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Clinical study on conversion therapy of hepatocellular carcinoma - summary and comparison of clinical data from a single center of consecutive four years

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Abstract

Aim The purpose of this study was to interpret real-world clinical data to analyze the surgical safety and survival outcomes of patients with initial unresectable hepatocellular carcinoma (uHCC) after conversion therapy.

Methods A retrospective analysis was performed on 2984 hepatocellular carcinoma (HCC) patients hospitalized in Shandong Cancer Hospital Affiliated to Shandong First Medical University from June 1st, 2019 to June 1st, 2023. Clinicopathological features, response to systemic and/or loco-regional treatments, surgical resection rate after conversion therapy, surgical safety, and postoperative recurrence were analyzed.

Results A total of 38 patients were successfully converted to obtain surgical resection. 35 patients underwent radical resection. A high objective response rate (ORR) (52.6% under RECIST v1.1 and 78.9% under mRECIST criteria) was observed in patients under conversion therapy, and the disease control rate (DCR) was 100%. Pathologic complete response (pCR) was 42.9%. Treatment-related adverse events (TRAEs) of any grade were observed in 37 patients (97.4%). Safety of conversion or direct surgery continues to improve. The median follow-up time was 19.3 months. The 1-year Disease-free survival (DFS) rate of patients with direct surgery and patients with conversion surgery were 91.4% and 86.8%, respectively.

Conclusions With conversion therapy, a small percentage (1.81%) of uHCC patients are likely to be converted to radical resection. Local combined systemic therapy is a relatively safe and effective conversion therapy, and the safety of surgery is gradually improved after successful conversion. Preliminary follow-up data showed satisfactory survival benefits for patients undergoing conversion surgery.

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Trial registration This was a retrospective study and it did not interfere with treatment decisions.
Keywords Hepatocellular carcinoma, Conversion therapy, Tumor response, Treatment-related adverse events (TRAEs)

Introduction

As of 2020, primary liver cancer (PLC) ranks sixth among the most prevalent cancers worldwide [1] and is the third leading cause of cancer-related deaths globally. Moreover, it is the second leading cause of cancer-related deaths in China [2]. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75-86% of cases [3]. For patients with early-stage HCC, curative resection is the recommended course of action and also one of the curative treatment options [4]. However, most HCC patients are diagnosed at an advanced stage, which means they have already missed the opportunity for curative resection [5], who rely on systemic therapy and/or loco-regional therapy. During the treatment process, some late stage patients experience tumor shrinkage in the short term, meeting the criteria for downstage and obtaining the opportunity for curative resection. This approach is listed conversion therapy as one of the treatment methods for unresectable HCC (uHCC). Conversion therapy is defined as the transformation of an uHCC into a resectable one that followed by surgical removal of the tumor [6].

In the last decade, advances in systemic therapy, including targeted drugs and immune checkpoint inhibitors (ICIs), have significantly improved the prognosis of patients with uHCC [7]. With atezolizumab plus bevacizumab, the median overall survival (OS) was 19.2 months, but with sorafenib, it was 13.4 months, according to the most recent data available in IMbrave150 [8]. HIMALAYA trail found that the STRIDE group significantly improved patients' OS compared to sorafenib: the median OS in the STRIDE group was significantly higher than that in sorafenib at data cut off (16.43 months vs. 13.77 months, HR 0.78, $P=0.0035$). The OS rates at 18, 24 and 36 months were 48.7% vs. 41.5%, 40.5% vs. 32.6%, 30.7% vs. 20.2%, respectively [9]. Nonetheless, despite tremendous advancements, uHCC patients who receive targeted and/or ICIs seldom have long-term survival, and the few incidences of patients who surviving over 5 years are discovered in case reports [10].

Transcatheter arterial chemoembolization (TACE) has been widely used in the treatment of advanced liver cancer. A retrospective study of 831 unresectable patients showed that in patients with vascular invasion or better response to TACE, conversion resection after TACE was associated with a higher survival benefit than TACE alone (5-year OS: 26% vs. 10%) [11]. Other studies have also shown that TACE provides an opportunity for radical resection of uHCC patients [12]. At present, hepatic artery infusion chemotherapy (HAIC) has been gradually applied to the treatment of advanced liver cancer, especially for patients with portal vein cancer embolism and portal vein invasion, and showing good potential for conversion therapy [13].

For the initially unresectable patients, combination therapy, as an option for conversion therapy, can provide patients with better survival benefits [10]. There have been some recent reports on conversion therapy for HCC. According to the report, most of the conversion therapy protocols used are based on tyrosine kinase inhibitors (TKIs) combination programmed death receptor 1 (PD-1) inhibitors and (or) loco-regional treatment options. Zhu et al. first reported a conversion therapy cohort study of TKIs combined with anti-PD-1 therapy for uHCC in 63 patients, of whom 10 (15.9%) eventually achieved R0 resection [14]. A Phase I b clinical trial in the United States included 15 HCC patients treated with cabozantinib combined with nivolumab, of whom 12 (80%) underwent surgical resection, of which 5 (42%) experienced major pathological reactions (MPR), and disease-free survival (DFS) was longer than those without MPR [15]. A randomized, open-label clinical trial demonstrated that median survival was much higher in the SoraHAIC group than in the sorafenib group (13.7 vs. 17.3 months) [16].

In the real world clinical practice of hepatocellular carcinoma conversion therapy, the treatment mode of uHCC is not uniform, showing diversity and heterogeneity. Based on the previous data of our center [17], this study added new cases in the past 1 year, interpreted the real-world clinical data to analyze the surgical safety and survival prognosis of patients with initial uHCC after conversion therapy.

Materials and methods

Patients

The clinical data of HCC patients admitted to Shandong Cancer Hospital Affiliated to Shandong First Medical University between June 1st, 2019 and June 1st, 2023 were retrospectively analyzed. The Chinese Ministry of Health's "Guidelines For The Diagnosis And Treatment Of Primary Liver Cancer" [18] and the AASLD guideline [19] served as the foundation for the HCC diagnosis. Consistent with our previous reports [17], we believe that patients with initially advanced uHCC need to meet any of the following criteria: extrahepatic metastases (EHM), major Venous thrombosis, or a large tumors with insufficient of future liver remnant (FLR). We included patients with initially unresectable HCC who met the criteria for clinically resectable HCC after systemic/loco-regional

therapy in the category of conversion therapy. The diagnosis and treatment options for all patients were determined after discussion with multidisciplinary team (MDT).

This study's research was carried out in compliance with the Istanbul and Helsinki Declarations which has been certified by the Ethics Committee of Shandong Cancer Hospital Affiliated to Shandong First Medical University, but we choose to give up the informed consent of patients, on the one hand, because this study is a retrospective analysis and does not involve patient privacy; On the other hand, the time span of this study is large, and the follow-up of patients is difficult.

Treatments

During the initial unresectable HCC patients (uHCC) conversion treatment, primary treatment including system treatment, local treatment and system & local combined treatment. Systemic therapy mainly included TKIs and PD-1/PD-L1 monoclonal antibodies. In this study, TKIs mainly included lenvatinib(8 mg/ day), apatinib (250 mg/ day) and sorafenib (800 mg/ day). PD-1/PD-L1 monoclonal antibodies included sintilimab (200 mg/3 weeks, IV) and camrelizumab (200 mg/3 weeks, IV). Local treatments included HAIC, TACE and radiotherapy, all performed by specialists. Combination therapy is a combination of systemic therapy and local therapy according to the patient's condition. All treatments were guided by reported standard-of-care practices. For uHCC patients whose tumor response rating reached surgical criteria after conversion therapy, radical resection was performed by the surgeon according to the patient's condition.

Response and toxicity evaluation

Tumor response was based on MRI and CT findings for each treatment cycle and was assessed according to RECIST v1.1 and Modified RECIST (mRECIST) criteria: complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). Objective response rate (ORR) is the sum of CR and PR, and disease control rate (DCR) were calculated as the sum of CR, PR and SD. Treatment-related Adverse reactions (TRAEs) were evaluated according to the National Cancer Institute standard v4.0 Common Terminology for Adverse events.

Surgical safety

Data of the last preoperative and first postoperative clinical examination were collected for patients undergoing surgery, including blood biochemical indexes (ΔRBC%, ΔHb%, ΔALT%, ΔAST%, Δbilirubin%, Δalbumin%), tumor markers (AFP), operative time, intraoperative blood loss, Postoperative abdominal drainage time and length of hospital stay and other surgical safety clinical data.

Postoperative management and follow-up

HCC patients enrolled in the study came to the hospital for re-examination at least every 3 months 1 year after discharge. The second year after surgery can be extended to every 6 months to come to the hospital for re-examination, the main examination items include imaging examination (abdominal MRI or CT), tumor markers (AFP), blood biochemical indicators, etc. Whether to conduct adjuvant therapy after surgery is decided by MDT after discussion and listening to the patient's own opinions. For patients with postoperative recurrence, the choice of treatment, whether continuation of previous therapy or change of treatment regimen, is determined by MDT after discussing the patient's condition. The main follow-up methods include patients coming to the hospital for re-examination or telephone contact. Primary endpoints are DFS, DFS refers to the time from receiving surgical treatment to tumor recurrence.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 26.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. The normal distribution of data is expressed as mean±standard deviation, and the non-normal distribution is expressed as median and interquartile distance. The Student t test or Mann-Whitney U test was used to compare the differences between the two groups, and the Chi-square ($\chi 2$) test was used to compare postoperative complications between the different groups. HRs and 95%CI analyses calculated by COX risk regression models were used to analyze the relationship between successful resection criteria and clinical baseline data in patients with initial uHCC. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Figure 1 illustrates patient flow. A total of 2,984 HCC patients were admitted to Shandong Cancer Hospital Affiliated to Shandong First Medical University between June 1st, 2019 and June 1st, 2023. Of these, 351 patients did not receive any anticancer therapy, while the remaining 2633 patients received various forms of anti-HCC therapy. 474 patients were considered to be directly resectable. Of the remaining 2098 patients with uHCC, 1351 received systemic plus local therapy and the rest received only local or systemic therapy. Following a combination of targeted, ICIs, and/or loco-regional therapy, 38 patients were considered suitable for surgical resection.

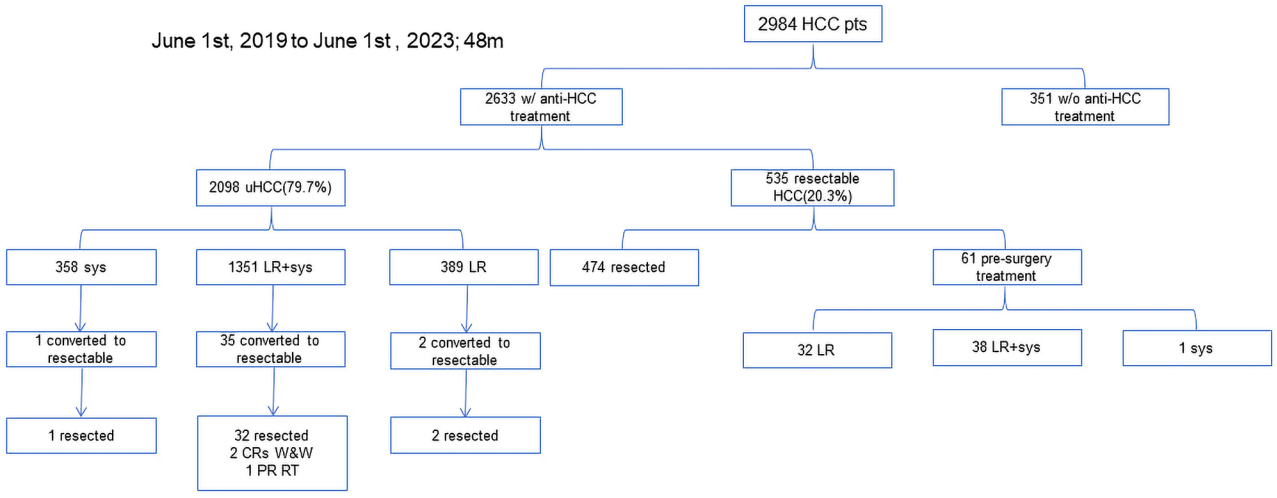

Fig. 1 Patient flow. The total number of HCC patients admitted to our center between June 1, 2019 and June 1, 2023, the number of patients who received or did not receive anti-HCC treatment, the number of patients with initially treatable or untreatable HCC (uHCC), the number of uHCC patients who received various treatment modalities, and the number of converted patients are all displayed; pts, patients; w/, with; w/o, without; uHCC, unresectable hepatocellular carcinoma; sys, systemic treatment; LR, loco-regional therapy; CR, complete response; W&W, watch & wait; PR, partial response; RT, radiotherapy

Of the 38 patients, the median age was 55 years (range, 28 to 76). B virus (HBV) infection exists in every patients (100%), and 17 patients (44.7%) had AFP levels over 400ng/ml. Out of the total patients, 37 patients (97.4%) had liver function grade A according to Child-pugh, 28 patients (73.7%) had Barcelona Clinical Stage of liver cancer (BCLC) stage C, and 28 patients (73.7%) had a single tumor. Table 1 summarizes each patient's initial status prior to the initiation of treatment, and Table 2 lists the specific reason(s) for each patient's initial unresectable condition.

Tumor response

Table 3 summarizes the treatment responses of 38 patients who underwent conversion therapy. The DCR was 100% since 20 patients (52.6%) met the RECIST v1.1 criteria's PR, no CR was observed, and all other patients were categorized as SD. 7 patients (18.4%) met the mRECIST criteria for CR, whereas 23 patients (60.5%) were classified as PR. This resulted in ORR of 78.9% and DCR of 100%. No patient experienced PD. After conversion therapy, R0 resection was performed in 35 patients (92.1%), and pCR was found in 15 patients (42.9%). 3 patients (2 CR and 1 PR) opted for "W&W" (watch and wait) and did not have their surgical operations. Table 4 summarizes the tumor response to various treatment regimens.

Of the patients who underwent surgery for initial unresectable HCC (uHCC) transformation, 7 (18.4%) had extrahepatic metastases with stage C BCLC. After conversion therapy, the tumors of these patients responded well: Among the 5 patients with portal vain lymph node metastasis, 1 patient was CR and the other 4 patients were PR according to the MRI results and mRECIST standard grading after conversion therapy, and no portal vain lymph node metastasis was found in intraoperative and postoperative pathology. 1 patient with bone metastasis was evaluated as CR before surgery after conversion therapy. Another patient with right lung metastasis was evaluated as SD by preoperative CT after conversion therapy. Of note, two patients with lung and bone metastases were negative on PET-CT at postoperative follow-up.

Figure 2 shows waterfall plots that demonstrate the ideal tumor response as well as line charts that show the dynamic changes of tumor response from each treatment cycle conducted under RECIST v 1.1 (A, B) and mRECIST (C, D).

Safety of conversion therapies

During conversion therapy, 37 of 38 patients(97.4%) underwent successful conversion surgery had TRAEs of any grades, including 17 patients(44.7%) with TRAE of grade 3 or above. Among the adverse reactions that occur, the most common is liver function injury characterized by elevated ALT, AST, and bilirubin. No death caused by treatment-related adverse reactions occurred, and all patients were cured by timely and effective treatment after adverse reactions occurred. The only grade 4 adverse event that occurred (1/38, 2.6%) was ICI associated myocarditis (irAE), which recovered after discontinuation of PD-1 and high-dose methylprednisolone shock therapy. There were no grade 4 adverse events in the latest year of data update. After recovery, the patient continued to receive preoperative conversion therapy. None

Table 1 Baseline data of 38 patients with successful conversion surgery

Characteristics	Patients($n=38$)
Median age, years(range)	55(28 ~ 76)
Age, years, n(%)	
<65	30(78.9%)
≥ 65	8(21.1%)
Sex, n(%)	
Female	6(15.8%)
Male	32(84.2%)
ECOG PS, n(%)	
0	17(44.8%)
1	20(52.6%)
2	1(2.6%)
Hepatitis B virus infection, n(%)	38(100%)
Serum AFP levels, n(%)	
<400ng/ml	21(55.3%)
400-1000ng/ml	1(2.6%)
≥ 1000ng/ml	16(42.1%)
Tumor number, n(%)	
Solitary	28(73.7%)
Multiple	10(26.3%)
Tumor size, n(%)	
<10 cm	23(60.5%)
≥ 10 cm	15(39.5%)
Child-pugh classification, n(%)	
A	37(97.4%)
B	1(2.6%)
BCLC staging, n(%)	
A	9(23.7%)
B	1(2.6%)
C	28(73.7%)
CNLC staging, n(%)	
I	9(23.7%)
II	1(2.6%)
III	28(73.7%)
Liver cirrhosis, n(%)	32(84.2%)
Hilar lymphatic metastasis, n(%)	5(13.2%)
Intrahepatic metastasis, n(%)	2(5.3%)
Extahepatic metastasis, n(%)	3(7.9%)
Reasons of unresectability, n(%)	
Vp2	5(13.2%)
Vp3	11(28.9%)
Vp4	4(10.5%)
Vv2	4(10.5%)
Vv3	4(10.5%)
Insufficient FLR	16(42.1%)
EHM	5(13.2%)

CNLC China liver cancer staging, BCLC Barcelona Clinic Liver Cancer, Vp2 Invasion of (or tumor thrombus in) second order branches of the portal vein, Vp3 Invasion of (or tumor thrombus in) frst order branches of the portal vein, Vp4 Invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe, Vv2 Invasion of (or tumor thrombus in) the right middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein, Vv3 Invasion of (or tumor thrombus in) the inferior vena cava, EHM Extrahepatic metastasis, FLR future liver remnant

Table 2 The stage and reasons of unresectablility of all patients($n=38$)

Patients	CNLC stage	BCLC stage	Reasons of unresectability
1	Ib	A	Insufficient FLR
2	Ib	A	Insufficient FLR
3	IIIa	C	Vp4
4	IIIb	C	Vp3,EHM
5	Ib	A	Insufficient FLR
6	IIIa	C	Vp3
7	IIIb	C	EHM
8	IIb	B	Insufficient FLR
9	IIIa	C	Vp3
10	IIIa	C	Vv3
11	IIIa	C	Vp2,Insufficient FLR
12	IIIa	C	Vp3,Insufficient FLR
13	IIIa	C	Vv2
14	IIIa	C	Vp3,Insufficient FLR
15	IIIa	C	Vp3
16	Ib	A	Insufficient FLR
17	IIIb	C	Vp3,Vv3,EHM
18	IIIa	C	Vp4
19	Ib	A	Insufficient FLR
20	IIIb	C	EHM
21	IIIa	C	Vp3,Vv3
22	Ib	A	Insufficient FLR
23	IIIa	C	Vp3,Vv3
24	IIIa	C	Vp4
25	IIIb	C	EHM
26	IIIa	C	Vp3,Insufficient FLR
27	Ib	A	Insufficient FLR
28	IIIa	C	Vv2
29	IIIa	C	Vv2
30	IIIa	C	Vp2
31	IIIa	C	Vp3
32	IIIa	C	Vp4
33	Ib	A	Insufficient FLR
34	IIIa	C	Vp2,Insufficient FLR
35	IIIa	C	Vp2,Insufficient FLR
36	IIIa	C	Vv2
37	Ib	A	Insufficient FLR
38	IIIa	C	Vp2

Vp2 Invasion of (or tumor thrombus in) second order branches of the portal vein, Vp3 Invasion of (or tumor thrombus in) frst order branches of the portal vein, Vp4 Invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe, Vv2 Invasion of (or tumor thrombus in) the right middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein, Vv3 Invasion of (or tumor thrombus in) the inferior vena cava, EHM Extrahepatic metastasis, FLR Future liver remnant

of the patients dropped out due to adverse reactions. Table 5 displayed the incidences of TRAEs.

Safety of conversion surgery

Compared with 474 patients who underwent direct R0 resection, 35 patients who underwent conversion surgery showed significantly longer operation time (213.3±54.4

Table 3 Assessment of objective response by RECIST and mRECIST criteria

Variable, *n*(%)	*n* = 38	
	RECIST v1.1	mRECIST
Complete response, n(%)	0(0)	7(18.4)
Partial response, n(%)	20(52.6)	23(60.5)
Objective response, n(%)	20(52.6)	30(78.9)
Stable disease, n(%)	18(47.4)	8(21.1)
Disease control rate, n(%)	38(100)	38(100)
Progressive disease, n(%)	0(0)	0(0)
R0 resection, n(%)	35(92.1)	
Pathologic complete response, n(%)	15(39.5)	

RECIST Response Evaluation Criteria in Solid Tumors, mRECIST Modifed RECIST criteria, CR Complete response, PR Partial response, SD Stable disease, PD Progressive disease, pCR Pathologic complete response, ORR Objective response, DCR disease control rate

Table 4 Tumor response of different treatment modalities(*n* = 38)

Treatment modalities	Patients(*n*,%)	ORR(%)[a]	ORR(%)[b]
TKI + PD-1/PD-L1 monoclonal antibody	1(2.6)	1(100)	1(100)
Sorafenib + Sintilimab	1	1(100)	1(100)
Locoregional therapies + TKI	4(10.5)	1(25)	3(75)
TACE + Lenvatinib	3	0(0)	1(33.3)
TACE + Radiotherapy + Lenvatinib	2	0(0)	1(50)
Locoregional therapies + TKI + Anti-PD-1	31(81.6)	16(51.6)	27(71.1)
HAIC + Lenvatinib + Camrelizumab	19	10(52.6)	15(78.9)
HAIC + Apatinib + Camrelizumab	4	2(50)	3(75)
TACE + Sorafenib + Sintilimab	2	0(0)	2(100)
TACE + Sorafenib + Camrelizumab	2	2(100)	2(100)
TACE + Lenvatinib + Camrelizumab	1	0(0)	1(100)
TACE + Apatinib + Camrelizumab	2	1(50)	2(100)
TACE + HAIC + Sorafenib + Camrelizumab	1	1(100)	1(100)
Locoregional therapies	2(5.3)	0(0)	2(100)
HAIC	2	0(0)	2(100)

[a] RECIST v1.1

[b] mRECIST

vs. 178.8±61.9, $p<0.01$) and increased blood loss (155.7±128.2 vs. 100.2±78.1, $p<0.01$). The hospitalization stay was extended (18.1±4.6 vs. 12.3±5.1, $p<0.01$), and RBC ($p=0.022$) and Hb ($p=0.040$) were decreased significantly (Table 6).When comparing BCLC stage C patients in the direct resection group with the conversion group, 25 patients undergoing conversion surgery showed postoperative hospital stay was prolonged (18.3±4.1 vs. 12.4±5.5, $p<0.01$) ,but the decrease in albumin was less severe than in patients who underwent direct surgery($p=0.036$) (Table 7). Patients who underwent conversion surgery between June 1, 2022 and June 1, 2023 showed shorter operation time (229.2±59.3 vs. 185.3±45.3, $p=0.025$) and shorter postoperative hospitalization stay (19.3±4.6 vs. 15.9±3.9, $p=0.038$) compared to patients who underwent conversion surgery between June 1, 2019 and May 31, 2022(Table 8). For direct surgery patients between June 1, 2022 and June 1, 2023, the results showed shorter operative time (189.1±62.7 vs. 165.8±55.5, $p<0.01$), less intraoperative blood loss (108.3±88.0 vs. 88.5±60.0, $p<0.01$), decreased effects of the surgery itself on liver function ($p<0.01$) and fewer postoperative complications($p=0.024$) compared to the patients between June 1, 2019 and May 31, 2022 (Table 9).

Survival

The survival data is shown in Figs. 3 and 4. 8 (21.1%) of the 38 patients who had successfully undergone conversion therapy had relapsed at the time of the most recent follow-up, with DFS of 1.1, 2.1, 4.2, 10.4, 10.6, 16.5, 17.5, and 40.8 months, respectively. Two patients (5.2%) died, of which 1 died due to tumor recurrence with brain metastasis, and the other died due to liver failure due to disease progression, with survival time of 15.9 months and 19.3 months, respectively. The remaining 36 patients are still alive and under follow-up. The median follow-up time of the 38 patients was 19.3 months (range, 11.9 to 31.6). The 1-year DFS rates in the direct surgery group and the conversion surgery group were 91.4% and 86.8%, respectively. 3 patients who met the criteria for curative surgery chose the "W&W" strategy, their results at the most recent review showed that two patients achieved CR under mRECIST criteria and one patient had disease progression with a PD rating. Among the 35 patients who successfully underwent surgery during conversion therapy, 31 patients (88.6%) received postoperative adjuvant therapy, 22 patients (62.9%) only received systemic therapy, 2 patients (6.5%) only received TACE, and the remaining 7 patients (22.6%) received combination therapy of systemic therapy plus TACE. The start time of postoperative adjuvant therapy was 37.1±9.8 days. Table 10 shows the results of the univariate and multivariate analyses of prognostic variables in 1351 patients with uHCC. A univariate analysis of 1351 uHCC patients undergoing systemic and local therapy revealed a strong correlation between effective conversion therapy and the number, size, and presence of cirrhosis in the tumor. Cirrhosis was a significant predictor of conversion success, according to multivariate COX analysis (HR = 0.201, 95%CI: 0.078–0.789, $P=0.032$).

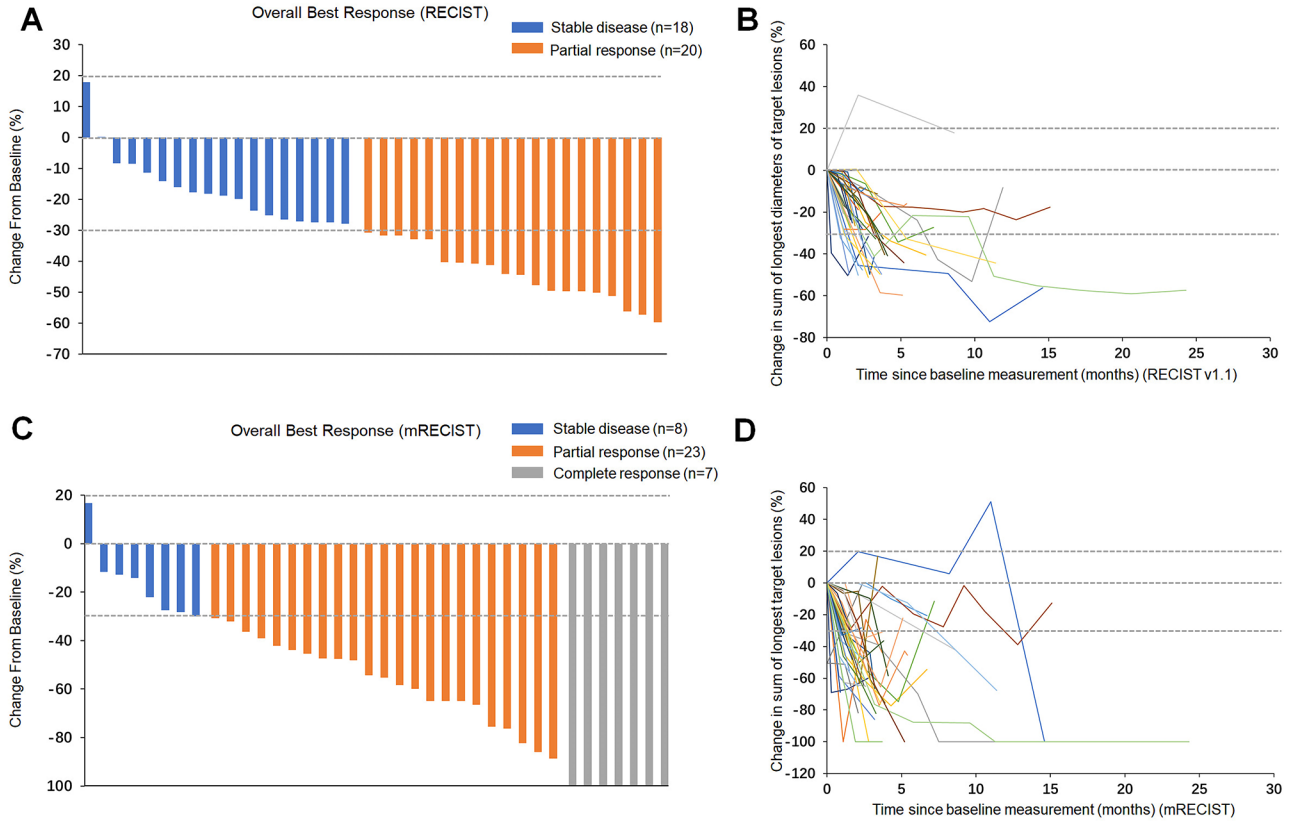

Fig. 2 Tumor responses in the conversion therapy. **A** Overall best responses of 38 patients under the RECIST 1.1 criteria. **B** Dynamic tumor responses of 38 patients at every evaluation under the RECIST 1.1 criteria. **C** Overall best responses of 38 patients under the mRECIST criteria. **D** Dynamic tumor responses of 38 patients at every evaluation under the mRECIST criteria

Table 5 TRAEs in 38 converted patients

TRAEs	Any grade (*n*, %)	Grade 1 ~ 2(*n*, %)	Grade ≥ 3 (*n*, %)
Hypertension	2(5.3%)	1(2.6%)	1(2.6%)
Decreased appetite	5(13.1%)	5(13.1%)	0(0)
Abdominal pain	4(10.5%)	4(10.5%)	0(0)
Nausea	5(13.1%)	5(13.1%)	0(0)
Elevated alanine aminotransferase, ALT	28(73.7%)	21(55.3%)	7(18.4%)
Elevated aspartate aminotransferase, AST	29(76.3%)	19(50%)	10(26.3%)
Elevated blood bilirubin	21(55.3%)	19(50%)	2(5.3%)
Hypothyroidism	3(7.9%)	2(5.3%)	1(2.6%)
Palmar-plantar erythrodysesthesia syndrome	2(5.3%)	2(5.3%)	0(0)
Fatigue	2(5.3%)	2(5.3%)	0(0)
Low leucocyte amount	6(15.8%)	5(13.1%)	1(2.6%)
Neutrocytopenia	2(5.3%)	2(5.3%)	0(0)
Thrombocytopenia	12(31.6%)	8(21.1%)	4(10.5%)
Oral mucositis	1(2.6%)	0(0)	1(2.6%)
Rash	1(2.6%)	1(2.6%)	0(0)
ICIs-associated myocarditis	1(2.6%)	0(0)	1(2.6%)
RCCEP	1(2.6%)	1(2.6%)	0(0)

TRAEs Treatment-related adverse events, ICIs Immune checkpoint inhibitors, RCCEP Reactive cutaneous capillary endothelial proliferation

Discussion

About 10% of patients with "ideal resection" were among the HCC patients diagnosed at 20 research centers globally between 2005 and 2011 who were part of the global HCC BRIDGE trial [20]. According to the clinical data of 2984 HCC patients collected in our medical center in the last 4 years, 535 (18%) patients underwent R0 resection. Between June 1, 2019 and June 1, 2022, approximately 17% of HCC patients underwent R0 resection, and in the most recent year, 19.2% of patients achieved R0 resection. The significant increase in the proportion of patients receiving R0 resection is largely due to the unprecedented improvement of social medical level, and the emergence of combination therapy has brought treatment opportunities for patients with advanced diseases; On the other hand, the increased awareness of national health examination enables cancer to be detected at an early stage, and early and timely treatment makes patients more likely to obtain radical resection. The continuous improvement and comprehensive implementation of the national health policy has also played a certain role in promoting it. However, for HCC, the vast majority of patients are still diagnosed at an advanced stage of the

Table 6 Comparison of perioperative conditions in the conversion treatment group and direct surgery group

	Conversion surgery ($n=35$)	Direct surgery ($n=474$)	t/Z/χ^2	*P* value
Age, years, n			0.145	0.704
<65	28	366		
≥65	7	108		
Sex, n			0.182	0.669
Male	30	393		
Female	5	81		
BCLC staging, n			131.317	<0.01
0 ~ B	10	440		
C	25	34		
The operation time, min	213.3 ± 54.4	178.8 ± 61.9	3.204	<0.01
The mean blood loss, ml	155.7 ± 128.2	100.2 ± 78.1	3.846	<0.01
The postoperative hospital stay, days	18.1 ± 4.6	12.3 ± 5.1	6.598	<0.01
The abdominal drainage time, days	6.9 ± 3.3	6.0 ± 4.5	2.200	0.282
ΔRBC%	-11.1(-20.3~-4.1)	-7.4(-13.4~-1.2)	2.284	0.022
ΔHb%	-10.3(-18.3~-2.5)	-7.1(-12.3~-1.7)	2.055	0.040
ΔALT%	733.12(321.34 ~ 1587.46)	611.14(286.53 ~ 1132.56)	-1.056	0.291
ΔAST%	618.46(360.14 ~ 1226.78)	593.22(306.31 ~ 1075.24)	-1.028	0.304
Δ Bilirubin%	68.7(29.2 ~ 104.4)	56.3(16.4 ~ 109.1)	-0.542	0.588
Δ Albumin%	-16(-20.3~-9.1)	-14.9(-22.8~-7.1)	-2.386	0.017
Postoperative complications	30($n=19$)	422 ($n=263$)	0.019	0.890
Fever caused by infection	4	68		
Biliary leakage	1	1		
Hypoproteinemia	7	102		
Massive ascites	6	86		
Spontaneous bacterial peritonitis	2	5		
Hydrothorax	4	108		
Kaliopenia	5	15		
Incision seepage	1	1		
DVT	0	5		
Pneumonia	0	21		
Pelvic effusion	0	10		

DVP Deep venous thrombosis

disease, thus missing the opportunity for curative surgical treatment. Therefore, conversion therapy deserves more attention.

Generally, literature and practice suggest that patients who have conversion surgery have also experienced long survival and better clinical outcomes. However, current study only partially approves it. According to a Chinese research, lenvatinib and anti-PD-1 antibodies enabled 28% (30/107) of patients with initially unresectable HCC effective R0 resection [21]. A prospective phase II clinical study(NCT05166771) from Tianjin medical University Cancer Hospital was presented at the annual meeting of the European Society for Medical Oncology(ESCO) in 2023, which mainly introduced initial results of HAIC in combination with donafenib and sintilimab for first-line treatment of unresectable liver cancer showed an objective response rate of 82.1% and achieved a conversion rate of 64.3% [22]. The results of the prospective phase II clinical study at the PLA General Hospital also reported at the ESCO 2023 Annual meeting, showed that sintilimab combined with lenvatinib had good efficacy and safety in first-line treatment of unresectable liver cancer, with an ORR of 54% according to mRECIST criteria and a conversion rate of 51% in 100 patients who could be evaluated for efficacy [23]. It is important to note that conversion rates in clinical trials do not accurately and objectively reflect our real-world clinical realities. In clinical practice, when the treatment of a uHCC starts, whether the aim is to convert or just to prolong the OS cannot always be set clearly; instead, it can be a policy of "treat and see"; if a patient responses well to the treatment and the curative resection becomes possible, he will undergo resection; otherwise the current treatment continues, or changes to the subsequent-line therapy. So, it is difficult to define the "conversion-intended" uHCC population, which is the denominator when calculating the conversion rate and the conversion rates from clinical trials cannot indicate the conversion rate accurately and objectively in the real-world clinical practice. So, in our current study, we did not define the inclusion criteria

Table 7 Comparison of perioperative conditions in the conversion treatment group and direct surgery group with BCLC stage C

	Conversion surgery ($n=25$)	Control group ($n=34$)	t/Z/χ^2	*P* value
Age, years, n			3.610	0.057
<65	19	29		
≥65	6	5		
Sex, n			0.090	1
Male	22	29		
Female	3	5		
The operation time, min	205.9±57.0	179.8±62.1	1.650	0.104
The mean blood loss, ml	132.0±64.4	101.2±53.9	1.949	0.057
The postoperative hospital stay, days	18.3±4.1	12.4±5.5	4.562	<0.01
The abdominal drainage time, days	6.7±3.4	6.1±3.3	0.727	0.470
ΔRBC%	-9.1(-16.2~-3.7)	-6.4(-12.1~-0)	-1.167	0.243
ΔHb%	-7.1(-15.2~-2.6)	-7.1(-13.4~-0.9)	-0.868	0.386
ΔALT%	691.23(259.97~1407.21)	701.34(332.78~1192.11)	-0.215	0.830
ΔAST%	564.22(277.24~1552.97)	628.31(349.15~1126.11)	-0.276	0.782
Δ Bilirubin%	74.7 (29.2~113.1)	52.3(4.5~95.4)	-0.859	0.390
Δ Albumin%	-15.3(-19.6~-7.4)	-20.2(-26.2~-12.4)	-2.095	0.036
Postoperative complications	20($n=13$)	39($n=22$)	0.946	0.326
Fever caused by infection	2	5		
Biliary leakage	1	0		
Hypoproteinemia	5	6		
Massive ascites	4	13		
Spontaneous bacterial peritonitis	1	1		
Hydrothorax	3	8		
Kaliopenia	3	3		
Incision seepage	1	0		
DVT	0	0		
Pneumonia	0	2		
Pelvic effusion	0	1		

DVP Deep venous thrombosis

of "being possibly convertible" to calculate the conversion rate upon "conversion-intended" patients; instead, we analyzed all hospitalized uHCC patients during the defined period of time, and hope our data could reflect the scenario that is more close to our everyday clinical practice. In our previous real-world study [17], instead of calculating the conversion rate of patients with "conversion intention", we calculated the conversion rate of the cross section of all uHCC patients in our center. The conversion rate among 1344 treated uHCC patients which we previous reported was 1.93%. Additionally, all 2098 treated uHCC patients in our trial with updated data this time was 1.81%. In our real-world clinical practice, our study shows that the conversion rate is not as high as expected and as reported in others, but considering that 80–90% of patients have already lost the opportunity to receive curative treatment at the first seek medical advice, we believe that the conversion success rate of 1–2% is still a significant improvement. The conversion rate increased to 2.59% for uHCC patients undergoing combination therapy, which is characterized as systemic plus loco-regional therapy. dramatically increases in tumor response rates were observed when systemic therapy was coupled with loco-regional therapy.

The tumors of 38 uHCC patients included in this study responded well to conversion therapy, and 36 patients (94.7%) had tumor reduced, with ORR of 52.6% and 78.9% under RECISTv1.1 and mRECIST criteria, respectively. The pathological results showed that 15 patients (39.5%) achieved pCR. Notably, It does not match the RECIST or mRECIST results exactly. According to mRECIST, pCR was reached by 3 of 8 (37.5%) SD, 8 of 23 (34.8%) PR, and 4 of 7 (57.1%) CR patients. We have recommended that criteria for more precisely defining "clinical complete response (cCR)" in HCC be developed in order to evaluate the tumor response of HCC by clinical characteristics [24].

During conversion therapy, 37 patients (97.4%) developed AE of any grade, and 1 patient developed TRAE of grade 4. Elevated ALT, AST, and bilirubin are indicators of weakened liver function, which is the most prevalent incidence of TRAE, regardless of grade. Symptomatic treatment and/or dose adjustment may alleviate symptoms in all patients, even though the prevalence

Table 8 Comparison of perioperative conditions in patients undergoing conversion surgery from 2019 ~ 2022 versus 2022 ~ 2023

	2019 ~ 2022(*n* = 23)	**2022 ~ 2023(*n* = 12)**	**t/Z/χ^2**	***P* value**
Age, years, n			1.553	0.423
<65	17	11		
≥ 65	6	1		
Sex, n			0.085	1
Male	20	10		
Female	3	2		
BCLC staging, n			0.114	1
0 ~ B	7	3		
C	16	9		
The operation time, min	229.2 ± 59.3	185.3 ± 45.3	2.345	0.025
The mean blood loss, ml	163.0 ± 152.4	141.7 ± 63.4	0.463	0.647
The postoperative hospital stay, days	19.3 ± 4.6	15.9 ± 3.9	2.157	0.038
The abdominal drainage time, days	7.9 ± 3.7	5.8 ± 2.9	1.345	0.188
ΔALT%	956.21(374.74 ~ 1592.11)	375.42(174.27 ~ 738.95)	-1.911	0.056
ΔAST%	865.34(425.11 ~ 1830.42)	473.24(257.13 ~ 827.96)	-1.599	0.110
ΔRBC%	-9.2(-17.4~-3.7)	-14.3(-23.1~-6.7)	-1.167	0.243
ΔHb%	-8.6(-16.4~-1.3)	-14.1(-23.3~-5.4)	-1.375	0.169
Δ Bilirubin%	68.1(29.4 ~ 104.3)	67.2(16.3 ~ 117.9)	-0.070	0.965
Δ Albumin%	-16.3(-20.1~-9.4)	-19.3(-21.2~-7.3)	-0.870	0.384
Postoperative complications	16(*n* = 13)	14(*n* = 6)	0.135	0.713
Fever caused by infection	2	2		
Biliary leakage	1	0		
Hypoproteinemia	2	5		
Massive ascites	2	4		
Spontaneous bacterial peritonitis	2	0		
Hydrothorax	1	3		
Kaliopenia	5	0		
Incision seepage	1	0		
DVT	0	0		
Pneumonia	0	0		
Pelvic effusion	0	0		

DVP Deep venous thrombosis

of grade ≥ 3 TRAE is rather high. Additionally, no fatal TRAEs were recorded.

Compared with patients who underwent direct R0 resection, patients who underwent conversion surgery showed significantly longer operation time and increased blood loss. The hospitalization stay was extended, and RBC and Hb were decreased significantly. To better demonstrate the safety of conversion surgery, we excluded the influence of tumor stage on surgical safety, and compared patients with BCLC stage C in the direct surgery group with those who underwent conversion surgery, the results showed that patients with conversion surgery had longer postoperative hospital stay, this may be the result of the difficulty of the surgical procedure caused by conversion therapy. However, the decrease in albumin was less severe than in patients who underwent direct surgery.

Then we compared the data of newly added direct surgery patients in the past 1 year with those of previous patients. The surgical safety of conversion therapy showed satisfactory results, with patients who underwent successful conversion between June 1, 2022 and June 1, 2023 shorter operation time and shorter postoperative hospital stay were observed compared to patients who underwent successful conversion between June 1, 2019 and May 31, 2022. For direct surgery patients between June 1, 2022 and June 1, 2023, the results also showed shorter operative time, less intraoperative blood loss, fewer postoperative complications, and decreased effects of the surgery itself on liver function compared to the patients between June 1, 2019 and May 31, 2022. This indicates that perioperative clinical practice for successful conversion patients is becoming more mature. This may be related to the accumulation of clinical experience in our center and the more careful selection of patient personalized treatment options.

For the conversion surgery patients in our study, the median follow-up time was 19.3 months (range,11.9 to 31.6). At the last follow-up, among the 38 conversion patients, 8 patients relapsed after surgery, and the

Table 9 Comparison of perioperative conditions in patients undergoing direct surgery from 2019 ~ 2022 versus 2022 ~ 2023

	2019 ~ 2022(*n* = 283)	2022 ~ 2023(*n* = 191)	t/Z/χ^2	*P* value
Age, years, n			7.506	0.006
<65	228	133		
≥ 65	55	58		
Sex, n			5.423	0.020
Male	244	149		
Female	39	42		
BCLC staging, n			0.065	0.799
0 ~ B	262	178		
C	21	13		
The operation time, min	189.1 ± 62.7	165.8 ± 55.5	4.123	<0.01
The mean blood loss, ml	108.3 ± 88.0	88.5 ± 60.0	2.697	<0.01
The postoperative hospital stay, days	10.0 ± 3.5	11.4 ± 5.2	0.874	0.348
The abdominal drainage time, days	6.0 ± 4.3	5.6 ± 2.8	1.821	0.069
ΔALT%	688.42(347.11 ~ 1160.32)	464.23(204.13 ~ 1116.34)	-2.767	0.006
ΔAST%	667.34(352.97 ~ 10.98)	479.22(246.96 ~ 9.96)	-2.895	0.004
ΔRBC%	-7.2(-13.3~-1.1)	-7.3(-13.1~-1.0)	-0.886	0.376
ΔHb%	-7.2(-12.3~-1.1)	-6.2(-12.1~-1.0)	-1.409	0.159
Δ Bilirubin%	58.2(15.9 ~ 109.1)	51.1(16.1 ~ 104.9)	-0.136	0.892
Δ Albumin%	-16.0(-22.9~-7.0)	-12.2(-19.3~-5.1)	-2.867	0.004
Postoperative complications	266(*n* = 169)	156(*n* = 94)	5.093	0.024
Fever caused by infection	48	20		
Biliary leakage	1	0		
Hypoproteinemia	77	25		
Massive ascites	60	26		
Spontaneous bacterial peritonitis	4	1		
Hydrothorax	50	58		
Kaliopenia	3	12		
Incision seepage	1	0		
DVT	4	1		
Pneumonia	14	7		
Pelvic effusion	4	6		

DVP Deep venous thrombosis

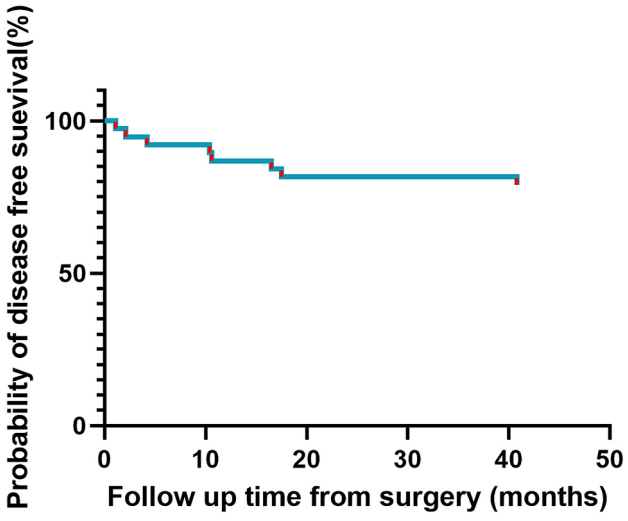

Fig. 3 Kaplan-Meier analysis showing disease free survival (DFS) in successful resected uHCC patients initially

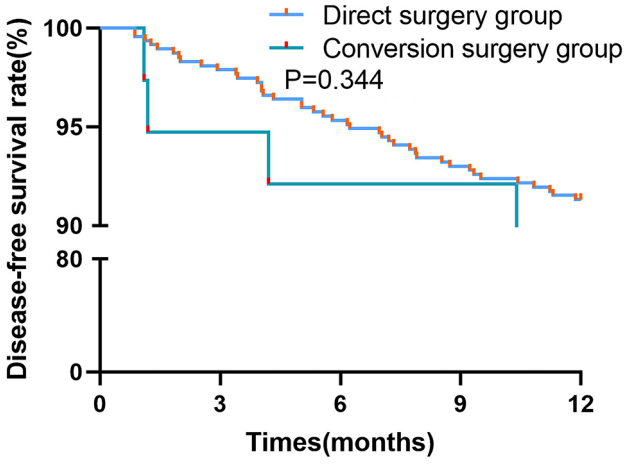

Fig. 4 Disease-free survival curves for HCC patients with different surgery patterns

Table 10 Univariate and multivariate analyses model analyzed predictors of successful conversion in 1351 patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (years, < 65 vs. ≥65)	0.578(0.203 ~ 1.734)	0.356		
Sex (female vs. male)	0.652(0.178 ~ 2.349)	0.794		
ECOG PS (0 ~ 2 vs. 3 ~ 4)	0.063(0.031 ~ 1.305)	0.682		
BCLC staging (A ~ B vs. C ~ D)	1.025(0.333 ~ 2.714)	0.776		
Child-Pugh classifcation (A ~ B vs. C)	0.401(0.036 ~ 2.125)	0.745		
Number of tumors (solitary vs. multiple)	0.301(0.166 ~ 0.899)	0.031	0.638(0.221 ~ 1.713)	0.488
Tumor size (cm, ≤ 10 vs. >10)	2.354(1.107 ~ 6.203)	0.056	3.013(0.964 ~ 6.226)	0.056
AFP(ng/ml,≤400 vs. >400)	1.896(0.793 ~ 5.648)	0.102	1.768(0.668 ~ 4.531)	0.281
HBV (no vs. yes)	0.387(0.154 ~ 1.327)	0.138	0.437(0.206 ~ 1.719)	0.583
ALT (u/L,≤40 vs. >40)	0.712(0.378 ~ 1.569)	0.336		
AST(u/L, ≤ 35 vs. >35)	0.857(0.374 ~ 5.215)	0.322		
Bilirubin(umol/L, ≤ 35 vs. >35)	0.866(0.116 ~ 4.086)	0.402		
Albumin (g/L, ≤ 35 vs. >35)	0.714(0.239 ~ 3.666)	0.972		
Liver cirrhosis (no vs. yes)	0.102(0.034 ~ 0.521)	< 0.001	0.201(0.078 ~ 0.789)	0.032
PVTT (no vs. yes)	1.102(0.456 ~ 2.112)	0.605		
HVTT (no vs. yes)	2.687(0.502 ~ 9.358)	0.369		
IVCTT (no vs. yes)	0.144(0.007 ~ 33.921)	0.612		
Ascites (no vs. yes)	0.326(0.068 ~ 1.212)	0.039	0.334(0.053 ~ 1.109)	0.166
Intrahepatic metastasis (no vs. yes)	0.276(0.056 ~ 2.149)	0.212		
Extrahepatic metastasis (no vs. yes)	0.195(0.028 ~ 0.869)	0.055	0.267(0.021 ~ 1.369)	0.126
lymphatic metastasis (no vs. yes)	0.667(0.159 ~ 2.158)	0.385		
Treatment (LR + TKI/anti-PD-1 vs. LR + TKI + anti-PD-1)	1.229(0.423 ~ 9.695)	0.492		

The association between successful conversion and those baseline factors, including age, sex, ECOG, BCLC staging, Child-Pugh classifcation, number of tumors, tumor size, serum AFP level, HBV infection, ALT, AST, bilirubin, albumin, liver cirrhosis, PVTT, HVTT, IVCTT, ascites, Intrahepatic metastasis, lymphatic metastasis, extrahepatic metastases and treatment methods, respectively, was analyzed by Cox proportional-hazards model to generate crude HRs and 95% CIs. Variables with $P < 0.2$ in univariate analysis were included in multivariate regression analysis model. $P < 0.05$ was considered to indicate a statistically signifcant

BCLC Barcelona Clinic Liver Cancer Staging System, PVTT Portal vein tumor thrombus, HVTT Hepatic vein tumor thrombus, IVCTT Inferior vena cava tumor thrombus, LR Loco-regional therapy

DFS time was 1.1, 2.1, 4.2, 10.4, 10.6, 16.5, 17.5 and 40.8 months, respectively. 36 patients were alive.1 patient died of tumor recurrence and brain metastasis, and the other died of other causes, with survival time of 15.9 and 19.3 months, respectively. At the last follow-up, the remaining 29 patients remained in DFS. The 1-year DFS rate of patients with direct surgery and patients with successful conversion surgery were 91.4% and 86.8%, respectively. Based on the above data, we preliminarily observed that the survival prognosis of patients undergoing successful conversion surgery was comparable to that of patients undergoing direct surgery.

Similar to previous research [17], in multivariate regression analyses, the only positive variable was the presence of cirrhosis, not the parameters from the tumor. The results showed that the better the liver function, the stronger the anti-liver cancer treatment and the higher the conversion rate.

The study is extension to the previous study by the group (PMID: 37210519), and has several limitations. First, it was a retrospective analysis of a single surgical tumor liver center, and although the study was large, the number of patients who eventually achieved translational resection was small, so the results were not universally representative. Secondly, the basic principles of conversion surgery are not validated by this kind of clinical research. Convertible uHCC patients are generally the minority segment that responds best to anti-HCC treatments. Consequently, conversion therapy chooses tumors with advantageous biological characteristics, making it challenging to determine whether patients gain anything from surgery in the long run. However, the high sample size required for analysis in a randomized trial environment is unlikely to be obtained in the near future, given the low percentage of patients who succeed in having conversion surgery.Finally, due to the relatively high probability of patients lost to follow-up in the retrospective study itself, even we have updated the most recent follow-up data, the follow-up time was still short, and the exact cure rate could not be accurately understood. To fully grasp the usefulness of this strategy, longer-term research involving a larger patient population is required. This study can be baseline for such future studies.

Conclusions

With conversion therapy, a small percentage (1.81%) of patients with initial uHCC are likely to be converted to radical resection. Local combined systemic therapy is a

relatively safe and effective conversion therapy, and the safety of surgery is gradually improved after successful conversion. Preliminary follow-up data showed satisfactory survival benefits for patients undergoing conversion surgery.

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Author contributions
Z.L. and L.Z.C. designed the study; C.Z.B. and S.Z.C collected clinical data; C.Z.B. and L.M.M. analyzed the data; C.Z.B. and L.Z.C. drafted the manuscript; L.L., Z.C.S., S.P.F., Z.J.T., Z.B., S.X.T. and C.K. did the operations; L.Z.G., Y.Y., X.L. and Z.J.X. followed-up the patients. All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Shandong Cancer Hospital affiliated to Shandong First Medical University, but informed consent needed to be waived for three reasons: First, the study lasted a long time; Second, it does not involve patient privacy information; In addition, this was a retrospective study and it did not interfere with treatment decisions.

Consent for publication
Not Applicable.

Clinical trial number
Not applicable.

Competing interests
L.Z. is on the speakers' bureau for Bayer, MSD, AstraZeneca, Roche, BeiGene, Innovent, Junshi Biosciences and Hengrui Medicine. The remaining authors declare no competing interests.

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