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A Comparative Study of Surgical Approaches for Hepatocellular Carcinoma: Conversion versus Direct Resection

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Purpose: The purpose of This study is exploring the intraoperative and perioperative differences between patients undergoing conversion surgery and those undergoing direct surgery, so as to improve preoperative preparation.

Methods: The retrospective study was approved by an ethics review committee. A total of 232 patients with hepatocellular carcinoma who underwent surgical resection at the First Affiliated Hospital of Chongqing Medical University from September 2022 to December 2023 were included, comprising 210 operating patients and 53 conversion patients. Propensity score matching was employed for comparison in order to minimize bias.

Results: The conversion group had more intraoperative bleeding (each P=0.001), longer operation time (P=0.033; PSM p=0.025), and higher intraoperative blood transfusion rate (p=0.001; PSM p=0.044). The incidence of perioperative complications, including perioperative ascites formation (p=0.011; PSM p=0.005), moderate to severe anemia (p=0.001; PSM p=0.002), postoperative blood transfusion (p=0.004; PSM p=0.036), and postoperative ICU transfer (p=0.041; PSM p=0.025), was higher in the conversion group compared to the operation group. The postoperative hospital stay (p=0.001; PSM p=0.003) was prolonged in the conversion group.

Conclusion: Post-conversion operations carry a higher risk of bleeding and are more likely to result in moderate to severe anemia and ascites formation in the perioperative period. However, the risk is reversible with adequate preoperative blood preparation and prompt postoperative symptomatic treatment. Conversion patients should be encouraged to undergo operating therapy when they can withstand surgical resection.

Keywords: conversion therapy, hepatocellular carcinoma, perioperative complications, hepatectomy, perioperative complications

Background

Hepatocellular carcinoma is currently the third leading cause of cancer death.[1] Surgical resection is currently the most effective radical treatment for hepatocellular carcinoma, but due to the lack of typical symptoms in the early stage, many patients have lost the opportunity to radical resection of hepatocellular carcinoma.[2] Conversion therapy refers to the opportunity for hepatocellular carcinoma patients who are not suitable for surgical resection to obtain surgical resection after intervention, which mainly includes functional future liver remnant volume (FLR) transformation and oncology transformation. Currently, palliative treatment programs such as drugs or TACE are commonly used to reduce tumor stage as much as possible.[3] To provide inoperable patients with the opportunity to undergo radical resection. In recent years, with the development of immunotherapy and chemotherapy drugs, the therapeutic effect of unresectable hepatocellular carcinoma has made significant progress, which also makes the conversion rate of unresectable has been significantly improved, and more and more patients have access to the opportunity of radical resection.[4]

Surgical resection represents a significant means for the long-term survival of patients patients after transformation. Several pieces of research evidence suggest that patients who undergo radical resection subsequent to palliative care often witness an enhanced overall survival rate.[5] For patients who have undergone transformative treatment, there is no

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explicit standard for the timing of surgical intervention. Presently, the decision to conduct radical surgery and the choice of surgical method largely hinge on the clinical judgment of the surgeon. However, there exists a deterministic disparity in the hepatic status of patients post-transformative treatment compared to the general population, notwithstanding the potential absence of significant differences in preoperative assessments such as liver function, routine blood tests, and coagulation function.

Research indicates that the success rate of transformation is higher when combining interventional treatments (TACE/HAIC) with targeted or immunotherapies, compared to standalone treatments.[6] In our institution, a combined approach incorporating interventional treatments along with targeted or immunotherapies is uniformly employed for patients with advanced hepatocellular carcinoma.The 2021 Chinese Consensus on Transformational Treatment elucidates that localized treatment could potentially induce hepatic injury, subsequently affecting the safety of surgical procedures post-transformation.[7] Previous research has identified that certain patients undergo liver displacement and adhesions between the liver and diaphragm following TACE treatment.[8] Hepatic injury, displacement, and adhesions are all potential factors that could impact the safety of radical surgery, and are often overlooked in preoperative assessments.There are no standardized studies and reports on the difference between the risk during and perioperative period of post-conversion surgery and common liver resection.[9]

This study aims to provide reference for the timing of conversion therapy surgery, reduce perioperative complications, and improve patient prognosis by comparing the perioperative characteristics of hepatocellular carcinoma patients who underwent conversion surgery with those underwent direct surgery.

Methodology

Patient

This study included patients with hepatocellular carcinoma who underwent surgical resection at the First Affiliated Hospital of Chongqing Medical University from September 2022 to December 2023.All patients underwent radical resection of hepatocellular carcinoma. Serological examination was performed both before and after operation.Patients with other systemic malignancies, recurrent hepatocellular carcinoma, and prior liver surgery were excluded.This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Research Ethics No: K2023-476) and conducted in accordance with the Helsinki Declaration. Clinical data were retrospectively extracted from our electronic medical records, and written informed consent for data use was obtained from all patients.

Treatment and group

All patients in the conversion group were initially diagnosed with hepatocellular carcinoma, which was accompanied by intrahepatic metastasis, cancer embolus in the blood vessels, and a large tumor volume. Following treatment with TACE/HAIC, targeted therapy, immunotherapy, as well as other local and systemic treatments, tumor progression was effectively controlled, leading to reduction in tumor volume and limited cancer thrombus. Subsequently evaluated by the hepatobiliary surgery department of the First Affiliated Hospital of Chongqing Medical University liver sub-professional group of doctors, the patient underwent radical surgery for hepatocellular carcinoma.

All patients in the direct surgery group were diagnosed with hepatocellular carcinoma and underwent radical surgery for hepatocellular carcinoma without systemic treatment after evaluation by physicians in the Hepatobiliary Surgery subprofessional group of the First Affiliated Hospital of Chongqing Medical University.

Clinical Information

Data were collected in three main phases: preoperative, intraoperative, and postoperative. The data collected preoperatively included patients' basic conditions (age, gender, BMI.). blood routine, liver function, coagulation function, and preoperative BCLC tumor stage. Intraoperative data collected included the patient's surgical approach (laparoscopic or open), intraoperative resection extent (number of liver segments resected, whether lymphatic clearance), intraoperative bleeding, intraoperative blood transfusion, and duration of surgery. Postoperative data collected included perioperative

complications, postoperative blood test results (blood count, liver function, coagulation function), postoperative hospitalization time.

Analysis

All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Normal distribution of continuous data was determined using the Kolmogorov–Smirnov test. Continuous data obeying normal distribution were expressed as mean and standard deviation (SD), while continuous data with non-normal distribution were expressed as median and interquartile range. Non-normally distributed continuous data were tested using nonparametric tests for independent samples. Categorical data were compared using chi-square tests or Fisher's exact tests. P value < 0.05 was considered statistically significant in all tests.

Result

A total of 686 patients with hepatocellular carcinoma who underwent surgical resection at the First Affiliated Hospital of Chongqing Medical University were included in this study, and 263 cases were finally included after screening according to the exclusion criteria. 53 cases were included in the post-conversion surgery group and 210 patients were included in the direct surgery group. Among all the included patients, only one case died of hemorrhagic shock due to the presence of special antibodies in the blood that caused difficulty in blood matching and low blood transfusion after surgery, and the rest of the patients recovered and were discharged from the hospital after postoperative symptomatic treatment.

Baseline Data

According to the Table 1, there were no significant differences in gender (P=0.121), comorbid cardiovascular system diseases (P=0.354), comorbid endocrine system diseases (P=0.575), comorbid respiratory system diseases (P=1), history of previous laparotomy (P=0.19), and BMI (P=0.059) between the patients in the conversion group and the operating group.

In the serological indexes of the two groups of patients before surgery, there were significant differences between the conversion group and the operating group in hemoglobin (P=0.002), blood albumin (P=0.001), total bilirubin (P=0.011), alanine aminotransferase (P=0.011), and the maximum diameter of a single tumor (P=0.003), and no significant differences existed between the two groups of patients in leukocyte (P=0.538), platelet (P= 0.461), aspartate aminotransferase (P=0.09), and prothrombin time (P=0.324). Notably, the levels of leukocytes (median, 5.25), hemoglobin (median, 132), platelets (median, 143), and blood albumin (median, 38) in the conversion group of patients compared with those in the operating group all had a decreasing trend. In contrast, the preoperative aspartate aminotransferase (median, 34) and alanine aminotransferase (median, 40) in the conversion group tended to be significantly higher compared with those in the operating group (median, 29, 32).

There were some differences in the preoperative serologic indices between the two groups of patients, but the differences had no significant effect on whether or not surgery when compared with the currently accepted normal range. However, in order to eliminate the disparity in serological indices between the two groups, we performed a propensity matching analysis (matching tolerance = 0.02) between the two groups of patients for the serological indices mentioned that differed, as well as the maximum diameter of individual tumor, and screened out 50 matched cases in each of the 53 patients in the conversion group and the 210 patients in the operating group.

As shown in the Table 2, in the PSM cohort, there were no significant differences in the preoperative serologic indices between the transformation and surgical groups: white blood cells (P=0.652), hemoglobin (P=0.751), platelets (P=0.41), blood albumin (P=0.95), total bilirubin (P=0.562), aspartate aminotransferase (P=0.157), alanine aminotransferase (P= 0.142), and prothrombin time (P=0.0.098).The maximum diameter of individual tumors also did not show significant differences between the two groups.

Comparison of Intraoperative Conditions

Based on the information contained in Table 3, there were significant differences in the extent of surgery (P=0.033), whether or not blood was transfused intraoperatively (P=0.001), surgical turnover rate (P=0.008), intraoperative bleeding (P=0.001), and duration of surgery (P=0.033) between the conversion group and the operating group. In addition, the

Table 1 Patients' Basic Characters

	Conversion group (n=53)	Operating group (n=210)	P
Sex			
Male	44 (83%)	190 (90.5%)	0.121
Female	9 (17%)	20 (9.5%)	
Age, years			
≥60	18 (34%)	87 (41.4%)	0.404
<60	35 (66%)	123 (58.6%)	
Combined cardiovascular diseases			
Yes	9 (17%)	48 (22.9%)	0.354
No	44 (83%)	162 (77.1%)	
Combined endocrine system diseases			
Yes	6 (11.3%)	30 (14.3%)	0.575
No	47 (88.7%)	180 (85.7%)	
Combined respiratory diseases			
Yes	3 (5.7%)	14 (6.7%)	1
No	50 (94.3%)	196 (93.3%)	
Previous laparotomy			
Yes	3 (5.7%)	28 (13.3%)	0.19
No	50 (94.3%)	182 (86.7%)	
Child-Pugh			
A	53 (100%)	206 (98.1%)	0.701
B	0	4 (1.9%)	
BMI(median)	21.96 (21.25–23.44)	22.93 (21.68–24.52)	0.059
WBC(*10^9/L, median)	5.25 (5.02–5.49)	5.4 (4.9–5.77)	0.538
HB(g/L, median)	132 (122–146)	140 (129.5–151.5)	0.002
PLT(*10^9/L, median)	143 (92–212.5)	153 (113.5–201)	0.461
ALB (g/L, median)	38 (35–42)	42 (30–50)	0.001
TB (umol/L, median)	10.5 (7.05–14.05)	12.9 (8.85–18.25)	0.011
AST (U/L, median)	34 (24–48)	29 (20–43)	0.09
ALT (U/L, median)	40 (29–49)	32 (23–47.5)	0.011
PT (s, median)	13.7 (11.3–14.15)	13.8 (13.2–14.4)	0.324
AFP (median)	19.6 (3.65–176.63)	12.2(4.2–289.6)	0.87
Tumor number (median)	1 (1–2)	1 (1–1)	0.065
Maximum tumor diameter (cm, median)	5.1 (3.1–8.5)	4 (2.75–6.25)	0.003

Table 2 PSM Group Patients' Basic Characters

	Conversion Group(n=50)	Operating Group(n=50)	P
WBC(*10^9/L, median)	5.3 (5.02–5.47)	5.34 (4.9–6)	0.652
HB(g/L, median)	133 (123.5–146.25)	133 (119.5–143)	0.751
PLT(*10^9/L, median)	144 (94–211.25)	162 (121–217)	0.41
ALB(g/L, median)	38 (35–42)	38 (35–41)	0.95
TB(umol/L, median)	10.65 (6.9–14)	11 (7.35–15.65)	0.562
AST(U/L, median)	34 (23.75–48)	27 (20–46)	0.142
ALT(U/L, median)	40 (29.5–49)	33 (22–52.5)	0.157
PT(s, median)	13.7 (13–14.15)	14 (13.35–14.45)	0.098
AFP(median)	19.6 (3.65–260.1)	12.2 (3–461.45)	0.385
Tumor number(median)	1 (1–2)	1 (1–2)	0.282
Maximum tumor diameter(cm, median)	5.1 (3.075–8.225)	4 (2.7–8.9)	0.528

Table 3 Comparison of Intraoperative Conditions Between Conversion Group and Operation Group

	Conversion Group (n=53)	Operating Group (n=210)	P
Scope of surgery (number of liver segments resected)			
1	9 (17%)	66 (31.4%)	0.033
2	17 (32.1%)	83 (39.5%)	
3	13 (24.5%)	31 (14.8%)	
4	14 (25.4%)	29 (13.8%)	
5	0	1 (0.5%)	
Intraoperative blood transfusion			
Yes	13 (24.5%)	10 (4.8%)	0.001
No	40 (75.5%)	200 (95.2%)	
Laparotomy			
Yes	10 (18.9%)	13 (6.2%)	0.008
No	43 (81.1%)	197 (93.8%)	
Perioperative bleeding (mL, median)	500 (400–700)	300 (200–400)	0.001
Operation duration (min, median)	310 (257–425)	270 (230–370)	0.033

conversion group had a greater extent of surgery, more intraoperative bleeding, longer duration of surgery, and a higher intraoperative transfusion rate and surgical turnover rate.

However, according to Table 4, in the PSM cohort, intraoperative bleeding (P=0.001), intraoperative transfusion rate (P=0.044), and operative duration (P=0.025) remained significantly different between the conversion and operating groups. Although there was no significant difference between the two groups in terms of surgical extent and transfer rate, the proportion of operations involving 3 or more liver segments in the conversion group (54%) was greater than that in the operating group (28%), and the transfer rate in the conversion group (20%) was higher than that in the operating group (8%), suggesting that the surgical extent of the conversion group was still increasing compared with that of the operating group, and the surgical transfer rate had a clear trend of elevation as well.

Table 4 Comparison of Intraoperative Conditions Between Conversion Group and Operation Group in PSM Cohert

	Conversion Group(n=50)	Operating Group(n=50)	P
Scope of surgery (number of liver segments resected)			
1	9 (18%)	15 (30%)	0.053
2	14 (28%)	21 (42%)	
3	13 (26%)	5 (10%)	
4	14 (28%)	9 (18%)	
5	0	0	
Intraoperative blood transfusion			
Yes	11 (22%)	3 (6%)	0.044
No	39 (78%)	47 (94%)	
Laparotomy			
Yes	10 (20%)	4 (8%)	0.15
No	40 (80%)	46 (92%)	
Perioperative bleeding (mL, median)	500 (200–700)	200 (100–400)	0.001
Operation duration (min, median)	280 (225–401.25)	252 (190–320)	0.025

Comparison of Postoperative Conditions

There were significant differences between the conversion group and the operating group in terms of ascites formation (P=0.011), moderate to severe anemia (P=0.001), whether or not blood transfused postoperatively (P=0.04), whether or not transferred to ICU postoperatively (P=0.041), and the duration of postoperative hospitalization (P=0.01) in the perioperative period, presented in Table 5. The perioperative rates of ascites formation, moderate to severe anemia, postoperative blood transfusion, and postoperative transfer to ICU were higher in the conversion group than in the operating group, and the duration of postoperative hospitalization was greater.

According to Table 6, In the PSM cohort, the rates of perioperative ascites formation (P=0.005), moderate to severe anemia (P=0.002), postoperative blood transfusion (P=0.036), the duration of postoperative hospitalization (P=0.03), and postoperative ICU transfer (P=0.025) remained significantly higher in the conversion group than in operating group. Although there was no significant difference between the two groups for coagulation abnormality (P=0.492), there was still a trend of elevation in the conversion group.

Subgroup Analysis by Extent of Resection

For anatomical liver resections, segmental resection, lobectomy, and hemihepatectomy are common. The standard left hemihepatectomies involves 3 liver segments, whereas the right hemihepatectomy involves 4 liver segments, with more extensive resection than localized segments and lobes. Considering the possible implications of the extent of resection on the intraoperative situation and perioperative short-term complications, this study intends to group all patients according to the number of hepatic segments resected during the operation, categorize intraoperative resection of less than 3 hepatic segments as minor subgroup, and greater than or equal to 3 hepatic segments are considered as massive subgroup, and compare the information related to the conversion patients and the non-conversion patients in the two groups.

Among the 53 patients in the conversion group, 26 patients were categorized into the minor resection subgroup and 27 patients were categorized into the massive resection subgroup. In the operating group 149 of 210 patients were categorized into the minor subgroup and 61 patients into the massive subgroup.

As shown in Table 7, in the minor resection subgroup, intraoperative bleeding (P=0.001) and duration of operation (P=0.015) were significantly higher in the conversion group compared with the operating group, and the intraoperative turnover rate (P=0.038) and blood transfusion rate (P=0.001) of the operation were significantly higher than those of the

Table 5 Comparison of Postoperative Conditions Between Conversion Group and Operation Group

	Conversion Group(n=53)	Operating Group(n=210)	P
Ascites formation			
Yes	16 (30.19%)	26 (12.4%)	0.011
No	37 (69.81%)	184 (87.6%)	
Abnormal coagulation (PT extension >3s)			
Yes	18 (34%)	67 (31.9%)	0.775
No	35 (66%)	143 (68.1%)	
Moderate to severe anemia (HB<90g/L)			
Yes	16 (30.2%)	20 (9.5%)	0.001
No	37 (69.8%)	190 (90.5%)	
Postoperative transfusion			
Yes	8 (15.1%)	9 (4.3%)	0.04
No	45 (84.9%)	201 (95.7%)	
Postoperative transfer to ICU			
Yes	10 (18.9%)	19 (9%)	0.041
No	43 (81.1%)	191 (91%)	
Postoperative hospitalization time (day, median)	10 (7–12)	7 (6–9)	0.01

Table 6 Comparison of Postoperative Conditions Between Conversion Group and Operation Group in PSM Cohert

	Conversion Group(n=50)	Operating Group(n=50)	P
Ascites formation			
Yes	16 (32%)	4 (8%)	0.005
No	34 (68%)	92 (46%)	
Abnormal coagulation (PT extension >3s)			
Yes	18 (36%)	12 (24%)	0.275
No	32 (64%)	38 (76%)	
Moderate to severe anemia (HB<90g/L)			
Yes	16 (32%)	3 (6%)	0.002
No	34 (68%)	47 (94%)	
Postoperative transfusion			
Yes	8 (16%)	1 (2%)	0.036
No	42 (84%)	49 (98%)	
Postoperative transfer to ICU			
Yes	10 (20%)	3 (6%)	0.025
No	40 (80%)	47 (94%)	
Postoperative hospitalization time (day, median)	9 (7–12)	7.5 (6–9)	0.03

Table 7 Comparison of Intraoperative Conditions Between Conversion Group and Operation Group in the Minor Resection Subgroup

	Conversion Group(n=26)	Operating Group(n=149)	P
Intraoperative blood transfusion			
Yes	7 (26.9%)	7 (4.7%)	0.001
No	19 (73.1%)	142 (95.3%)	
Laparotomy			
Yes	4 (15.4%)	7 (4.7%)	0.038
No	22 (84.6%)	142 (95.3%)	
Perioperative bleeding (mL, median)	425 (230–500)	200 (150–380)	0.001
Operation duration (min, median)	317.5 (250–400)	235 (180–320)	0.015

operating group. And in the massive resection subgroup, only intraoperative bleeding (P=0.002) and blood transfusion rate (P=0.013) were significantly higher in the conversion group compared with the operating group, whereas the duration of operating time (P=0.37) and intraoperative turnover rate (P=0.221) were not significantly different, which we can see in the Table 8.

According to Table 9, patients in the transformed group after minor resection had significantly higher rates of ascites formation (P=0.015), moderate to severe anemia (P=0.001), postoperative transfusion (P=0.019), and postoperative transfer to the ICU (P=0.013), as well as significantly longer postoperative hospital duration (P=0.006). In contrast, by the information in Table 10, in the extensive resection subgroup, there were no significant differences in all of the previously mentioned perioperative complications and postoperative hospitalization duration.

Subgroup Analysis by Stage of BCLC

Considering the impact of surgery due to different tumor stages, this study compares and analyzes the perioperative complications of patients in the conversion group who were evaluated preoperatively as stage A\B\C with those in the operating group, respectively, according to the BCLC stage.

Table 8 Comparison of Intraoperative Conditions Between Conversion Group and Operation Group in the Massive Resection Subgroup

	Conversion Group(n=27)	Operating Group(n=61)	P
Intraoperative blood transfusion			
Yes	6 (22.2%)	3 (4.9%)	0.013
No	21 (77.8%)	58 (95.1%)	
Laparotomy			
Yes	6 (22.2%)	6 (9.8%)	0.221
No	21 (77.8%)	55 (90.2%)	
Perioperative bleeding (mL, median)	500 (300–750)	300 (200–520)	0.002
Operation duration (min, median)	270 (225–425)	310 (210–440)	0.37

Table 9 Comparison of Postoperative Conditions Between Conversion Group and Operation Group in the Minor Resection Subgroup

	Conversion Group(n=26)	Operating Group(n=149)	P
Ascites formation			
Yes	8 (30.8%)	16 (10.7%)	0.015
No	18 (69.2%)	184 (80.3%)	
Abnormal coagulation (PT extension >3s)			
Yes	7 (26.9%)	39 (26.2%%)	0.936
No	19 (73.1%)	110 (73.8%)	
Moderate to severe anemia (HB<90g/L)			
Yes	8 (30.8%)	9 (6%)	0.001
No	18 (69.2%)	140 (94%)	
Postoperative transfusion			
Yes	4 (15.4%)	4 (2.7%)	0.019
No	22 (84.6%)	145 (97.3%)	
Postoperative transfer to ICU			
Yes	6 (23.1%)	9 (6%)	0.013
No	20 (76.9%)	140 (94%)	
Postoperative hospitalization time (day, median)	8 (6–13)	7 (5–10)	0.006

Among patients with BCLC staging of A in Table 11, there was a significant increase in the proportion of patients in the conversion group who developed moderate to severe anemia (P=0.001) and postoperative blood transfusion (P=0.005) postoperatively compared to the operating group. Although there was no significant difference in the proportion of postoperative hospitalization (P=0.054) and postoperative ICU admission (P=0.051), there was a tendency for the proportion in the conversion group to be elevated compared to the operating group.

We can see that from Table 12, in patients with BCLC stage B, there were still significant differences between the two groups in the proportions of patients who developed moderate to severe anemia (P=0.017) and postoperative blood transfusion (P=0.048), and there were no significant differences between the two groups in terms of postoperative ascites formation, coagulation abnormality, postoperative transfer to the ICU, and postoperative duration of hospitalization.

According to Table 13, among patients with BCLC staging in group C, patients in the conversion group were more likely to develop ascites formation (P=0.016) and have a longer hospital stay (P=0.034) than patients in the operating group, while there was no significant difference in the incidence of other perioperative complications.

Table 10 Comparison of Postoperative Conditions Between Conversion Group and Operation Group in the Massive Resection Subgroup

	Conversion Group(n=27)	Operating Group(n=61)	P
Ascites formation			
Yes	6 (22.2%)	10 (16.4%)	0.36
No	21 (77.7%)	51 (83.6%)	
Abnormal coagulation (PT extension >3s)			
Yes	11 (40.7%)	28 (45.9%)	0.603
No	16 (59.3%)	34 (54.1%)	
Moderate to severe anemia (HB<90g/L)			
Yes	8 (29.6%)	11 (18%)	0.244
No	19 (70.4%)	50 (82%)	
Postoperative transfusion			
Yes	4 (14.8%)	5 (8.2%)	0.44
No	23 (85.2%)	56 (91.8%)	
Postoperative transfer to ICU			
Yes	6 (22.2%)	10 (16.4%)	0.36
No	21 (77.7%)	51 (83.6%)	
Postoperative hospitalization time (day, median)	9.5 (6–15)	8 (6–14.25)	0.419

Table 11 Comparison of Postoperative Conditions Between Conversion Group and Operation Group of Patients with a Stage (BCLC)

	Conversion Group(n=13)	Operating Group(n=91)	P
Ascites formation			
Yes	2 (15.4%)	12 (13.2%)	0.828
No	11 (84.6%)	79 (86.8%)	
Abnormal coagulation (PT extension >3s)			
Yes	5 (38.5%)	29 (31.9%)	0.635
No	8 (61.5%)	62 (68.1%)	
Moderate to severe anemia (HB<90g/L)			
Yes	6 (46.2%)	4 (4.4%)	0.001
No	7 (53.8%)	87 (95.6%)	
Postoperative transfusion			
Yes	4 (30.8%)	4 (4.4%)	0.005
No	9 (69.2%)	87 (95.6%)	
Postoperative transfer to ICU			
Yes	3 (23.1%)	4 (4.4%)	0.054
No	10 (76.9%)	87 (95.6%)	
Postoperative hospitalization time (day, median)	7 (6–12)	7 (6–8)	0.419

Discussion

With the development of interventional therapy combined with targeted, immunologic and other systemic therapies, the treatment options for patients with unresectable hepatocellular carcinoma are changing, and their efficacy has been recognized to varying degrees. These systemic treatment options have benefited more patients, and more unresectable hepatocellular carcinoma patients have been given the opportunity of operating.[10] It has been shown that translational regimens based on localized treatment with interventional procedures combined with targeted or immunotherapy have

Table 12 Comparison of Postoperative Conditions Between Conversion Group and Operation Group of Patients with B Stage (BCLC)

	Conversion Group(n=19)	Operating Group(n=60)	P
Ascites formation			
Yes	4 (21.1%)	8 (13.3%)	0.414
No	15 (78.9%)	52 (86.7%)	
Abnormal coagulation (PT extension >3s)			
Yes	2 (10.5%)	18 (30%)	0.162
No	17 (89.5%)	42 (70%)	
Moderate to severe anemia (HB<90g/L)			
Yes	7 (36.8%)	6 (10%)	0.017
No	12 (63.2%)	54 (90%)	
Postoperative transfusion			
Yes	4 (21.1%)	3 (5%)	0.048
No	15 (78.9%)	57 (95%)	
Postoperative transfer to ICU			
Yes	4 (21.1%)	8 (13.3%)	0.414
No	15 (78.9%)	52 (86.7%)	
Postoperative hospitalization time (day, median)	8 (7–11)	8 (6–9.5)	0.419

Table 13 Comparison of Postoperative Conditions Between Conversion Group and Operation Group of Patients with C Stage (BCLC)

	Conversion Group(n=20)	Operating Group(n=41)	P
Ascites formation			
Yes	7 (35%)	4 (9.8%)	0.016
No	13 (65%)	37 (90.2%)	
Abnormal coagulation (PT extension >3s)			
Yes	11 (55%)	15 (36.6%)	0.172
No	9 (45%)	26 (63.4%)	
Moderate to severe anemia (HB<90g/L)			
Yes	3 (15%)	6 (14.6%)	0.97
No	17 (85%)	35 (85.4%)	
Postoperative transfusion			
Yes	2 (10%)	2 (4.9%)	0.448
No	18 (80%)	39 (95.1%)	
Postoperative transfer to ICU			
Yes	3 (15%)	6 (14.6%)	0.97
No	17 (85%)	35 (85.4%)	
Postoperative hospitalization time (day, median)	10 (7–12)	8 (6–9)	0.419

a higher success rate,[11–13] and all of the translational patients in this study received systemic treatment based on interventional procedures as well.

Different from neoadjuvant therapy, the goal of conversion therapy is the radical removal of the tumor, and patients may be in poorer condition before receiving systemic therapy. It has been shown that during systemic therapy, patients' liver function and intra-abdominal conditions may be affected to varying degrees, and it has been reported that patients' hepatic reserve function tends to decline during bevacizumab and atirizumab treatments,[14–16] while multiple interventions may lead to liver injury and hepatic cisplacental translocation.[17,18] All of these conditions caused during the

conversion process may have an impact on the subsequent resection operation. There is no generally accepted standard for the timing of operation for transformed patients, and it depends on the surgeon's judgment, during which the difference between transformed patients caused by pre-treatment and those who directly undergo radical resection may be overlooked.[19]

This study showed that although there was no significant difference between the preoperative conditions of the converted and operated patients in the preoperative evaluation, the converted patients had significantly higher rates of intraoperative bleeding, intraoperative transfusion, and longer operating times than the operated group.It has been suggested that interventions are more likely to result in neutropenia and thrombocytopenia but do not show a significant decrease in red blood cells.[11] The destruction of the liver itself by the chemotherapeutic agents used in the intervention may have contributed to the increased intraoperative bleeding, which may have led to a greater likelihood of moderate-to-severe anemia in the postoperative period in transformed patients.

The results of the subgroup analysis of the resection extent in this study suggested that the intraoperative bleeding in the conversion patients was significantly higher compared with the normal patients in both minor and massive liver resections, and the probability of moderate-to-severe postoperative anemia and postoperative blood transfusion was significantly higher in the conversion patients with minor resections compared with those who had been directly operated on. This may be related to the intervention-induced interstitial hypertension around the tumor, the targeted drug damage to small blood vessels, such microenvironmental changes help to promote the distribution of chemotherapeutic drugs and inhibit tumor growth,[20,21] and in combination with the previously mentioned intervention-induced liver injury, it may lead to an increase in blood seepage from the surgical wound, even if intrahepatic blood vessels are not damaged during the operation. Therefore, in order to cope with more bleeding during preoperative preparation, doctors should make corresponding preparations when facing patients with post-conversion surgery, such as more adequate blood preparation, more careful and frequent hemostasis during operation and so on.

Considering the impact of small hepatocellular carcinoma on the results, a comparison according to BCLC staging was also performed, removing patients with stage 0. In addition to the previously mentioned difference in bleeding, it can be seen that the proportion of postoperative transfers to the ICU in the transformed group compared with the normal surgery group had a trend of elevation in stage A patients, but with the progression of staging, whether or not to undergo conversion therapy had a decreasing impact on the operating as well as the perioperative complications. For patients with stage C, those with limited vascular invasion, whether or not undergoing preoperative conversion therapy had no significant effect on perioperative complications.

In combination with the prognosis of the patients, only one patient died in the postoperative period due to severe anemia due to the presence of specific antibody matching difficulties, and all other patients were discharged from the hospital cured. This suggests that although converted patients have more intraoperative bleeding and a higher rate of moderate-to-severe anemia and ascites formation in the perioperative period, such adverse effects can be reversed with treatment. It has been shown that the prognosis of post-conversion surgery is better than that of continued maintenance therapy,[22] and that the prognosis of converted patients undergoing resection is comparable to that of patients undergoing direct resection for early-stage hepatocellular carcinoma [24]. Therefore, if the measures of adequate preoperative blood preparation and timely treatment of ascites in the postoperative period are well developed, conversion patients should be encouraged to undergo surgical treatment.

However, as a single center study, the number of patients still needs to be further expanded, and there is a certain bias in the selection of conversion therapy methods, which lead to the lack of horizontal comparison of different conversion methods in this paper. The follow-up time needs to be further extended to more accurately evaluate the long-term prognosis of patients undergoing surgical treatment, and to continue studying the relevant factors that affect patient prognosis.

Conclusion

Post-conversion operations carry a higher risk of bleeding and are more likely to result in moderate to severe anemia and ascites formation in the perioperative period. However, the risk is reversible with adequate preoperative blood

preparation and prompt postoperative symptomatic treatment. Conversion patients should be encouraged to undergo operating therapy when they can withstand surgical resection.

Data Sharing Statement

The data in this study are extracted from other studies, are completely open and can be downloaded and used on their own.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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