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ORIGINAL ARTICLE

A propensity score-matched case-control comparative study of laparoscopic and open liver resection for hepatocellular carcinoma

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Summary

Purpose: *Few results regarding the long-term survival from laparoscopic liver resection have been reported. The purpose of this study was to evaluate the long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma.*

Methods: *IOf 638 patients who underwent open or laparoscopic liver resection for hepatocellular carcinoma, 184 treated by laparoscopic liver resection and 184 treated by open liver resection were studied using the propensity score matching method. The short-term surgical outcomes and long-term survival outcomes of these matched groups were compared.*

Results: *The two study groups were well matched with respect to age, sex, body mass index (BMI), liver function, underlying liver disease, American Society of Anesthesiologists (ASA) score, tumor location and type of resection. The laparoscopy group had a significantly longer operative time but significantly less intraoperative blood loss. Postoperatively, no significant intergroup differences were found for hospital stay, morbidity or mortality. The 5-year overall survival and disease-free survival were similar between the two groups.*

Conclusion: *Laparoscopic liver resection for hepatocellular carcinoma is technically safe and feasible compared with open resection. The long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma are considered acceptable.*

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

Introduction

Hepatocellular carcinoma is one of the most common malignancies in China [1-4]. Surgical resection is the standard treatment for resectable hepatocellular carcinoma [5-8]. Since laparoscopic liver resection for resectable hepatocellular carcinoma was first described in 1995 [9], it is used frequently. Laparoscopic liver resection is an option for patients with resectable hepatocellular carcinoma due to the development of new surgical techniques and devices [10-17]. Previous studies have shown that the short-term outcomes for those who underwent laparoscopic liver resection were better than for those who underwent open liver resection, which indicates the progress of laparoscopic liver resection for hepatocellular carcinoma [10-17]. As a result, the number of laparoscopic hepatectomies for resectable hepatocellular carcinoma has increased exponentially in recent years [10-17]. There are few studies that have reported long-term survival outcomes of patients who were subjected to laparoscopic liver resection and these studies included only a small number of patients [14-17]. In our study, we evaluated the outcomes of laparoscopic liver resection for resectable hepatocellular carcinoma and compared long-term survival outcomes after laparoscopic and open liver resection cases that were matched using the propensity score matched method.

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Methods

A total of 638 patients were identified in a prospectively constructed database who were subjected to liver resection for primary hepatocellular carcinoma between January 2007 and January 2015. Undergoing a hepatectomy with radical intent either by open or laparoscopic surgery was the inclusion criterion. Previous hepatectomy for hepatocellular carcinoma, not including percutaneous radiofrequency ablation or transarterial chemoembolization, noncurative resection or R2 resection, were the exclusion criteria. For propensity score matching, 349 patients with open liver resection and 289 patients with laparoscopic liver resection were included. A logistic regression model was used to calculate propensity scores. Age, sex, BMI, liver function, and underlying liver disease were covariates in the analysis. This method employed randomly ordering control subjects and cases, i.e., selecting a case and identifying a control subject with the closest propensity score. Using the propensity score matching method, 184 patients with laparoscopic liver resection and 184 patients with open liver resection were identified.

The routine preoperative evaluation included liver function, serum alpha fetoprotein (AFP), abdominal computed tomographic scan (CT) or magnetic resonance imaging (MRI). Positron emission tomography-computerized tomography (PET-CT) was performed in selected cases. Indication for laparoscopic liver resection was as follows: Child-Pugh class A cirrhosis, tumor size <5cm, tumor located in the peripheral segments and resectable by limited segments, and no previous upper abdominal surgery. Four surgeons with considerable experience with both laparoscopic and open hepatectomy performed the operations. The Brisbane 2000 classification system was used to determine the types of liver resection. After an indocyanine green test showed that liver function could tolerate anatomical hepatectomy, anatomical resections were chosen rather than non-anatomical hepatectomies. In the cases of small peripheral lesions, non-anatomic resections were performed. The details of open liver and laparoscopic resection have been reported in previous studies [2].

Results regarding surgical details, demographic characteristics, pathological data, morbidity and mortality were reviewed. The 7th edition of the TNM classification of hepatocellular carcinoma that was proposed by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) was used for staging [18]. A standardized clinical pathway protocol was used for perioperative management regardless of the operative approach. Postoperative complications and morbidity occurring within 30 postoperative days, were classified using the Clavien-Dindo classification, which simplified the definition of postoperative complications and graded the severity of these events. Details of Clavien-Dindo classification have been reported in previous studies [19-22]. Grades 3b, 4a, 4b and 5 were considered as major complications. Grades 1, 2 and 3a were considered as minor complications.

Follow-up data were reviewed from the follow up database. Patient follow-up was scheduled to perform liver function tests, serum AFP, abdominal CT or MRI every 3-4 months after hepatectomy [23]. The overall survival was assessed from the date of hepatectomy until the last follow up or death of any cause. The disease-free survival was calculated from the date of hepatectomy until the date of cancer recurrence or death from any cause. The last follow up was in December 2015.

The therapeutic protocol was conducted in accordance with the Declaration of Helsinki. This research was approved by our local ethics committee. The need for informed consent from patients was waived because of the retrospective nature of the study.

Statistics

SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t* test. For data following non-normal distribution, the results were expressed as median and range and were compared by Wilcoxon test. Differences of semiquantitative results were analyzed by Mann–Whitney *U* test. Differences of qualitative results were analyzed by chi-square test or Fisher exact test as appropriate. Survival rates were analyzed using the Kaplan-Meier method and differences between the two groups were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic data related to overall survival and disease-free survival. Univariate variables with probability values <0.05 were selected for inclusion in the multivariate Cox regression model. $P < 0.05$ was considered statistically significant.

Results

The clinicopathological characteristics of the two groups are summarized in Table 1. No significant differences were found in the clinicopathological data, including age, sex, BMI, liver function, underlying liver disease, ASA score, tumor location, type of resection, and pathological stage. Details on the surgical outcomes for both groups are shown in Table 2. There was a significantly longer operative time on average in the laparoscopy group; however, there was significantly less blood loss intraoperatively. No significant differences in the length of hospital stay between the two groups were noticed (Table 3) and no deaths occurred. The incidence and severity of postoperative complications tended to be lower among the patients undergoing laparoscopy than among the patients undergoing open resection (Table 3).

The median follow-up period was 39 months (range 7-100) and, at this point, 64 (34.8%) patients in the laparoscopy group and 80 (43.5%) in the open group had died. Figure 1 shows the 5-year overall survival rate was 56% in the laparoscopy group and 48% in the open group (p=0.448). The

5-year overall survival rate for patients with pathological stage I was 83% for the laparoscopy group and 77% for the open group. The 5-year overall survival rate for patients in pathological stage II was 38% for the laparoscopy group and 35% for the open group. In relation to prognostic factors for overall survival, age, underlying liver disease, operation time, tumor size, and pathological stage were prognostic factors in univariate analysis. In multivariate analysis, age and pathological stage were independent prognostic factors for overall survival (Table 4).

Four patients undergoing laparoscopic resection relapsed, all with intrahepatic recurrence. Five patients undergoing open resection relapsed, three with intrahepatic recurrence, and two with brain metastasis. The 5-year disease-free survival rate was 32% in the open group and 38% in the laparoscopy group (p=0.113; Figure 2). The tumor size, underlying liver disease, and pathological stage were prognostic factors according to univariate analysis of disease-free survival. Age and pathological stage were independent prognostic factors in multivariate analysis of disease-free survival (Table 5).

Table 1. Comparison of clinicopathological data between laparoscopy and open group

	Laparoscopy (n=184)	*Open (n=184)*	*p value*
Age, years, median (range)	56 (39-75)	55 (39-74)	0.110
Sex, n			0. 656
Male	128	120	
Female	56	64	
BMI (kg/m^2), median (range)	22 (18-27)	23 (17-29)	0.277
ASA score, n			0.864
I	140	136	
II	36	44	
III	8	4	
Child-Pugh class A, n	184	184	1.000
ICG retention at 15 min (%), median (range)	22 (11-36)	23.5 (9-35)	0.3.56
Underlying liver disease, n			0.766
Hepatitis B virus	168	160	
Hepatitis C virus	4	8	
Alcoholic hepatitis	12	16	
Tumor location			0.830
Right lobe	116	112	
Left lobe	68	72	
Type of resection			0.810
Left lateral sectionectomy	44	48	
Subsectionectomy	140	136	
Pathological stage			0.663
I	116	124	
II	68	60	

ICG: indocyanine green, BMI: body mass index, ASA: American Society of Anesthesiologists

Table 2. Comparison of surgical outcomes between laparoscopy and open group

	Laparoscopy (n=184)	*Open (n=184)*	*p value*
Conversion	4	-	-
Operative time (min), median (range)	180 (120-260)	150 (100-200)	0.012
Blood loss (ml), median (range)	200 (120-430)	280 (160-840)	0.000
Length of hospital stay (days), median (range)	11 (8-16)	12 (10-20)	0.846
Red blood cell transfusion (units)	4	12	0.609

Table 3. Comparison of complications between laparoscopy and open group

	Laparoscopy (n=184)	*Open (n=184)*	*p value*
Overall complications,n (%)	20 (10.9)	44 (23.9)	0.099
Major complications			
Intraabdominal bleeding	4	8	
Bile leakage	0	4	
Minor complications, n			
Wound infection	0	12	
Pneumonia	4	8	
Postoperative ascites	8	4	
Bile leakage	4	8	

Table 4. Prognostic factors for overall survival after hepatectomy

Factors	*Univariate p value*	*Multivariate p value*
Age	0.011	0.018
Sex	0.625	
Underlying liver disease	0.021	
Operative time	0.020	
Morbidity	0.700	
Tumor size	0.012	
Tumor location	0.520	
Type of resection	0.542	
Pathological stage	0.018	0.012
Adjuvant therapy	0.423	

Table 5. Prognostic factors for disease-free survival after hepatectomy

Factors	*Univariate p value*	*Multivariate p value*
Age	0.020	0.003
Sex	0.320	
Underlying liver disease	0.020	
Operative time	0.333	
Morbidity	0.235	
Tumor size	0.003	
Tumor location	0.325	
Type of resection	0.081	
Pathological stage	0.013	0.013
Adjuvant therapy	0.309	

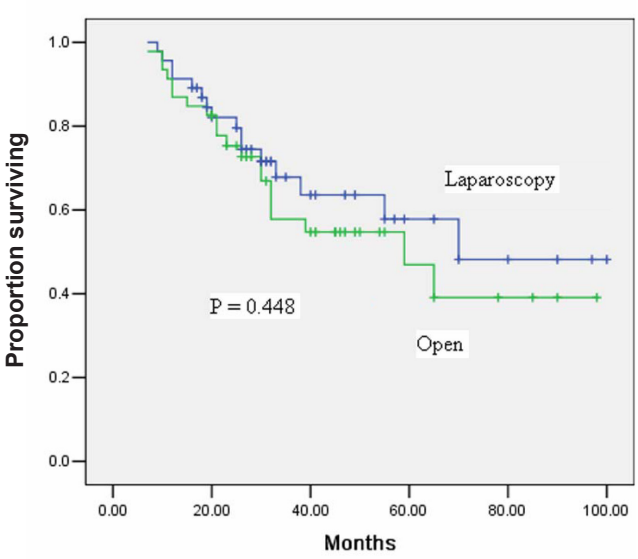

Figure 1. Kaplan-Meier overall survival of liver resection for hepatocellular carcinoma. No significant difference was observed between the two groups (p=0.448).

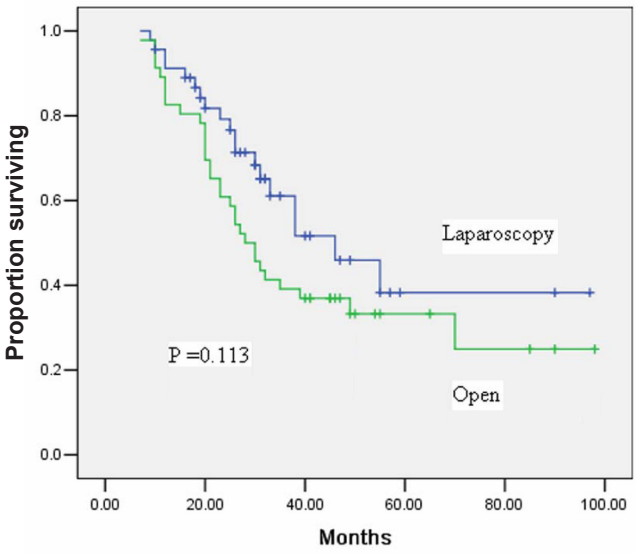

Figure 2. Kaplan-Meier disease-free survival of liver resection for hepatocellular carcinoma. No significant difference was observed between the two groups (p=0.113).

Discussion

Previous studies that compared laparoscopic liver resection and open liver resection included only small numbers of patients [10-17]. In our study, we assessed the surgical complications and outcomes and long-term survival of patients who had laparoscopic liver resection and compared these results with patients who had open liver resection. Our results showed that the rate of postoperative complications in patients who had laparoscopic liver resection was not significantly different from the rate for patients who had open hepatectomy. Survival rates for the two groups were also similar.

Previous studies have reported operative times for laparoscopic liver resection to range from 148 to 325 min [10-17]. In the present study 180 min was the median operative time for laparoscopic liver resection, which was comparable to results from previous studies. No significant differences in operative times between laparoscopic and open groups were reported in previous studies [10-13]. However, some studies have found that there were longer operative times for the laparoscopic group [14-17]. Technical difficulties may be responsible for the longer operative times with laparoscopic liver resection. New surgical techniques and new innovative instruments might contribute to the shortening of operative times for laparoscopic hepatectomies [10-17].

The incidence of postoperative complications, such as bile leakage and liver failure after laparoscopic hepatectomy has been reported to be 3.8-50% [10-17]. The incidence of complications has been reported to be similar between the laparoscopic and open groups in hepatocellular carcinoma [10-14]. Other studies, however, showed a lower or higher rate of complications in the laparoscopy group [15-17]. The laparoscopy group in our study had a similar incidence of complications compared with the open group. Short-term outcomes are not completely dependent on the surgical approach. Perioperative care, including multiple interventions, can affect short-term outcomes [24-26]. Patients in our study received the same standardized perioperative care, and this may have led to similar short-term outcomes for hospital stay and postoperative complications. Patients with laparoscopic hepatectomies, however, had smaller wound sizes and less pain.

To date, oncologic outcome after laparoscopic versus open hepatectomy for the treatment of hepatocellular carcinoma has been reported in few series. Although oncologic outcome seems to be identical between the groups, the number of

patients was relatively small and some series analyzed only left lateral sectionectomy. All patients in our series were treated with curative intent, with median follow-up of over 36 months and the overall survival rates at 5 years after laparoscopic and open liver resection were 83 and 77% for stage I tumor, and 38 and 35% for stage II tumor, respectively. Previous reports on open liver resection showed 5-year overall survival of 75.2-100% for stage I disease, and 29-39% for stage II disease [27-32]. It is difficult to directly compare these results with our series, but the rate of 5-year overall survival from our study seemed to be comparable to previous studies from Eastern Asia and some specialized Western centers.

Every study had limitations. The main limitation of this study remains its retrospective nature. Imbalance between patient characteristics that were not recorded could bias the results. This limitation should be taken into account when interpreting the results to be used into clinical practice. In addition, the follow-up period was relatively short, so tumor recurrence or death may not have been observed during the time of analysis.

Conclusion

In conclusion, patient overall survival and disease-free survival rates were similar between the two study groups. Laparoscopic liver resection can be considered as a feasible and safe procedure for treating hepatocellular carcinoma.

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Conflict of interests

The authors declare no confict of interests.

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