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ORIGINAL ARTICLE

Laparoscopic versus open hepatectomy for elderly patients with hepatocellular carcinoma

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Summary

Purpose: *The number of surgical operations for elderly patients with hepatocellular carcinoma increases as the population ages. The aim of this study was to evaluate surgical and survival outcomes in elderly patients who underwent laparoscopic or open hepatectomy for hepatocellular carcinoma.*

Methods: *We analyzed the data of 169 patients aged 70 or over who underwent hepatectomy for hepatocellular carcinom between January 2013 and December 2018. Sixty-four pairs were selected after propensity score matching for laparoscopic or open hepatectomy for hepatocellular carcinoma. Baseline data, surgery time, length of hospital stay, postoperative complications, pathological data, overall survival, and disease-free survival were investigated.*

Results: *Operative time in the laparoscopic group was longer than in the open group. Blood loss and postoperative hospital stay were shorter in the laparoscopic group than in the open group. The rate of postoperative 30-day minor or major complications was similar between the two groups. There was no significant difference in pathological data between the two groups. There was no significant difference in overall survival and disease-free survival between the two groups.*

Conclusion: *This study suggests that laparoscopic hepatectomy for elderly patients with hepatocellular carcinoma may be safe and feasible, with better short-term outcomes and similar long-term outcomes*

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

Introduction

Improvements in the healthcare systems and rapid advances in medicine have led to an increase in life expectancy [1]. The aging of the global population is an irreversible trend. The increased incidence of hepatocellular carcinoma is closely related to the aging of the population [2-4]. Due to the reduction in physiological reserve, it is difficult for elderly patients to tolerate hepatectomy. Elderly patients are more likely to have medical diseases, especially pulmonary and cardiovascular. The clinical use of laparoscopic hepatectomy is increasingly common, and its benefits include reduced postoperative pain, faster recovery, and shorter hospital stay [5-10]. The advantages of laparoscopic hepatectomy may be more beneficial for elderly patients with hepatocellular carcinoma.

There are five studies reported the outcomes of laparoscopic hepatectomy for elderly patients with hepatocellular carcinoma [11-15]. However, four studies were limited to report only the short-term outcomes [12-15]. One study reporting long-term survival results was limited by small sample size [11]. Therefore, we conducted a propensity score-matched analysis comparing laparoscopic and open

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hepatectomy in elderly patients with hepatocellular carcinoma. The aim of this study was to evaluate surgical and survival outcomes of laparoscopic hepatectomy compared with those of open hepatectomy in elderly patients with hepatocellular carcinoma.

Methods

The protocol was conducted in accordance with the Declaration of Helsinki and Good Practice guidelines. The research was approved by our local ethics committees. The requirement of informed consent from patients was waived because of the retrospective nature of the research, since it was not a prospective study.

We analyzed the short- and long-term outcomes of patients with primary hepatocellular carcinoma aged 70 years or older who underwent radical hepatectomy in our institution between January 2013 and December 2018. Exclusion criteria included patients with palliative hepatectomy, other primary malignancies, combined surgery for other diseases, and emergency surgery. Of the 169 patients in the study, 72 underwent laparoscopic surgery and 97 open surgery. To adjust for differences in baseline characteristics between the two groups, a propensity score was established using a logistic regression model. Variables used in the propensity model included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson comorbidity index, underlying liver disease, tumor location and type of hepatectomy [16-20]. Subsequently, the nearest neighbor matching was performed using the caliper method, and a one-to-one match between the two groups was obtained. Among the 169 patients, 128 were matched using propensity scoring. After performing propensity score matching for the entire study population, 64 matched pairs of patients were selected.

Table 1. Baseline data in matched cohorts of laparoscopic and open hepatectomy

Characteristics	*Laparoscopic hepatectomy (n=64)*	*Open hepatectomy (n=64)*	*p value*
Age (years)	71 (70-77)	72 (70-76)	0.210
Sex			0.585
Male	41	38	
Female	23	26	
BMI (kg/m^2)	20 (19-23)	21 (18-27)	0.128
ASA score			0.346
I	38	43	
II	19	16	
III	7	5	
Charlson comorbidity index			0.467
<3	59	61	
≥3	5	3	
Underlying liver disease	41	44	0.575
Tumor laterality			0.588
Left	37	40	
Right	27	24	
BCLC stage			0.665
0	23	21	
A	41	44	
Type of resection			0.627
Left lateral sectionectomy	24	26	
Segmentectomy	17	20	
Partial resection	23	18	

BMI: Body Mass Index, ASA: American Society of Aneshesiologists, BCLC: Barcelona Clinic Liver Cancer

Table 2. Short-term surgical outcomes of laparoscopic and open hepatectomy

Characteristics	*Laparoscopic hepatectomy (n=64)*	*Open hepatectomy (n=64)*	*p value*
Converted to open surgery	0	-	-
Operative time (min)	180 (160-290)	150 (130-260)	0.015
Blood loss (ml)	200 (140-400)	260 (190-650)	0.028
Postoperative stay (d)	10 (7-21)	12 (9-28)	0.010

Indication for laparoscopic hepatectomy was as follows: Child-Pugh class A, cirrhosis, tumor size smaller than 5cm, tumor located in the anterolateral segments (Couinaud segments 2, 3, 4b, 5, and 6) and resectable by minor hepatectomy. Types of hepatectomy were adopted from the Brisbane 2000 classification [21]. All operations were performed with radical intent. This study adopted a fast-track method for perioperative management [22,23].

The severity of postoperative 30-day complications was graded according to Clavien-Dindo classification. Minor complications are defined as grades 1 and 2, and major complications are defined as grades 3, 4, and 5 [24-29]. Postoperative mortality is defined as death due to any cause within 30 days after surgery.

Follow-up visits were planed one every 3 months in 2 years after surgery and then one every 6 months [30]. The overall survival was assessed from the date of surgery until the last follow-up or death of any cause. The disease-free survival was calculated from the date of surgery until the date of cancer recurrence or death from any cause. The last follow-up was in March 2019.

Statistics

All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed using *t*-test and are presented as mean and standard deviation when the variables followed a normal distribution. Data following non-normal distribution were compared using Wilcoxon test and the results are expressed as median and range. Differences in semi-quantitative results were analyzed with the Mann–Whitney U test. Differences in qualitative results were analyzed with the chi square (x^2) test or Fisher's 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 variables related to overall and disease-free survival. Univariate variables with p values <0.10 were selected for inclusion in a multivariate Cox proportional hazards regression model. Adjusted hazard ratios and the corresponding 95% confidence intervals were calculated. P<0.05 was considered statistically significant.

Results

Baseline characteristics are shown in Table 1. The two groups were balanced in terms of age, gender, BMI, ASA score, Charlson comorbidity index, underlying liver disease, tumor location, type of hepatectomy and Barcelona Clinic Liver Cancer (BCLC) stage.

Table 3. Postoperative mortality and morbidity of laparoscopic and open hepatectomy

Characteristics	*Laparoscopic hepatectomy (n=64)*	*Open hepatectomy (n=64)*	*p value*
Mortality within 30 postoperative days	0	0	1.000
Overall complications, n	10	11	0.811
Major complications	1	2	
Minor complications	9	9	
Postoperative ascites	4	4	
Hepatic insufficiency	3	1	
Intraabdominal abscess	1	1	
Bile leakage	1	0	

Table 4. Comparison of pathological data between laparoscopy and open group

Characteristics	*Laparoscopic hepatectomy (n=64)*	*Open hepatectomy (n=64)*	*p value*
Histology			0.372
Well differentiated	26	31	
Moderately differentiated	21	19	
Poorly differentiated	17	14	
Surgical margin size (cm)	2 (0.5-1.0)	3 (0.4-0.9)	0.520
Surgical margin status			1.000
R0	64	64	
R1	0	0	
R2	0	0	
Pathological TNM stage (AJCC – UICC, 7th Edn)			0.723

TNM: tumor, node, metastasis, AJCC: American Joint Committee on Cancer, UICC: Union Internationale Contre le Cancer

The results of the short-term surgical outcomes are shown in Table 2. There was no patient conversion to open surgery in the laparoscopic group. Operative time in the laparoscopic group was longer than in the open group. Blood loss was less in the laparoscopic group than in the open group. The postoperative hospital stay was shorter in the laparoscopic group than in the open group. There was no significant difference in pathological data between the two groups.

Postoperative complications occurred in 10 and 11 patients in the laparoscopic and open group, respectively (Table 3). In the open group, the most common complication was ascites in 4 patients, followed by wound infection in 2 patients, and pneumonia in one patient. In the laparoscopic group, the most common morbidity was ascites in 4 patients, followed by hepatic insufficiency in 3 patients. The incidence of major postoperative complications was not significantly different between the two groups. There was no postoperative 30-day mortality in the two groups.

The median follow-ups for the laparoscopic and open groups were 31 and 34 months, respectively,

Table 5. Univariate analysis of overall survival

Variable	*Five-year overall survival*	*p value*
Age, years		0.215
<75	64	
≥75	55	
Gender		0.301
Male	63	
Female	57	
AFP, ng/ml		0.021
≥400	54	
< 400	70	
ASA score		0.458
I-II	62	
III	57	
Tumor laterality		0.780
Left	62	
Right	58	
Charlson comorbidity index		0.128
<3	64	
≥3	53	
Tumor size, cm		0.028
≤3	69	
>3	45	
Histology		0.054
Well-moderately differentiated	66	
Poorly differentiated	54	
TNM stage (AJCC – UICC, 7th Edn)		0.008
I	69	
II	47	

AFP: alpha fetoprotein

Table 6. Cox proportional hazards model for overall survival

Variables	*Hazard ratio (95% CI)*	*p value*
AFP < 400 ng/ml versus ≥400 ng/ml	1.254 (0.754- 2.086)	0.109
TNM stage I versus II	2.012 (1.584- 2.555)	0.029
Ttumor size ≤3 cm versus >3 cm	2.879 (1.159- 7.152)	0.011
Well-moderately versus poorly differen-tiated	1.358 (0.698- 2.642)	0.197

and this difference was not statistically significant (Table 4). The 5-year overall survival rates for the laparoscopic and open groups were 62 and 59%, respectively, and this difference was not statistically significant (p=0.774) (Figure 1).

AFP≥ 400 ng/ml, TNM stage II, tumor size≥ 3cm, and poorly differentiated status were associated with poorer overall survival in univariate analysis (Table 5). In multivariate analysis with these variables (Table 6), TNM stage II and tumor size≥ 3cm were the significant prognostic factors affecting overall survival.

The 5-year disease-free survival rates for the laparoscopic and open groups were 51 and 48%, respectively, and this difference was not statistically significant (p=0.344) (Figure 2). AFP≥400 ng/ml, TNM stage II and tumor size ≥3cm were associated with poorer disease-free survival in univariate analysis (Table 7). Among these variables, prognostic factors affecting disease-free survival were AFP≥400 ng/ml and TNM stage II (Table 8). Surgical method (either laparoscopic or open surgery) was not associated with overall and disease-free survival in multivariate analysis.

Table 7. Univariate analysis of disease-free survival

Variables	*Five-year overall survival*	*p value*
Age, years		0.387
<75	53	
≥75	47	
Gender		0.484
Male	52	
Female	48	
AFP, ng/ml		0.012
≥400	42	
< 400	55	
ASA score		0.128
I-II	54	
III	48	
Tumor laterality		0.648
Left	52	
Right	48	
Charlson comorbidity index		0.248
<3	53	
≥3	48	
Tumor size, cm		0.018
≤3	58	
>3	39	
Histology		0.118
Well-moderately differentiated	54	
Poorly differentiated	48	
TNM stage (AJCC – UICC, 7th Edn)		0.012
I	61	
II	42	

AFP: alpha fetoprotein

Table 8. Cox proportional hazards model for disease-free survival

Variables	*Hazard ratio (95% CI)*	*p value*
AFP < 400 ng/ml versus ≥400 ng/ml	1.478 (1.257- 1.738)	0.028
TNM stage I versus II	1.789 (1.254- 2.552)	0.010
Ttumor size ≤3 cm versus >3 cm	1.428 (0.748- 2.726)	0.187

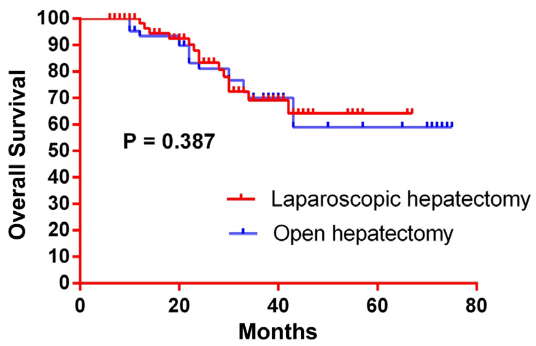

Figure 1. Overall survival in matched cohorts of laparoscopic and open hepatectomy for elderly patients with hepatocellular carcinoma.

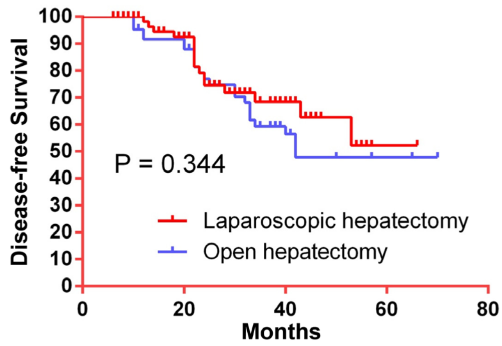

Figure 2. Disease-free survival in matched cohorts of laparoscopic and open hepatectomy for elderly patients with hepatocellular carcinoma.

Discussion

Surgical resection is one of the most effective treatments of choice for early hepatocellular carcinoma, with open hepatectomy being the traditional surgical approach adopted in the treatment of this malignancy [31-34]. Since the first report on the use of laparoscopy in the excision of benign liver lesions by Reich et al in 1991 [35], the application of laparoscopic techniques in benign and malignant liver disease has become increasingly widespread [36]. With the continuous maturation of laparoscopic techniques, laparoscopic hepatectomy has been adopted by an increasing number of medical centers, and the indications of laparoscopic hepatectomy have expanded from local resection initially to hemihepatectomy and subsequently to extended hemihepatectomy [36]. The 2008 Louisville Statement states that laparoscopic hepatectomy is a safe and effective approach to the management of surgical liver disease in the hands of trained surgeons with extensive experience in liver surgery and laparoscopic surgery [37]. As laparoscopic hepatectomy is associated with several benefits, including minor surgical trauma, shorter postoperative recovery time, shorter hospitalization, and long-term outcomes similar to that of open hepatectomy, it is widely applied in the treatment of hepatocellular carcinoma. With the increase in average life expectancy and enhancement of hepatocellular carcinoma screening techniques, there has been a continuous increase in elderly hepatocellular carcinoma patients in clinical settings and reports on the use of laparoscopic hepatectomy in the treatment of elderly hepatocellular carcinoma patients. However, the vast majority of relevant studies have only been focused on short-term outcomes [11-15]. Based on our searches of databases, such as Medline, Embase and Google Scholar, it appears that there are no studies in English comparing the long-term outcomes of laparoscopic hepatectomy and open hepatectomy in the treatment of hepatocellular carcinoma in elderly patients. Therefore, the present study is the first reported study written in English on the comparison of the outcomes of laparoscopic hepatectomy and open hepatectomy in treating elderly hepatocellular carcinoma patients. This study compared short- and long-term outcomes in elderly hepatocellular carcinoma patients undergoing laparoscopic or open surgery. Our results suggest that laparoscopic surgery in older patients with hepatocellular carcinoma achieved better short-term outcomes and similar long-term outcomes.

In the present study, prehepatocellular carcinoma treatment staging was performed using the BCLC staging system, while post-hepatocellular carcinoma treatment staging was performed using the TNM staging system [38]. Differences in the BCLC and TNM stages between the two groups of patients were not statistically significant, indicating good comparability of the results.

Malignant tumor staging enables the determination of the degree of malignancy, formulation of appropriate treatment regimens by physicians, understanding of the prognosis and sequelae of malignant tumors, and the establishment of a common language for the communication of disease conditions of patients among physicians [38]. A mature staging system, namely the TNM system, exists for gastrointestinal malignancies, such as esophageal cancer and gastric cancer. However, there is currently no universally accepted staging system for hepatocellular carcinoma [38]. At present, over a dozen hepatocellular carcinoma staging systems have been reported in the literature, with the BCLC and TNM staging systems being most commonly reported. The BCLC staging system has been recommended as the best staging system for hepatocellular carcinoma by the European Association for the Study of the Liver [39] and the American Association for the Study of Liver

Diseases [40]. Although the treatment guidelines of the BCLC staging system have been widely accepted in Europe and the Americas, a significant number of liver surgery specialists in East Asia are of the opinion that the scope of application of hepatectomy recommended by these guidelines is too narrow [41-43]. TNM staging of hepatocellular carcinoma is based on pathological results, such as vascular invasion; therefore, the TNM stages of hepatocellular carcinoma are pathological stages.

The liver receives a dual blood supply from the hepatic arteries and portal vein as well as blood return from the hepatic venous system. As the hepatic arteries, portal vein, and hepatic veins form a dense vascular network, control of bleeding is a key aspect of laparoscopic hepatectomy, and bleeding is the main reason for conversion to open laparotomy [44]. In particular, elderly laparoscopic hepatectomy patients are prone to major intraoperative bleeding due to significant vascular stiffness and low vascular elasticity. In the present study, none of the selected patients were converted to open laparotomy because of two major reasons: (1) All selected patients had undergone minor hepatectomy. With the low difficulty of the procedure and the extensive laparoscopic experience of the surgeons at our institution, conversion to laparotomy was effectively avoided; (2) Controlled low central venous pressure was adopted during all operations, which effectively reduced intraoperative bleeding and lowered the possibility of conversion to open laparotomy.

In recent years, novel laparoscopic hepatectomy techniques have been applied in clinical settings to reduce the difficulty of laparoscopic hepatectomy. Robot-assisted laparoscopic hepatectomy provides several benefits, including three-dimensional imaging, higher magnification of the operative field, clearer images, and higher precision of maneuvers through the use of robotic arms and wrists [45,46]. Therefore, it is highly suitable for complex and precision surgery. In developed countries, robot-assisted laparoscopic hepatectomy has been widely applied in medical institutions. However, this procedure also has its disadvantages, such as costly equipment and complicated maintenance. As China is a developing country, most patients are unable to bear the high costs of robot-assisted laparoscopic hepatectomy. Therefore, traditional laparoscopic hepatectomy will become the mainstream laparoscopic technique in China within a certain period of time.

To enable better evaluation of the degree of difficulty of laparoscopic hepatectomy, researchers have proposed a difficult scoring system, which includes tumor size, tumor location, relationship with major blood vessels, hepatic function, and proposed scope of resection as scoring criteria [47]. With this system, the degree of difficulty of laparoscopic hepatectomy can be classified as low, moderate, or high. Although the surgical procedures performed by selected subjects of the present study were of low difficulty, an increasing number of moderate- and high-difficulty laparoscopic hepatectomy, such as laparoscopic major hepatectomy, have been performed at our institution in recent years.

This study has limitations. First, it is a retrospective study with inherent selection bias. To minimize this, patients undergoing laparoscopic hepatectomy were carefully matched to patients undergoing open hepatectomy using propensity scoring. Second, we did not analyze cancer-specific survival. Since elderly patients are at higher risk of dying from other disorders, it is important to know death rates associated with hepatocellular carcinoma.

This study showed that laparoscopic hepatectomy in elderly patients with hepatocellular carcinoma achieved better results than open hepatectomy in terms of blood loss, length of hospital stay, and postoperative complications. Survival outcomes following laparoscopic and open hepatectomy were similar in the elderly population. These findings suggest that laparoscopic hepatectomy in elderly patients with hepatocellular carcinoma is safe and feasible, and should be considered as a treatment option.

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Conflict of interests

The authors declare no conflict of interests.

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