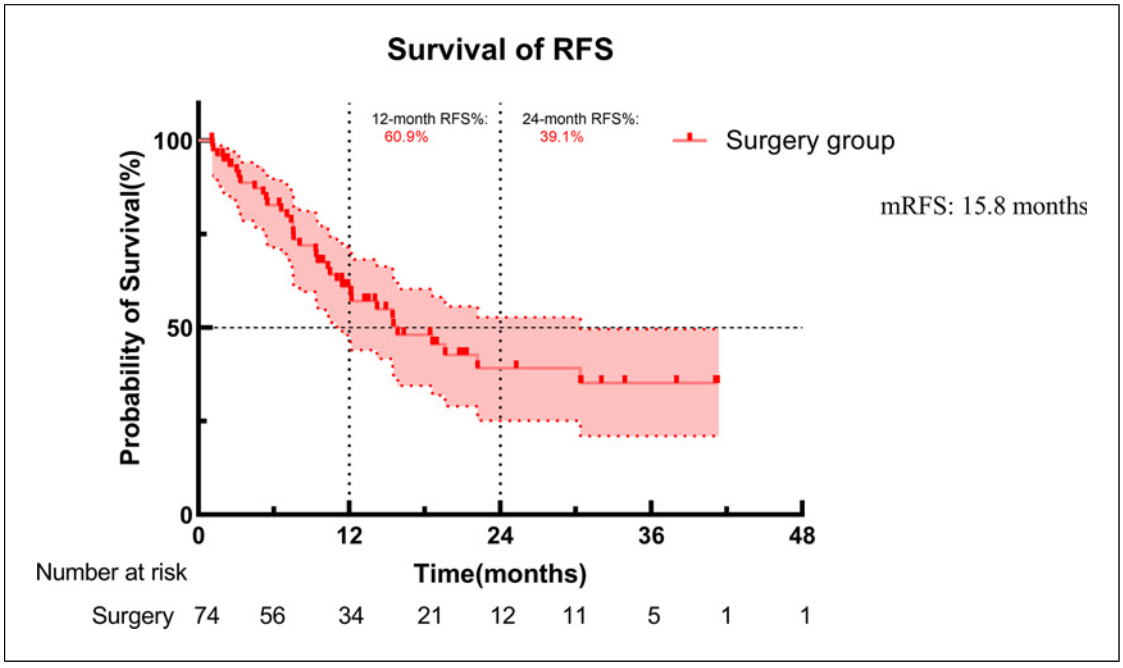


Fig. 6. Kaplan-Meier analysis of RFS of surgery group. RFS, recurrence-free survival; HR, hazard ratio.

mRECIST, showing significant tumor size reduction, and none of the patients experienced pseudoprogression during treatment. For patients with extrahepatic metastases, a complete response or significant loss of activity based on PET-CT was required. Specific information on extrahepatic metastases, including the local treatment modalities, in patients who initially had extrahepatic metastases and subsequently underwent conversion surgery is provided in online supplementary Table S2. Tumor response rates for RECIST 1.1 in the surgery group are detailed in Figure 3. In this group, the objective response rate was 85.1% (63/74) for mRECIST and 59.5% (44/74) for RECIST 1.1.

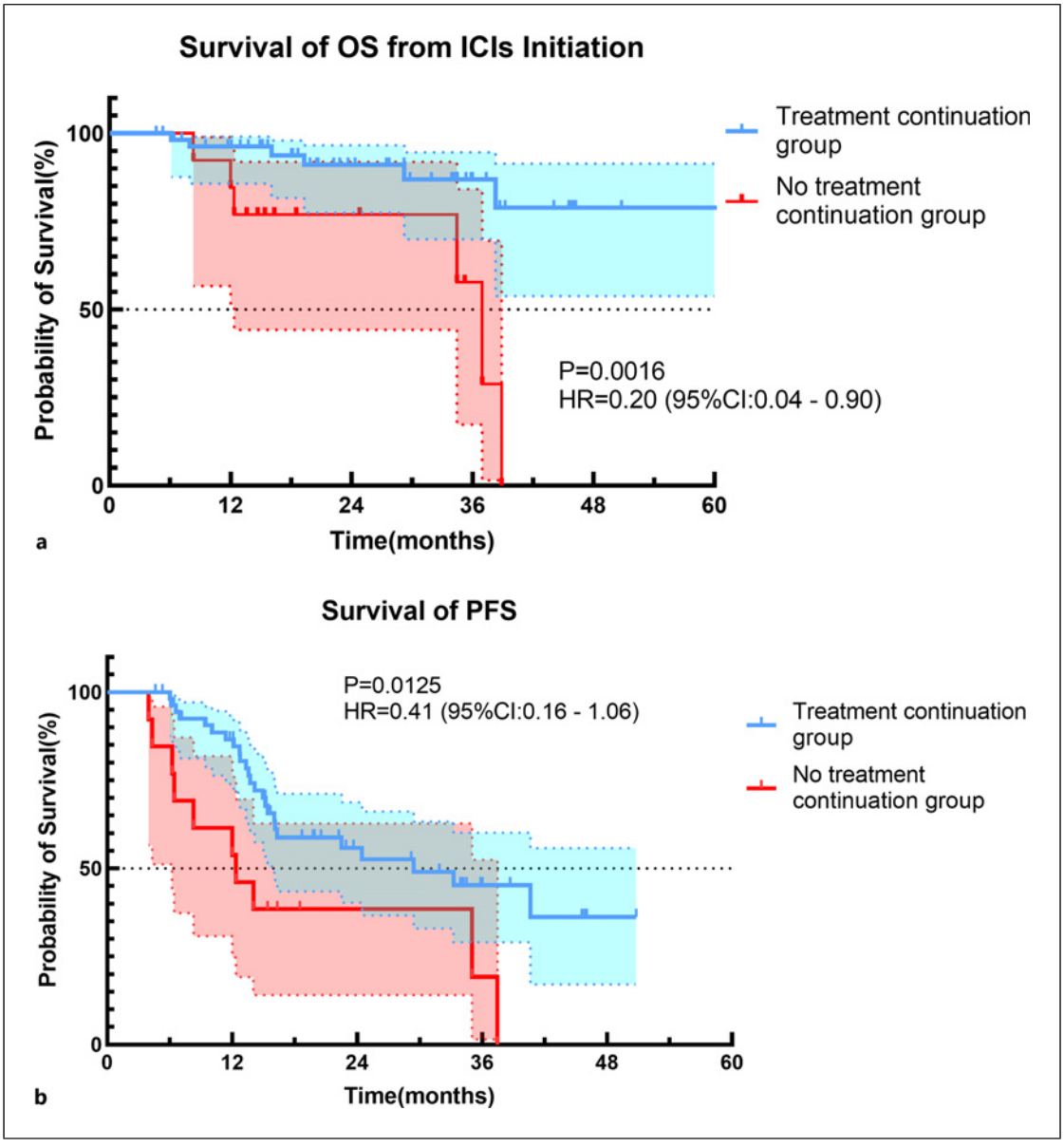
Surgical Resection of Tumors

Of the eligible patients, 74 underwent conversion surgery. The initial cause of unresectability for all patients and their tumor stage before and after conversion therapy are detailed in online supplementary Table S3. Preoperative systemic treatment details and surgery-related information are presented in Table 3. These patients received a median of four ICI cycles (IQR: 3–6 cycles), with a median time from initial treatment to surgery of 4.5 months. The proportions of open and laparoscopic surgeries were comparable (54.1% vs. 46.0%, respectively). R0 resection was achieved in 68 patients (91.9%), with 23 (31.1%) patients showing pCR on postoperative pathology results. Median intraoperative blood loss was 200 mL (IQR: 100–400 mL), and 27 patients (36.5%) required intraoperative blood transfusions.

Only 3 patients experienced grade III or higher postoperative complications, including gastric emptying obstruction, deep vein thrombosis, and massive ascites due to infection. No grade IV or fatal complications were reported. There were no patients in the surgical group who died within 90 days of surgery. The median hospital stay for operated patients was 11 days (IQR: 9.0–14.0). Postoperatively, 57 patients (81.4%) resumed their preoperative conversion regimen 1–2 months after surgery until at least 2 years after ICI initiation. Thirteen patients (18.6%) either did not continue the original regimen or only received lenvatinib, depending on their tolerance and willingness. Postoperative treatment protocols were unclear for 4 patients due to loss to follow-up and were not included in the analysis.

Survival

As of the data cutoff on June 29, 2024, the median follow-up time was 24.1 months (range: 4.6–60.6 months) for the surgery group and 42.5 months (range: 3.6–62.6 months) for the non-surgery group. The surgery group demonstrated significantly longer PFS and OS compared to that of the non-surgery group. The median PFS was 29.4 months in the surgery group versus 11.2 months in the non-surgery group ($p < 0.0001$, HR = 0.39 [0.24–0.63]) (Fig. 4, 5). In the surgery



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group, the 1-, 2-, and 3-year PFS rates were 81.1%, 57.6%, and 40.1%, respectively. The median OS was not reached in the surgery group, compared to 25.4 months in the non-surgery group ($p < 0.0001$, HR = 0.26 [0.14–0.46]). The 1-, 2-, and 3-year OS rates in the surgery group were 94.1%, 86.5%, and 79.0%, respectively. Subgroup analyses indicated longer OS and PFS in most subgroups within the surgery group compared to the non-surgery group (online suppl. Fig. S1, S2). Patients with HBV infection, cirrhosis, and BCLC-C stage disease particularly benefited more from conversion surgery and had longer PFS and OS. The median RFS in the surgery group was 15.8 months, with 1-year and 3-year RFS rates of 60.9% and 39.1%, respectively (Fig. 6).

Multivariable Cox regression analysis of the entire cohort ($n = 128$) identified conversion surgery as an independent factor positively associated with both PFS (HR = 2.35, 95% CI: 1.40–3.94; $p < 0.001$) and OS (HR = 0.31, 95% CI: 0.16–0.60; $p < 0.001$) (online suppl. Tables S4, S5; Fig. S3, S4). We analyzed the incidence of recurrence in the surgical group patients. Tumor recurrence occurred in 36 patients, of which 29 had intrahepatic recurrence, 2 had pulmonary metastases, 1 had peritoneal metastases, 2 died of non-tumoral causes,

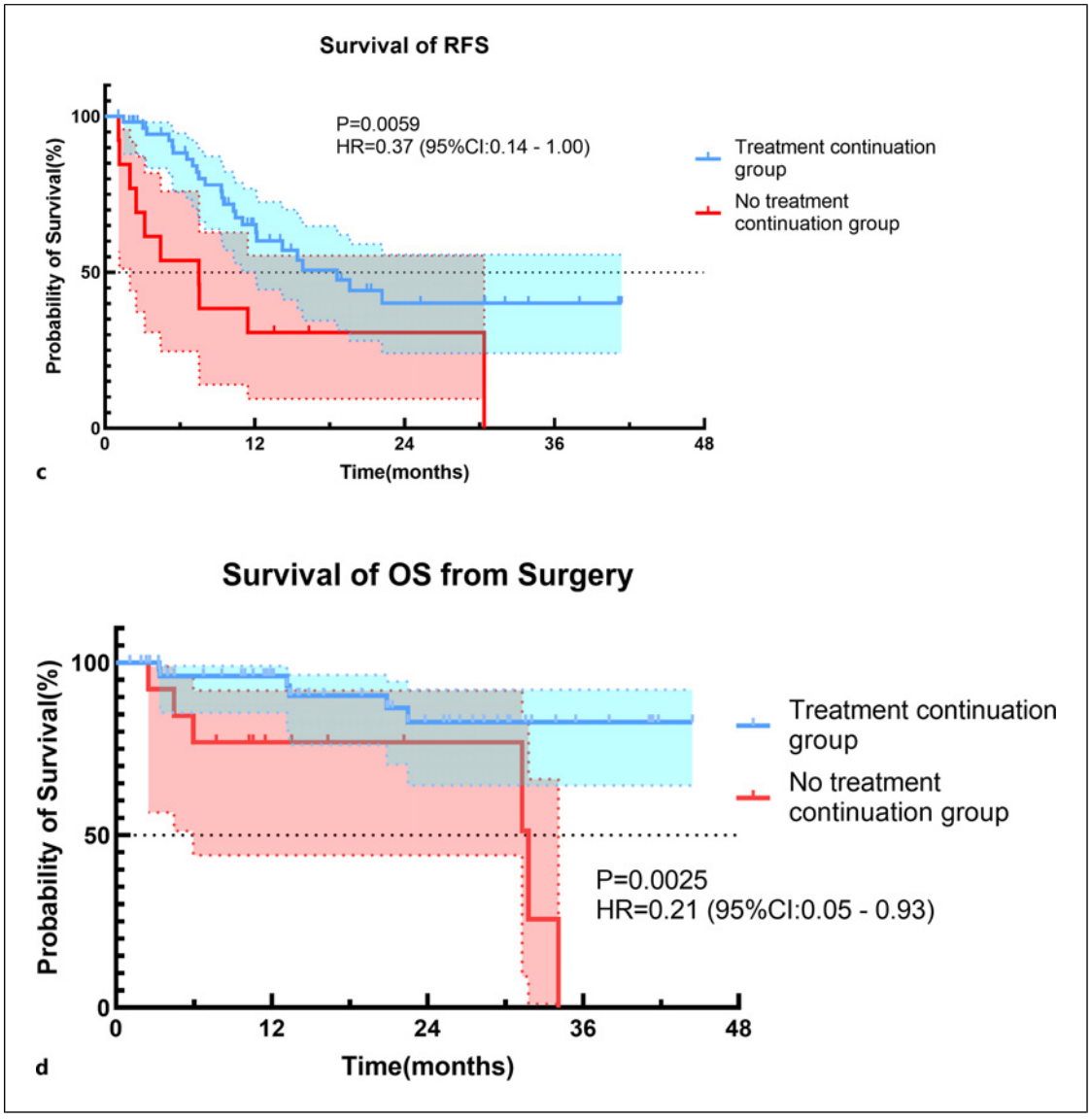

Fig. 7. Kaplan-Meier analysis of survival of treatment continuation group and treatment discontinuation group in surgery patients. **a** Kaplan-Meier estimates of overall survival from ICI initiation. **b** Kaplan-Meier estimates of PFS. **c** Kaplan-Meier estimates of RFS. **d** Kaplan-Meier estimates of overall survival from surgery. OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; HR, hazard ratio; ICIs, immune checkpoint inhibitors.

and 2 died of liver failure. An Eastern Cooperative Oncology Group score of 1 was a risk factor for reduced PFS in all patients (HR = 1.79, 95% CI: 1.06–3.05; p = 0.030) and for reduced RFS in the surgery group. Additionally, multivariate Cox regression analysis within the surgical cohort revealed that continuation of the original regimen post-surgery was an independent factor influencing RFS, OS, and PFS (online suppl. Tables S6, S7). Survival analysis of patients in the surgery group who received regular postoperative adjuvant therapy (n = 57) versus those who did not (n = 17) showed significant differences in RFS, PFS, and OS after ICI initiation and OS after surgery (Fig. 7). Based on this result, to further validate the important role of surgery as a local treatment in patients receiving full course immunotherapy, we separately compared OS and PFS in patients treated with adjuvant therapy with the active original regimen after conversion surgery to the non-operated group, which were also similarly statistically different, as detailed in online supplementary Figures S5 and S6.

Table 4. Most common AEs in two groups

	All, *n* (%)		Surgery, *n* (%)		No surgery, *n* (%)	
	any grade	3–4 grade	any grade	3–4 grade	any grade	3–4 grade
Total	606 (100.0)	72 (100.0)	271 (44.7)	32 (44.4)	335 (55.3)	40 (55.6)
Nausea	14 (10.9)	0 (0.0)	7 (9.5)	0 (0.0)	7 (13.0)	0 (0.0)
Hypothyroidism	31 (24.2)	2 (1.6)	15 (20.3)	1 (1.4)	16 (29.6)	1 (1.9)
Fever	15 (11.7)	0 (0.0)	6 (8.1)	0 (0.0)	9 (16.7)	0 (0.0)
Fatigue	43 (33.6)	11 (8.6)	21 (28.4)	6 (8.1)	22 (40.7)	5 (9.3)
Abdominal pain	27 (21.1)	1 (0.8)	14 (18.9)	1 (1.4)	13 (24.1)	0 (0.0)
Diarrhea	23 (18.0)	2 (1.6)	9 (12.2)	0 (0.0)	14 (25.9)	2 (3.7)
Proteinuria	3 (2.3)	0 (0.0)	3 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	47 (36.7)	17 (13.3)	22 (29.7)	7 (9.5)	25 (46.3)	10 (18.5)
Vomiting	15 (11.7)	0 (0.0)	7 (9.5)	0 (0.0)	8 (14.8)	0 (0.0)
Skin rash	22 (17.2)	3 (2.3)	12 (16.2)	1 (1.4)	10 (18.5)	2 (3.7)
Decreased appetite	54 (42.2)	3 (2.3)	21 (28.4)	2 (2.7)	33 (61.1)	1 (1.9)
Peripheral sensory disorder	12 (9.4)	2 (1.6)	4 (5.4)	0 (0.0)	8 (14.8)	2 (3.7)
Dysphonia	9 (7.0)	0 (0.0)	5 (6.8)	0 (0.0)	4 (7.4)	0 (0.0)
Decreased PLT	32 (25.0)	5 (3.9)	9 (12.2)	1 (1.4)	23 (42.6)	4 (7.4)
Muscle pain	18 (14.1)	2 (1.6)	8 (10.8)	2 (2.7)	10 (18.5)	0 (0.0)
Decreased WBC	24 (18.8)	3 (2.3)	10 (13.5)	2 (2.7)	14 (25.9)	1 (1.9)
Elevated ALT	57 (44.5)	8 (6.3)	31 (41.9)	8 (10.8)	26 (48.1)	0 (0.0)
Elevated AST	38 (29.7)	2 (1.6)	16 (21.6)	1 (1.4)	22 (40.7)	1 (1.9)
Decreased RBC	37 (28.9)	2 (1.6)	18 (24.3)	0 (0.0)	19 (35.2)	2 (3.7)
Increased blood bilirubin	38 (29.7)	5 (3.9)	11 (14.9)	0 (0.0)	27 (50.0)	5 (9.3)
Periodontal disease	15 (11.7)	1 (0.8)	7 (9.5)	0 (0.0)	8 (14.8)	1 (1.9)
Pancreatitis	1 (0.8)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	5 (3.9)	1 (0.8)	1 (1.4)	0 (0.0)	4 (7.4)	1 (1.9)
Blurred vision	1 (0.8)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hand-foot syndrome	17 (13.3)	2 (1.6)	9 (12.2)	0 (0.0)	8 (14.8)	2 (3.7)
Constipation	8 (6.3)	0 (0.0)	3 (4.1)	0 (0.0)	5 (9.3)	0 (0.0)

PLT, platelet; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC, red blood cell.

Safety of ICIs

In the surgical group, 52 patients (70.3%) experienced AEs of varying severity during ICI treatment, compared to 42 patients (77.8%) in the nonsurgical group. Table 4 provides a comprehensive overview of AEs in both cohorts, including all-grade and grade 3–4 AEs. The most common AEs were elevated alanine transaminase or aspartate transaminase levels, increased blood bilirubin levels, decreased appetite, hypertension, and fatigue. However, due to vigilant monitoring and management by the specialized MDT, no AEs led to delays in surgery or treatment-related deaths.

Discussion

This study represents the largest retrospective analysis to date comparing survival and prognosis after successful conversion therapy for advanced HCC in a real-world

setting. Our findings demonstrate that in the era of ICIs, patients with initially unresectable HCC who underwent conversion surgery after successful systematic therapy experienced significantly prolonged survival and had a favorable safety profile. This evidence underscores the critical role of conversion surgery in improving patient outcomes and may influence future treatment strategies for advanced HCC.

Among patients who met the surgical criteria after conversion therapy, no significant differences were observed between the surgical and nonsurgical groups in terms of demographic characteristics (e.g., sex and age) or baseline tumor (e.g., stage, extrahepatic metastases, and macrovascular invasion) characteristics. However, patients who underwent conversion surgery showed a significantly improved prognosis, with high rates of R0 resection and pCR, leading to slower tumor recurrence and prolonged PFS and OS. Previous studies have suggested the conversion success of lenvatinib and immunotherapy-based combination regimens in patients with initially unresectable HCC, as well as the effectiveness of conversion surgery [24–28]. However, these studies discussed the options for conversion therapy, whereas the present study confirms, for the first time, in a large cohort, the necessity of conversion surgery after successful conversion of unresectable HCC with various types of regimens. Surgical intervention as a local treatment is extremely effective and safe in prolonging patient survival and improving prognosis, compared with continuing systemic regimens alone.

In this retrospective cohort study, we analyzed ICI-based combination regimens used in conversion therapy for advanced HCC to transform unresectable lesions into resectable ones. As this was a real-world study, treatment decisions, including whether to proceed with surgery and the choice of postoperative adjuvant therapy, were made by an MDT in collaboration with the patients, following thorough discussions of risks and benefits. Most treatment regimens adhered to current guidelines, with common combinations including atezolizumab + bevacizumab or anti-PD-1 antibody + lenvatinib [6, 8, 14].

The conversion success rate for advanced HCC at our center was 22.0% (135/613), aligning with the 10%–55% range reported by other centers for systemic therapy [26, 29–31]. However, our rate may be lower due to the inclusion of only patients with unresectable HCC, variability in baseline data, and the lack of exclusion of patients ineligible for conversion therapy at diagnosis. The variation in conversion rates across centers likely stems from differences in study design and definitions of "initially unresectable" and "successful conversion." Additionally, most studies on conversion therapy have involved small sample sizes and single treatment modalities, whereas our study included a broader patient population treated with multiple ICIs and TKIs, making our conclusions more generalizable. While similar studies, such as those by Wang et al. in biliary tract cancer, confirmed the clinical benefits of conversion surgery [32], few have specifically compared the impact of surgery after conversion therapy on survival in advanced HCC or examined the safety of conversion surgery in large samples, which remains a critical need in clinical practice.

The pCR rate in our study was 31.1%, demonstrating the effectiveness of the conversion regimen. However, postoperative pathology in most patients indicated the presence of viable tumor cells, suggesting that these cells may drive recurrence or metastasis. This highlights the importance of timely conversion surgery once surgical criteria are met and explains the differences in recurrence and survival between surgical and nonsurgical patients. Almost all patients had intrahepatic recurrence, indicating that the metastases showed a complete response during conversion therapy and the chance of recurrence was reduced. However, the high incidence of intrahepatic recurrence emphasizes the importance of postoperative liver imaging. Additionally, the physical status of the patient, which may be related to age, impacts tumor recurrence. Several studies have demonstrated that high levels of physical fitness and physical activity are beneficial to the immune system and reduce the risk of tumor recurrence [33].

As preoperative pCR was uncertain, and imaging and serology were not always reliable for assessing tumor activity, surgical resection remained the primary objective. We believe that aggressive systemic treatment should continue postoperatively to prevent recurrence, a view supported by our Cox regression analysis, which showed that patients without regular adjuvant therapy were more prone to recurrence and had shorter survival, consistent with the findings of Zhang et al. [29]. In our study, most patients (57/74, 77.0%), regardless of pathology type or R0 resection status, continued their preoperative systemic regimen postoperatively; however, 25 patients (43.9%) experienced recurrence. In contrast, 76.9% of patients who did not continue the original regimen post-surgery experienced recurrence. Our findings do not conflict with the IMbrave 050 trial, which demonstrated the benefits of adjuvant therapy after HCC resection [34]. Unlike the trial, our study focused on patients with initially unresectable HCC who responded well to immunotherapy, achieving significant tumor shrinkage, necrosis of macrovascular thrombi, or complete response of extrahepatic metastases. These patients were specifically selected based on their response to immunotherapy, and our results emphasize the importance of continuing immunotherapy post-conversion surgery to prevent recurrence in patients who respond to immunotherapy. Despite achieving a high R0

resection rate, the conversion surgery we performed cannot overlook the fact that all patients involved was initially unresectable with advanced tumors prior to conversion therapy. These patients have multiple high-risk factors for recurrence (e.g., extrahepatic metastases, vascular invasion, and microvascular invasion) and may still have residual tumor cells in their bodies [35, 36]. These patients have been identified as responders to ICIs during preoperative conversion therapy, and it is reported that T cells in patients after ICI treatment could persist with a less differentiated state at extratumoral sites. They could interact with tumor cells in the presence of ICIs, allowing cytotoxic responses [37, 38]. Preoperative immunotherapy allows for the expansion of tumor-specific memory T cells, and adjuvant therapy also reverses immunosuppression, overcoming the direct prometastatic and pro-angiogenic effects of surgery, and eliminating tumor cells that may remain during surgery [39]. So, it is possible that effective adjuvant immunotherapy could sustain the antitumor T-cell status and prevent or delay recurrence and prolong survival by eradicating micrometastatic tumors. Understood differently, surgical resection is one of the local treatment modalities, and the surgery is more encouraged to be performed in a timely manner after the surgical criteria have been met during the phase of the full course immunotherapy in the immunotherapy-active population, in order to obtain a longer survival benefit. We recognize that the conclusion is biased, which may be due to the study's limitations including its small sample size, lack of randomization, and variability in postoperative therapy, which was largely determined by patient preferences and clinical guidance. While our findings provide valuable real-world insights, they require validation in larger, controlled trials. The optimal choice of postoperative therapy, whether targeted, immunologic, or combination therapy, remains to be determined.

Regarding surgical timing, our center typically schedules surgery after a patient achieves partial response and the tumor has shrunk or been downstaged to meet surgical criteria. Surgery is usually performed after an additional cycle of ICIs and TKIs. This timing considers the radiological and serological characteristics of the tumor, such as size, activity, and tumor markers, to ensure surgery occurs during the drug response period. This approach aligns with findings in other tumor types, where the long-term effects of ICIs are beneficial in preventing recurrence [40]. Preoperative systemic therapy was discontinued approximately 1 week before surgery to minimize its impact, which is consistent with previous studies [22, 28, 29]. Therefore, the decision and timing of conversion surgery must be personalized for each patient by an experienced MDT, considering the patient's initial physical status, tolerance, personal preferences, tumor characteristics, remission rate, and extent of disease. For some BCLC stage C patients with extrahepatic metastases, it has been argued that conversion therapy is not recommended. However, in our study, after conversion therapy in BCLC stage C patients, all extrahepatic lesions were significantly reduced or inactivated, and intrahepatic lesions were resectable. Only after this assessment did the MDT conclude that the criteria for conversion surgery were met ensuring that conversion surgery has the potential to eradicate the tumor. However, this assessment still carries a risk of recurrence, which emphasizes the importance of continued adjuvant therapy post-surgery.

The safety profiles of ICIs and conversion surgery were favorable. The incidence of serious postoperative complications was low, with only a few grade III complications, which were related to the underlying disease and tumor progression. Most patients recovered well and tolerated treatment. However, the safety profile may have been influenced by selection bias because patients with successful conversion are more likely to tolerate the regimen and achieve tumor shrinkage. Surgery is now a well-established radical treatment for HCC, with low surgical risks and few postoperative complications. Most patients can continue postoperative adjuvant therapy, ensuring long treatment cycles and extended survival.

This study had some limitations. As this was a single-center retrospective study, selection bias was unavoidable. In addition, the follow-up period for some patients was short, with unknown or incomplete outcomes. Variability in treatment regimens, particularly immunological drugs, may have influenced surgical and therapeutic outcomes. These inconsistencies stem from real-world complexities. Treatment decisions were based on patient consent, adherence to ethical guidelines, and compassionate use principles. Given the high morbidity and mortality rates associated with advanced HCC and the promising potential of immunotherapy, exploring the feasibility, efficacy, and safety of conversion surgeries is crucial. Current standards for resectability and surgical approaches remain inadequate, with much of the feasibility of tumor resection depending on the surgical team's experience. Nonetheless, our findings indicate that conversion surgery, when adhering to current criteria, is not only effective but also holds great promise for future research.

In conclusion, our study confirms that surgical intervention following successful conversion therapy in patients with advanced HCC significantly improves survival and prognosis, with a favorable safety profile

compared to continuing systemic therapy without surgery. For patients who respond to immunotherapy and undergo conversion surgery, aggressive postoperative adjuvant therapy with the original regimen can delay tumor recurrence and survival. Future studies should explore the optimal timing and regimen for postoperative adjuvant therapy in advanced HCC patients undergoing conversion surgery. Exploring optimal conversion therapy options and the role of conversion surgery in large randomized controlled trials, identifying factors affecting recurrence, and refining criteria for resectability could further enhance patient outcomes and survival rates.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board and the Ethics Committee of PUMCH [No. JS-1391]. Verbal informed consent was obtained from all patients and was approved by the Institutional Review Board and the Ethics Committee of PUMCH [No. JS-1391].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.Z. and X.Y.: conception/design. M.P., C.L., Z.H., N.Z., and J.L.: data analysis and interpretation and drafting of the manuscript. Z.X., B.S., S.L., and L.Z.: patient follow-up and contributed to data collection. X.Y., S.W., and T.Z.: conception and writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data supporting the results of the study can be found in the article. Further inquiries can be directed to the corresponding author.

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