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Unplanned conversion during minimally invasive liver resection for hepatocellular carcinoma: risk factors and surgical outcomes

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Purpose: Unplanned conversion is sometimes necessary during minimally invasive liver resection (MILR) of hepatocellular carcinoma (HCC). The aims of this study were to compare surgical outcomes of planned MILR and unplanned conversion and to investigate the risk factors after unplanned conversion.
Methods: We retrospectively analyzed 286 patients who underwent MILR with HCC from January 2006 to December 2017. All patients were divided into a MILR group and an unplanned conversion group. The clinicopathologic characteristics and outcomes were compared between the 2 groups. In addition, surgical outcomes in the conversion group were compared with the planned open surgery group (n = 505). Risk factors for unplanned conversion were analyzed.
Results: Of the 286 patients who underwent MILR, 18 patients (6.7%) had unplanned conversion during surgery. The unplanned conversion group showed statistically more blood loss, higher transfusion rate and postoperative complication rate, and longer hospital stay compared to the MILR group, whereas no such difference was observed in comparison with the planned open surgery group. There were no significant differences in overall and disease-free survival among 3 groups. The right-sided sectionectomy (right anterior and posterior sectionectomy), central bisectionectomy and tumor size were risk factors of unplanned conversion.
Conclusion: Unplanned conversion during MILR for HCC was associated with poor perioperative outcomes, but it did not affect long-term oncologic outcomes in our study. In addition, when planning right-sided sectionectomy or central bisectionectomy for a large tumor (more than 5 cm), we should recommend open surgery or MILR with an informed consent for unplanned open conversions.
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Key Words: Hepatocelluar carcinoma, Minimally invasive liver resection, Open conversion

INTRODUCTION

Since the introduction of laparoscopic liver resection in the early 1990s, current laparoscopic liver resection is considered as an oncologically safe and standard procedure owing to the development of technical advances and postoperative management [1,2]. Previous studies on surgical outcomes between laparoscopic and open liver resection showed that laparoscopic liver resection provided improved perioperative outcomes and comparable long-term oncologic outcomes [1-3].

Although laparoscopic liver resection has increased in recent years, it is still difficult for many surgeons to perform because of the inherent limitation of laparoscopic techniques such as the fulcrum effect and the restricted degrees of motions of the instrument [4]. Regardless of technical limitations, the 3-dimensional complex anatomy of the liver, with its

accompanying high risk for significant bleeding, has made laparoscopic liver resection the last area of laparoscopy to be developed [5]. According to the Morioka consensus conference in 2014, laparoscopic major liver resection was considered to be an innovative procedure, even though they agreed that laparoscopic minor liver resection had become a standard procedure [5]. The main concern of minimally invasive liver resection (MILR) is unplanned open conversion, the rate of which varies from 0.0% to 55.0% depending on the extent of liver resection and according to the literature [6-10]. According to recent studies comparing planned surgery and unplanned conversion during MILR, this unplanned conversion is known to have a negative effect on perioperative outcomes [2,7-9,11]. However, there are few studies about the effect of unplanned conversion on long-term outcomes in patients with hepatocellular carcinoma (HCC) [2].

The aims of this study were to compare the short- and long-term outcomes of MILR and unplanned conversion and to investigate the risk factors after unplanned conversion.

METHODS

Data from all consecutive patients who underwent MILR from January 2006 to December 2017 at Severance Hospital, Yonsei University College of Medicine, were retrospectively collected from electronic medical records. Patients who underwent open hepatectomy during the same period were also included for analysis. This study was approved by the Severance Hospital's Institutional Review Board (IRB No. 4-2019-0603) that waived the requirement of informed consent.

The initial selection criterion for laparoscopic liver resection was strictly based on the Louisville Statement [12]: a solitary lesion, tumor size of 5 cm or less, and located in peripheral liver segments 2 to 6 [13]. Robotic liver resection program in our institute was started in 2008 [4]. Unlike laparoscopic liver resection, initial indications of robotic liver resection were mainly major liver resection [4,14]. As surgeon's experience accumulated, laparoscopic liver resection has been extended into major liver resection and right-sided anatomic liver resection [1,13]. Currently, tumor size and number are no longer limiting factors for MILR, while curative removal of HCC is anticipated.

Comparison of short- and long-term outcomes between planned surgery and unplanned conversion groups

Short-term outcomes were evaluated using operative time, blood loss, transfusion rate, complications, and length of hospital stay. Postoperative complications were assessed according to the Clavien-Dindo classification. R0 status and resection margin were also compared to assess short-term oncologic outcomes. To assess long-term surgical outcomes, disease-free and overall survivals were analyzed. Disease-free survival was defined as the duration from the date of surgery to the day of HCC recurrence diagnosis. Overall survival was defined as the duration from the date of operation to the last follow-up day or death date from any cause.

Risk factors for unplanned open conversion

Risk factors associated with unplanned open conversion were investigated using age, sex, body mass index (BMI), tumor size, American Joint Committee on Cancer (AJCC) 8th T stage, presence of liver cirrhosis, platelet count, and extent of resection. Extent of resection was classified into minor liver resection, right-sided sectionectomy and central bisectionectomy, and major hemihepatectomies. Minor hepatic resection included wedge resection, segmentectomy, and left lateral sectionectomy. Right-sided sectionectomy included right anterior sectionectomy and right posterior sectionectomy. Right and left hemihepatectomy were defined as major hemihepatectomies.

Statistical analysis

Clinicopathologic findings and long-term oncologic outcomes of this study were analyzed using the IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). For each clinicopathologic finding, each categorical and continuous variable were analyzed with the chi-square and Student t-test. Overall and disease-free survival were analyzed using the Kaplan-Meier method, and the difference in survival curves between groups was expressed using the log-rank test. All P-values <0.05 (2-sided) were considered statistically significant. A logistic regression model was used to examine the risk factor of unplanned conversion, which was assessed by the Hosmer-Lemeshow goodness-of-fit test.

RESULTS

Comparison of clinicopathologic characteristics and reasons for unplanned conversion

Patient- and tumor-specific variables of each group are described in Table 1. Of the 286 patients who underwent MILR, 18 patients (6.7%) proceeded to unplanned conversion during surgery. There were no significant differences in liver function, tumor marker, and demographic characteristics such as age, sex, BMI, and comorbid status of each patient. When comparing the operation type between the groups, right-sided sectionectomy and central bisectionectomy have relatively higher unplanned conversion rate. In the pathologic finding, there were no significant differences in the presence of liver cirrhosis and tumor number, T stage according to AJCC 8th classification, microvascular invasion, satellite nodule, R status, and resection

Table 1. Comparison of clinicopathologic characteristics and operation type for hepatocellular carcinoma patients

Variable	MILR (n = 268)	Unplanned conversion (n = 18)	P-value	Unplanned conversion (n = 18)	Planned open (n = 505)	P-value
Age (yr)	57.7 ± 9.8	60.2 ± 11.6	0.438	60.2 ± 11.6	58.0 ± 9.7	0.384
Sex			0.766			0.817
Male	200 (74.6)	14 (77.8)		14 (77.8)	404 (80.0)	
Female	68 (25.4)	4 (22.2)		4 (22.2)	101 (20.0)	
Body mass index (kg/m^2)	23.5 ± 2.8	24.0 ± 3.4	0.476	24.0 ± 3.4	24.0 ± 3.2	0.950
Hypertension	84 (31.3)	7 (38.9)	0.506	7 (38.9)	128 (25.3)	0.197
Diabetes mellitus	50 (18.7)	4 (22.2)	0.708	4 (22.2)	76 (15.0)	0.406
Etiology			0.343			0.491
HBV	226 (84.3)	14 (77.8)		14 (77.8)	411 (81.4)	
HCV	14 (5.2)	0 (0)		0 (0)	28 (5.5)	
Alcoholism	5 (1.9)	1 (5.6)		1 (5.6)	11 (2.2)	
NBNC	23 (8.6)	3 (16.7)		3 (16.7)	55 (10.9)	
Platelet count (10^3/μL)	167.1 ± 56.9	170.3 ± 54.8	0.817	170.3 ± 54.8	168.3 ± 68.0	0.903
Serum creatinine (mg/dL)	0.85 ± 0.16	0.86 ± 0.19	0.788	0.86 ± 0.19	0.87 ± 0.20	0.832
Serum albumin (g/dL)	4.3 ± 0.4	4.2 ± 0.4	0.088	4.2 ± 0.4	4.3 ± 1.6	0.662
AST (IU/L)	41.1 ± 36.8	45.3 ± 30.9	0.639	45.3 ± 30.9	35.7 ± 24.9	0.114
ALT (IU/L)	38.8 ± 38.1	36.9 ± 24.0	0.833	36.9 ± 24.0	35.0 ± 25.7	0.767
Total bilirubin (mg/dL)	0.82 ± 0.36	0.78 ± 0.40	0.733	0.78 ± 0.40	0.78 ± 0.36	0.948
INR	1.08 ± 0.84	1.01 ± 0.10	0.736	1.01 ± 0.10	1.00 ± 0.85	0.422
α-FP (ng/mL)	439.0 ± 2,615.0	133.5 ± 305.0	0.621	133.5 ± 305.0	1,048.2 ± 336.1	0.608
PIVKA-II (mAU/mL)	481.4 ± 4,677.0	234.7 ± 401.3	0.823	234.7 ± 401.3	1,071.7 ± 5,145.0	0.491
Pathology						
Liver cirrhosis	135 (50.4)	8 (44.4)	0.626	8 (44.4)	298 (59.0)	0.218
Tumor number			0.279			0.638
Single	244 (91.0)	15 (83.3)		15 (83.3)	440 (87.1)	
Multiple	24 (9.0)	3 (16.7)		3 (16.7)	65 (12.9)	
Tumor size (cm)	2.6 ± 1.2	3.5 ± 1.4	0.002	3.5 ± 1.4	3.7 ± 2.2	0.729
AJCC 8th T stage			0.774			<0.001
T1	167 (62.3)	10 (55.6)		10 (55.6)	438 (86.7)	
T2	99 (36.9)	8 (44.4)		8 (44.4)	52 (10.3)	
T3	2 (0.7)	0 (0)		0 (0)	15 (3.0)	
T4	0 (0.0)	0 (0)		0 (0)	0 (0.0)	
Microvascular invasion	116 (43.9)	7 (38.9)	0.676	7 (38.9)	245 (48.5)	0.422
Satellite nodule	6 (2.2)	1 (5.6)	0.378	1 (5.6)	28 (5.5)	0.982
Minimally invasive approach			0.435			<0.001
Laparoscopy	227 (84.7)	14 (77.8)		14 (77.8)	0 (0.0)	
Robot	41 (15.3)	4 (22.2)		4 (22.2)	0 (0.0)	
Operation type			<0.001			<0.001
Wedge resection	100 (37.3)	5 (27.8)		5 (27.8)	66 (13.1)	
Segmentectomy	44 (16.4)	2 (11.1)		2 (11.1)	107 (21.2)	
Left lateral sectionectomy	41 (15.3)	0 (0)		0 (0)	26 (5.1)	
Right-sided sectionectomy	29 (10.8)	9 (50.0)		9 (50.0)	61 (12.1)	
Central bisectionectomy	3 (1.1)	1 (5.6)		1 (5.6)	38 (7.5)	
Left hemihepatectomy	30 (11.2)	0 (0)		0 (0)	56 (11.1)	
Right hemihepatectomy	24 (9.0)	1 (5.6)		1 (5.6)	10 (2.0)	

Values are presented as mean ± standard deviation or number of patients (%).
Right-sided sectionectomy included right anterior sectionectomy and posterior sectionectomy.
MILR, minimally invasive liver resection; NBNC, non-B non-C hepatitis; INR, international normalized ratio; PIVKA-II, protein induced by vitamin K absence or antagonist II; AJCC, American Joint Committee on Cancer.

margin, but tumor size was found to be larger in the unplanned conversion group than in the MILR group. In the planned open surgery group, the mean tumor size was similar to that of the unplanned conversion group.

The reasons for unplanned conversion are described in Table 2. Bleeding was the most common cause, followed by lack of progression and poor access. Among 18 cases, oncologic concern, diaphragm injury, and severe adhesion were found. Vital signs during conversion were reviewed in the unplanned conversion group. When unstable vital signs were defined as both systolic blood pressure <90 mmHg and heart rate >120 beats/min, none showed unstable vital sign because bleeding was temporarily controlled using hemostatic agents before conversion.

Comparison of perioperative outcomes

Table 3 shows a comparison of perioperative outcomes

Table 2. Reasons for conversion from MILR to open laparotomy

Reasons for conversion	No. of patients (%)
Bleeding	11 (61.1)
Lack of progression	2 (11.1)
Poor access	2 (11.1)
Oncologic concern	1 (5.6)
Diaphragm injury	1 (5.6)
Severe adhesion	1 (5.6)
Total conversions from MILR to open laparotomy	18 (6.7)

MILR, minimally invasive liver resection.

Table 4. Detailed postoperative complications

Complication	MILR (n = 268)	Unplanned conversion (n = 18)	P-value
Liver-related complications	10 (3.7)	4 (22.2)	0.001
Bile leakage	2 (0.7)	0 (0)	
Ascites	6 (2.2)	4 (22.2)	
Biliary stricture	2 (0.7)	0 (0)	
Surgical-related complications	21 (7.8)	5 (27.8)	0.006
Wound complication	9 (3.4)	2 (11.1)	
Intraabdominal fluid collection	10 (3.7)	1 (5.6)	
Ileus	1 (0.4)	2 (11.1)	
Fever (no definite focus, antibiotics use)	1 (0.4)	0 (0)	
General complications	23 (8.6)	2 (11.1)	0.759
Atelectasis	9 (3.4)	0 (0)	
Pneumonia	2 (0.7)	0 (0)	
Pleural effusion	1 (0.4)	1 (5.6)	
Atrial fibrillation	2 (0.7)	0 (0)	
Urinary retention	4 (1.5)	0 (0)	
Delirium	3 (1.1)	1 (5.6)	
Stroke	1 (0.4)	0 (0)	
Pseudomembranous colitis	1 (0.4)	0 (0)	

Values are presented as number of patients (proportion per each group).
In 6 cases, there are more than one complications (first case, ascites and pleural effusion; second case, delirium and pseudomembranous colitis; third case, wound complication and intraabdominal fluid collection; fourth case, ileus and delirium; fifth case, delirium and stroke; sixth case, ascites, wound complication, intraabdominal fluid collection, and pleural effusion).
MILR, minimally invasive liver resection.

Table 3. Comparison of perioperative outcomes for hepatocellular carcinoma patients

Variable	MILR (n = 268)	Unplanned conversion (n = 18)	P-value	Unplanned conversion (n = 18)	Planned open (n = 505)	P-value
Estimated blood loss (mL)	221.8 ± 409.6	847.8 ± 547.3	<0.001	847.8 ± 547.3	532.3 ± 512.8	0.011
Operative time (min)	302.5 ± 152.0	441.2 ± 251.2	<0.001	441.2 ± 251.2	267.4 ± 104.1	<0.001
Blood transfusion	9 (3.4)	6 (33.3)	<0.001	6 (33.3)	59 (11.7)	0.006
Complication[a]	49 (18.3)	7 (38.9)	0.048	7 (38.9)	134 (26.5)	<0.001
Grade I	13 (4.9)	0 (0)		0 (0)	36 (7.1)	
Grade II	29 (10.8)	6 (33.3)		6 (33.3)	699 (13.7)	
Grade III	6 (2.2)	1 (5.6)		1 (5.6)	20 (4.0)	
Grade IV	1 (0.4)	0 (0)		0 (0)	7 (1.4)	
Grade V	0 (0)	0 (0)		0 (0)	2 (0.4)	
Length of stay (day)	7.6 ± 4.5	11.2 ± 4.9	0.001	11.2 ± 4.9	13.2 ± 17.9	0.631
R0 status			0.652			0.296
R0	265 (98.9)	18 (100)		18 (100)	477 (94.3)	
R1	3 (1.1)	0 (0)		0 (0)	28 (5.7)	
Resection margin (cm)	1.6 ± 1.4	1.5 ± 1.1	0.723	1.5 ± 1.1	1.4 ± 1.5	0.834

Values are presented as mean ± standard deviation or number of patients (%).
MILR, minimally invasive liver resection.
[a]Clavien-Dindo classification.

between each group. First, the unplanned conversion group had significantly more blood loss, longer operative time, and higher transfusion rate than the MILR group and planned open surgery group. The incidence of complication according to the Clavien-Dindo classification was higher in the unplanned conversion group. Each complication is categorized as liver-related, surgical-related, and general complications and described in Table 4. Liver- and surgical-related complications were significantly higher in the unplanned conversion group. The mean postoperative hospital stay was longer in the unplanned conversion group (P = 0.001) compared to the MILR group, but there was no such difference between the unplanned conversion group and thee planned open surgery group (P = 0.631).

Risk factors associated with unplanned conversion

Logistic regression analysis was performed with multiple factors that could affect unplanned conversion. Age, sex, BMI, presence of liver cirrhosis, and platelet count had no effects on unplanned conversion (Table 5). Tumor size was found to be a significant risk factor for unplanned conversion. Additionally, extent of resection was also a risk factor for unplanned conversion. With respect to extent of resection, right-sided sectionectomy and central bisectionectomy were found to be more associated with unplanned conversion compared to minor and major hepatic resections.

Comparison of long-term oncologic outcomes

Long-term oncologic outcome was analyzed using overall and disease-free survival. In survival analysis, there were no statistically significant differences in overall (P = 0.722) (Fig. 1) and disease-free survival (P = 0.541) (Fig. 2) among 3 groups. Regarding overall survival, MILR and unplanned conversion showed comparable 1- (95.2% vs. 94.2%), 3- (89.9% vs. 94.4%), and 5-year overall survival (88.3% vs. 94.4%; Fig. 1). There were no significant differences in 1- (86.2% vs. 77.8%), 3- (68.2% vs. 71.3%), and 5-year disease-free survival (57.1% vs. 42.8%) (Fig. 2) between the MILR group and the unplanned conversion group.

DISCUSSION

There has been a dramatic development in laparoscopic liver resection during the last few decades [1,5,8,12,15,16]. Recently introduced robotic systems have accelerated the progress of MILR [4,14]. The main advantages of MILR are that they provide patients with smaller scars, better cosmesis, less pain and analgesic requirements, shorter hospital stay, and early return

Table 5. Risk factors associated with unplanned conversion

Variable	P-value	HR	95% CI
Age	0.121	1.043	0.989–1.100
Sex			
Male	Reference		
Female	0.871	1.112	0.307–4.029
Body mass index	0.780	1.029	0.840–1.261
Liver cirrhosis			
No	Reference		
Yes	0.923	0.943	0.288–3.086
Platelet count (10^3/μL)	0.598	0.997	0.987–1.007
Tumor size	0.008	1.769	1.163–2.690
AJCC 8th T stage			
T1	Reference		
T2	0.752	1.198	0.390–3.678
T3	0.999	0.000	
Extent of resection			
Minor hepatic resection	Reference		
Right-sided sectionectomy and central bisectio-nectomy	0.001	6.793	2.283–20.209
Major hepatic resection	0.179	0.202	0.020–2.085

Right-sided sectionectomy included right anterior sectionectomy and posterior sectionectomy.
HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.
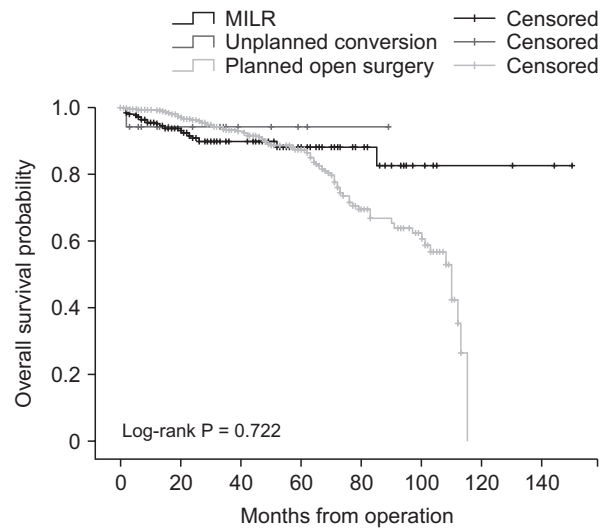

OS	OS 1 year (%)	OS 3 years (%)	OS 5 years (%)
MILR	95.2	89.9	88.3
Unplanned conversion	94.4	94.4	94.4
Planned open surgery	99.2	93.2	87.4

Fig. 1. Comparison of overall survival (OS) among the MILR group, the unplanned conversion group, and the planned open surgery group. MILR, minimally invasive liver resection.

Fig. 2. Comparison of disease-free survival (DFS) among the MILR group, the unplanned conversion group, and the planned open surgery group. MILR, minimally invasive liver resection.
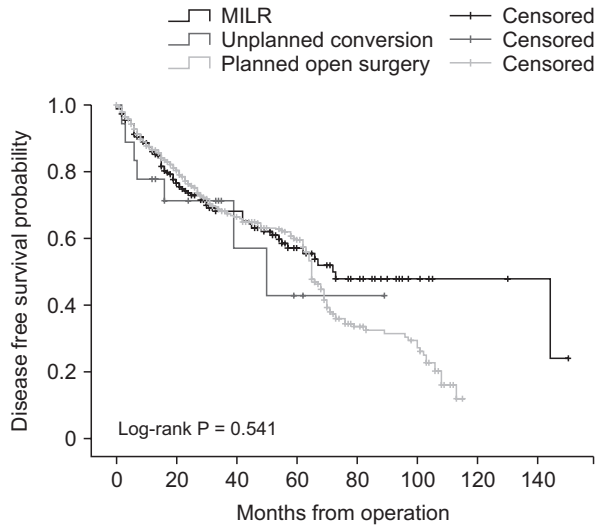
DFS	DFS 1 year (%)	DFS 3 years (%)	DFS 5 years (%)
MILR	86.2	68.2	57.1
Unplanned conversion	77.8	71.3	42.8
Planned open surgery	86.7	68.1	59.5

to social activity without compromising short- and long-term oncologic outcomes [1,5,8,12]. From the Louisville Statement to the Morioka consensus conference, laparoscopic liver resection has been rapidly popularized, and minor liver resection is now considered a standard procedure, regardless of the size, number, and location of the tumor [5,12]. However, major liver resections are still regarded as an innovative procedure and allowed only in expert centers [5]. The main concern regarding the broader adoption of MILR is an emergency open conversion caused by major bleeding, which may affect postoperative morbidity, mortality, and long-term outcomes [9,10,17,18].

In our study, unplanned open conversion during MILR for HCC was associated with poor short-term outcomes, with significantly longer operative time; more blood loss, and therefore, more requirements for blood transfusion; higher postoperative complication rates; and longer hospital stays. These results are in agreement with those of previous studies [1,4,8,11,18]. In particular, bleeding and perioperative blood transfusion are well known to be risk factors for postoperative morbidity [7-11]. The complication rates of the unplanned conversion group were 2 times higher than those of the planned surgery group (38.9% *vs.* 18.3%) and grade II complications were more common in the unplanned conversion group; however,

severe complications (grade > III) were not statistically different in this study.

Compared to the accumulating evidence of negative effects of unplanned open conversion on short-term outcomes, clinical significance of unplanned open conversion group in long-term aspect has been rarely investigated, especially in patients with HCC. Stiles et al. [2] reported the long-term outcomes after unplanned conversion during laparoscopic liver resection in patients with HCC. They found that the unplanned conversion group showed poor overall survival, and the difference was more predominant in patients who experienced open conversion during laparoscopic major hepatectomy. These results may be related to the recent European multicenter study, which found that emergency conversion for unfavorable intraoperative events such as bleeding and oncologic concern was associated with significantly poor short-term outcomes during laparoscopic liver resection, compared to elective conversion for unfavorable intraoperative findings such as adhesions and poor access [18]. Taken together with these 2 studies, conversion during laparoscopic major liver resection may have been performed under emergency conditions due to uncontrolled major bleeding. However, the unplanned conversion group did not show any difference in disease-free and overall survival compared to the planned surgery group in our study. This result might be caused by the small number of patients in the unplanned conversion group, but more importantly, the different situations and timing of conversion may have rendered our results different from those of previous studies. Even though the main cause of conversion was bleeding like previous studies, open conversion was not performed urgently with unstable vital signs in our patients. When bleeding occurred during MILR, all attempts were applied to control bleeding temporarily. Considering operative time and difficulty in proceeding with the operation, an early decision was made for an open procedure in our study. Costi et al. [19] also demonstrated that not delaying conversion may reduce blood loss and operative time. Nonemergency conditions and early decision for open conversion may have made similar long-term outcomes between the unplanned conversion and planned surgery groups in our study.

Many studies have been conducted assessing the risk factors of such unplanned conversion. Troisi et al. [7] presented tumor location (posterosuperior segments; I, IVa, VI, and VII) and major hepatectomy as predictors of conversion, and Cauchy et al. [11] considered high BMI and large tumor size (>10 cm; P = 0.014) as risk factors. Of the recent papers, Stiles et al. [6] and Vigano et al. [10] analyzed major hepatectomy with predictor of conversion, and Silva et al. [9] found that those with hypertension and those who underwent right hepatectomy had a higher risk of conversion. Previous studies demonstrated that operative difficulty is the most common risk factor for

conversion. In this study, tumor size, right-sided sectionectomy and central bisectionectomy were identified as risk factors for unplanned conversion. As the tumor size increases, the more major liver resection is required. Right-sided sectionectomy and central bisectionectomy needs 2 different transection planes and the largest transection area possible, which inevitably increases the risk for bleeding and sometimes poor exposure in the deep area during MILR [5].

In conclusion, unplanned open conversion during MILR for HCC was associated with poor perioperative outcomes, but did not affect long-term oncologic outcomes in our data. It may be related to the early decision for open conversion. Therefore, open conversion should not be regarded as a failure of MILR. Moreover, findings from this study suggest that when planning right-sided sectionectomy (right anterior and posterior sectionectomy) or central bisectionectomy for a large tumor (more than 5 cm), we should recommend open surgery or MILR with an informed consent for unplanned open conversions.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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