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ORIGINAL ARTICLE

Laparoscopic versus open hepatectomy for hepatocellular carcinoma: long-term outcomes

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Summary

Purpose: *This study compared the longterm survival outcomes of patients with hepatocellular carcinoma (HCC) who underwent laparoscopic hepatectomy with those who were subjected to open hepatectomy.*

Methods: *This was a retrospective, case-control study; patients in the 2 groups were matched according to age, sex, body mass index (BMI), liver function, underlying liver disease, American Society of Anesthesiologists (ASA) score, tumor location and type of resection. A total of 118 patients (laparoscopy, N = 59; open, N = 59) were assessed.*

Results: *Patient characteristics did not differ between the groups. Postoperative 30-day complication rates did not differ between the groups. Pathological data did not differ between the two groups. The 5-year overall survival (OS) and disease-free survival (DFS) were not different between the laparoscopy and open groups. The laparoscopic approach was not an independent risk factor for tumor recurrence or mortality compared with the open approach.*

Conclusion: *We found no differences in the oncologic outcomes between laparoscopic and open hepatectomy groups, suggesting that laparoscopic hepatectomy for HCC is a safe and effective option that does not increase the risk of serious complications.*

Key words: *hepatectomy, hepatocellular carcinoma, laparoscopic, minimally invasive surgery, survival*

Introduction

With the recent adoption of laparoscopic hepatectomy for resectable HCC, the trend in the current treatment of resectable disease is favoring a laparoscopic approach [1-3]. Laparoscopic surgery for resectable HCC yields short-term advantages, including faster recovery, less postoperative pain, and decreased duration of hospital stay [4-13]. The long-term survival outcomes from laparoscopic hepatectomy, however, for the treatment of HCC have not been fully elucidated because of lack of randomized controlled trials. The oncologic adequacy of laparoscopic hepatectomy for HCC, however, still remains controversial. Therefore, this study aimed to analyze the oncologic safety of laparoscopic vs open hepatectomy for HCC and to compare the long-term oncologic outcomes.

Methods

The protocol was conducted in accordance with the Declaration of Helsinki. This research was approved by Ethics Committee of The First Affiliated Hospital of University of South China. The need for informed consent from patients was waived because of the retrospective nature of the research.

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Between April 2008, and December, 2013, 389 patients diagnosed with HCC were selected from the database of The First Affiliated Hospital of University of South China. Among these patients, we identified a group comprising 59 patients who underwent laparoscopic hepatectomy for HCC. Propensity score matching was used to match this group in a 1:1 ratio with 59 patients who underwent open hepatectomy. The propensity matching was conducted using R software the SPSS R Essentials plug-in. Logistic regression was used to estimate propensity scores for each group. Eight covariates were included in the logistic regression model for calculating the propensity score. Covariates used for matching were the age, sex, BMI, preoperative liver function [12], underlying liver disease, ASA score, tumor location and type of resection.

The enrollment criteria included the following: Child-Pugh class A cirrhosis [12], tumor size less than 5cm, tumor located in the peripheral segments and resectable by limited segments, and no previous upper abdominal surgery. All the patients were assessed preoperatively with liver function, serum alpha fetoprotein (AFP), abdominal computed tomographic scan or magnetic resonance imaging. Positron emission tomography-computerized tomography (PET-CT) was performed in selected cases.

All operations were performed with radical intent. Types of hepatectomy were adopted by the Brisbane 2000 classification [13]. Anatomical resections were preferred over non-anatomical hepatectomy when an indocyanine green test showed that the liver function could tolerate anatomical hepatectomy. Non-anatomic resections were performed for HCC located in single, small peripheral lesions. Details of laparoscopic and open hepatectomy have been reported in previous studies [1,2,14].

Postoperative 30-day complications were defined as any deviations from the general postoperative course. We used the modified Clavien-Dindo classification that included 5 grades of severity to analyze the severity of complications [15]. All patients were followed at 3-month intervals for the first 2 years. Follow-up intervals were increased to every 6 months during the third through the fifth years and annually thereafter. OS was assessed from the date of hepatectomy until the last follow up or death of any cause. DFS was calculated from the date of hepatectomy until the date of cancer recurrence or death from any cause. The last follow up was in April 2015.

Statistics

All statistical analyses were performed using SPSS 14.0 version (SPSS Inc., Chicago, IL, USA). Data were presented as mean and ±standard deviations for variables following normal distribution and were analyzed by Student's t-test. For data following non-normal distribution, results were expressed as median and range and were compared with Wilcoxon signed rank test. Differences of semiquantitative results were analyzed by Mann–Whitney *U*-test. Differences of qualitative results were analyzed by x^2 test or Fisher's exact test as appropriate. Survival rates were analyzed using the Kaplan-Meier method and differences between the

Table 1. Comparison of clinicopathological characteristics between laparoscopy and open hepatectomy groups

Characteristics	*Laparoscopy (N=59) N (%)*	*Open (N=59) N (%)*	*p value*
Age, years, median (range)	51 (36-68)	50 (38-70)	0.358*
Sex			
Male	42 (71.2)	38 (64.4)	0.431**
Female	17 (28.8)	21 (35.6)	
BMI (kg/m^2), median (range)	20 (17-25)	22 (18-28)	0.120*
ASA score			
I	44 (74.6)	43 (72.9)	1.000**
II	14 (22.0)	15 (25.4)	
III	2 (3.4)	1 (1.7)	
ICG retention at 15 min, median (range)	22 (11-35)	24 (10-34)	0.405*
Underlying liver disease			
Hepatitis B virus	35 (59.3)	32 (54.2)	0.854**
Hepatitis C virus	5 (8.5)	3 (5.1)	
Alcoholic hepatitis	12 (20.3)	10 (16.9)	
Tumor location			
Right lobe	26 (44.1)	30 (50.8)	0.461**
Left lobe	33 (55.9)	29 (49.2)	
Type of resection			
Left lateral sectionectomy	29 (49.2)	24 (40.7)	0.355**
Subsectionectomy	30 (50.8)	35 (59.3)	

*Wilcoxon signed rank test, **Mann-Whitney U test
ICG: indocyanine green

Table 2. Comparison of surgical outcomes and complications between laparoscopy and open hepatectomy groups

Surgical outcomes	*Laparoscopy (N=59)* N *(%)*	*Open (N=59)* N *(%)*	*p value*
Operative time min, median (range)	200 (150-300)	160 (100-240)	0.015*
Blood loss, ml, median (range)	230 (180-450)	300 (190-640)	0.001*
Length of hospital stay, days, median (range)	11 (8-23)	14 (10-36)	0.020*
Overall complications	12 (20.3)	16 (27.1)	0.452**
Major complications			
Intraabdominal bleeding	1 (1.7)	0 (-)	
Bile leakage	1 (1.7)	1 (1.7)	-
Intra-abdominal abscess	0 (-)	1 (1.7)	
Liver failure	0 (-)	1 (1.7)	
Minor complications			
Wound infection	2 (3.4)	3 (5.1)	
Pneumonia	2 (3.4)	2 (3.4)	-
Postoperative ascites	2 (3.4)	2 (3.4)	
Bile leakage	4 (6.8)	6 (10.1)	

*Wilcoxon signed rank test, **Mann-Whitney U test

two groups were assessed with the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS. Univariate variables with probability values less than 0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted odds ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. $p<0.05$ was considered statistically significant.

Results

Demographic data, postoperative details, and complications within 30 days are presented in Tables 1 and 2. No relevant differences were observed between the two groups in terms of age, sex, BMI, liver function, underlying liver disease, ASA score, tumor location and type of resection. In the analysis of postoperative outcomes, 3 patients (5.0%) initially in the laparoscopy group were converted to open surgery because of intractable bleeding from a major vessel. Patients in the laparoscopy group had less blood loss and shorter duration of hospital stay than patients in the open group. Overall, postoperative 30-day complications were reported in 16 of 59 patients (17.0%) in the open group and 12 of 59 patients in the laparoscopy group (p=0.452). There were no mortality within postoperative 30-day occurred.

Table 3 provides details of pathological characteristics of the two groups. Pathological studies showed that the 2 groups had no difference in histology, tumor size, margin status, and TNM stage (UICC 2010).

Overall tumor recurrence after primary surgery occurred at a median of 15 months in the open group and 17 months in the laparoscopy group (Table 4). The 5-year DFS rate was 40% in the open group vs 44% in the laparoscopy group (p=0.270) (Figure 1). The 5-year OS rate was not different between the groups (p=0.524) (Figure 2). When patients were analyzed according to disease stage, the 5-year OS was 82% for the open group vs 85% for the laparoscopy group for stage I (p=0.651) and 51 vs 53% for stage II (p=0.458). The 5-year DFS was 75% for the open group vs 71% for the laparoscopy group for stage I (p=0.032) and 37 vs 42% for stage II (p=0.520).

Univariate and multivariate analysis of all patients who underwent radical hepatectomy for HCC showed that pathological T stage and tumor differentiation independently contributed to tumor recurrence (Table 5). Pathological T stage and tumor with vascular invasion were independent factors OS (Table 6).The laparoscopic hepatectomy was not an independent risk factor for tumor recurrence or longterm prognosis compared with the open approach.

Discussion

Although there has been strong evidence demonstrating the short-term efficacy of laparoscopic hepatectomy for HCC [16-19], there is a lack of evidence regarding its long-term oncologic safety. There are oncologic concerns with laparoscopic hepatectomy over postoperative intrahepatic or extrahepatic recurrence and potentially different recurrence patterns due to the possibili-

Table 3. Comparison of pathological data between laparoscopy and open hepatectomy groups

Pathological data	*Laparoscopy (N=59) N (%)*	*Open (N=59) N (%)*	*p value**
Histology			
Well differentiated	24 (40.7)	28 (47.5)	0.453
Moderately well differentiated	23 (39.0)	21 (35.6)	
Poorly differentiated	12 (20.3)	10 (16.9)	
Tumor size, cm, median (range)	3 (2-5)	3 (1-6)	0.581
Margin status (R0/R1/R2)	56/3/0	58/1/0	0.311
Pathological TNM stage			
I	39 (66.1)	41 (69.5)	0.695
II	20 (33.9)	18 (30.5)	

*Wilcoxon signed rank test

Table 4. Tumor recurrence following laparoscopic and open hepatectomy

Recurrences	*Laparoscopy (N=59) N (%)*	*Open (N=59) N (%)*	*p value*
Tumor recurrence	26 (44.1)	30 (50.8)	0.461**
Recurrence site			
Brain	1 (1.7)	3 (5.1)	
Liver	14 (23.7)	16 (27.1)	
Lung	3 (5.1)	4 (6.8)	0.969**
Distant lymph nodes	2 (3.4)	3 (5.1)	
Bone	3 (5.1)	2 (3.4)	
Adrenal gland	3 (5.1)	2 (3.4)	
Time to recurrence, months, median (range)	17 (5-66)	15 (4-36)	0.220*
Main treatment for recurrence			
Repeat hepatectomy	4 (6.8)	5 (8.5)	
Chemotherapy	12 (20.3)	21 (35.6)	0.695**
Radiofrequency ablation	3 (5.1)	2 (3.4)	
Supportive care	12 (20.3)	13 (22.0)	

*Wilcoxon signed rank test, **Mann-Whitney U test

ty of positive surgical margin related to technical difficulty and the different surgical environment compared with resection (carbon dioxide pneumoperitoneum). We observed no differences in the rate of positive surgical margin, OS and DFS rates, or recurrence patterns between the open and laparoscopy groups.

In a single-center study from Hongkong, China, Cheung et al. [14] reported on the long-term oncologic outcomes of 32 patients who underwent laparoscopic hepatectomy for HCC. The 5-year OS and DFS rates according to the pathological TNM stage were 100% and 53.6% in pathological stage I, 31.2% and 49.6% in pathological stage II, respectively. They recommended that laparoscopic liver resection for HCC does not compromise survival. In our series, we found that DFS and OS stratified by the pathological TNM stage were comparable to those of open resection. Although long-term results of the phase 3 trial [13] were lacking, laparoscopic hepatectomy can be considered as an acceptable therapeutic modality for HCC.

Intrahepatic recurrence is the major source of HCC metastasis [19]. We observed that not only were the laparoscopy DFS rates similar to open surgery, but so were the recurrence patterns, indicating that the laparoscopic hepatectomy for HCC did not increase the rates of tumor recurrence.

Surgical margin is a readily measurable key performance indicator of resection quality, especially when the specimen is evaluated in the same pathology laboratory [17-19]. Recent series found no significant difference between the rate of positive surgical margin in laparoscopic hepatectomy compared with open hepatectomy [20-27]. Our findings were in keeping with this, since we

Table 5. Multivariate Cox regression analysis of tumor recurrence

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T1	1.00		
T2	3.38	1.88-4.08	0.025
Tumor differentiation			
Good	1.00	-	-
Moderate	1.57	1.23-2.02	0.035
Poor	2.89	2.05-4.58	0.003

Table 6. Multivariate Cox regression analysis of mortality

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T1	1.00		
T2	2.35	1.54-3.78	0.010
Tumor with vascular invasion			
No	1.00		
Yes	3.25	1.88-4.60	0.008

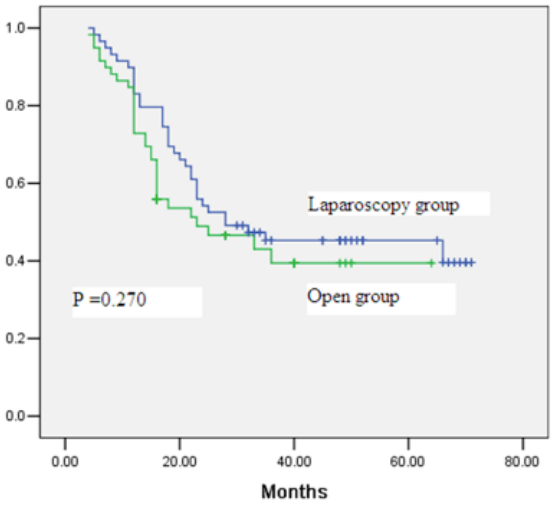

Figure 1. Disease-free survival in the laparoscopic and the open hepatectomy groups.

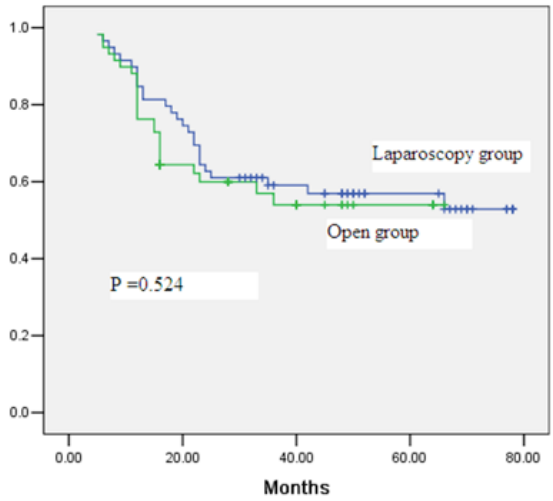

Figure 2. Overall survival in the laparoscopic and the open hepatectomy groups.

did not find any significant difference between the laparoscopy and open groups with respect to rate of positive surgical margin.

The shorter postoperative hospital stay and less blood loss for the laparoscopic hepatectomy patients appear to be related to their faster recovery and lesser degree of trauma. These results suggest that laparoscopic hepatectomy is a less invasive technique than open hepatectomy for HCC. It is possible that, when laparoscopic hepatectomy is performed in Western countries, postoperative hospital stay after open hepatectomy will be much shorter [28-30]. Postoperative hospital stay in China is known to be longer than those in Western countries. In the laparoscopy and open groups, the median duration of postoperative hospital stay was 11 and 14 days, respectively. Patients in our series prefer to stay in the hospital until they feel good. Furthermore, because the Chinese health insurance system covers most of the cost of hospitalization, patients frequently choose to remain in the hospital for as long as possible after surgery.

Our results may be associated with some drawbacks since the study was retrospective. While we found similar rates of recurrence between laparoscopic hepatectomy and open hepatectomy, one of the limitations of this paper is the relatively shorter follow-up in our series. This is a result of laparoscopic surgery being a relatively new treatment method for HCC.

Despite these limitations, the results of this study suggest that, in a carefully matched group of patients undergoing laparoscopic and open surgery, patients undergoing laparoscopic hepatectomy enjoyed several short-term benefits in terms of less blood loss and shorter hospitalization. These advantages, when examined in the context of potential equivalent oncological outcomes, support the use of the minimally invasive approach to hepatectomy. In conclusion, laparoscopic hepatectomy for HCC was oncologically safe with DFS rates comparable to open hepatectomy, and there were no differences in recurrence patterns between the two procedures, suggesting the radical nature of laparoscopic resection.

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