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ORIGINAL ARTICLE

# Short- and long-term outcomes of laparoscopic hepatectomy in elderly patients with hepatocellular carcinoma

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## Summary

***Purpose:*** *To compare short- and long-term outcomes of laparoscopic hepatectomy (LH) in elderly and non-elderly patients with hepatocellular carcinoma (HCC).*

***Methods:*** *Clinical and follow-up data of patients with HCC who underwent LH in our Institute from January 2011 to December 2016 were retrospectively analyzed. The patients were divided into elderly (48 cases, 70 years old or older) or non-elderly group (97 cases, <70 years) according to their age at the time of operation. The short- and long-term outcomes of both groups were compared.*

***Results:*** *The Charlson comorbidity index and American Society of Anesthesiologists (ASA) score of patients in the elderly group were higher than those of patients in the non-elderly group, and the rates of hepatitis virus infection and cirrhosis in the elderly group were lower than those in the non-elderly group. The rest of the preoperative data showed no statistical significance. Short-term outcomes, including operation time, intraoperative blood loss, transfer rate, length of hospital stay, incidence of complications and their severity within 30 days after surgery, and pathological findings, showed no significant difference between the elderly and non-elderly groups. Recurrence rates, treatment of the recurrence, overall survival (OS) rates, and disease-free survival (DFS) rates were similar in both groups. Multivariate analysis showed that age was not an independent predictor of OS and DFS.*

***Conclusions:*** *LH in elderly patients can achieve short- and long-term outcomes similar to those in non-elderly patients with liver cancer. Old age is not a contraindication for LH in patients with HCC.*

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

## Introduction

HCC is a malignant tumor with poor prognosis [1]. According to relevant statistics, HCC is the fifth most common malignant tumor, and in recent years, its incidence shows an increasing trend [2-4]. With the increase in average life expectancy, its incidence in the elderly population also shows an increasing trend [5-8]. Hepatectomy is the most important treatment of HCC [1]. However, elderly patients have more medical comorbidities and insufficient organ reserves than non-elderly patients; thus, the proportion of elderly patients undergoing hepatectomy is lower than that of non-elderly patients [9-12]. In recent years, LH started as a treatment for HCC [13-17]. LH shows advantages, such as less blood loss, shorter hospital stay, similar or decreased incidence of postoperative complications, and similar long-term outcomes, compared with open hepatectomy [13-20]. However, the

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above conclusions are derived from studies on non-elderly patients with HCC. Currently, no study has compared the short- and long-term outcomes of LH between elderly and non-elderly patients with HCC. In the present study we evaluated the short- and long-term outcomes of LH for HCC in elderly patients in order to provide more information for clinical reference.

## Methods

The protocol methodology 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.

*Inclusion/exclusion criteria*

From January 2011 to December 2016, 145 patients with HCC who underwent LH met the following criteria: Inclusion criteria: (1) Patients with HCC who underwent radical hepatectomy at our Institute, and no other treatments were used before surgery. (2) Patients' clinical and follow-up data were complete. Exclusion criteria: (1) Patients who received palliative hepatectomy and (2) lack of clinical and follow-up data.

*Examinations performed*

Patients' preoperative liver and cardiopulmonary functions were evaluated to determine whether surgery could be tolerated. All patients were subjected to brain, chest, and abdominal computed tomography (CT), abdominal magnetic resonance imaging (MRI), and abdominal ultrasound examinations to clarify the location, size, and number of HCC lesions and to determine indications of LH. If necessary, positron emission computed tomography (PET-CT) examination was used. All operations were performed with radical intent. Types of hepatectomy were adopted from the Brisbane 2000 classification [21]. Anatomical resections were preferred over non-anatomical hepatectomy when an indocyanine green test showed that liver function could tolerate anatomical hepatectomy. Non-anatomic resections were performed for HCC located in single, small peripheral lesions. Details on LH have been reported in previous articles [22].

The severity of 30-day postoperative complications was graded according to Clavien-Dindo classification system [23-30], in which the postoperative complications are divided into 5 grades of severity: minor complications are defined as grades 1 and 2, and major complications are defined as grades 3, 4, and 5. Postoperative mortality was defined as death due to surgery or complications within 30 days after surgery.

*Follow-up*

Patients' permanent home address and contact information were recorded. Clinic and home visits and telephone follow-up were used. Follow-up visits were scheduled once every 3 months within 2 years after surgery and then changed to once every 6 months. Follow-up exams included routine physical examination, tumor marker estimation, abdominal ultrasound, or abdominal CT examination. When recurrence or presence of other discomforts was suspected, patients were treated promptly in our hospital or local hospitals [1-4]. OS was assessed from the date of hepatectomy until the last follow-up or death from 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 September 2017.

*Statistics*

All statistical analyses were performed using the SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). Data were analyzed using t-test and presented as mean and standard deviation when the variables followed a normal distribution. Data following non-normal distribution were compared using a non-parametric test (Mann-Whitney *U* test), and the results were 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 $x^2$ 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 OS. Univariate variables with $p<0.05$ were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HRs) along with corresponding 95% confidence intervals (CIs) were calculated. p value <0.05 was considered statistically significant.

## Results

Table 1 shows the comparison of preoperative clinical data between the two groups. Compared with that in the non-elderly group, the Charlson comorbidity index and ASA score in the elderly group were higher than those in the non-elderly group. The incidence rates of hepatitis virus infection and cirrhosis in the elderly group were lower than those in the non-elderly group. Other preoperative general data, such as gender, body mass index (BMI), tumor stage and tumor location, showed no significant difference between the two groups.

Table 2 shows the short-term outcomes of patients in both groups. No significant difference was found in terms of operation time, intraoperative blood loss, transfer rate, length of hospital stay and incidence of postoperative complications within 30 days after surgery and their severity between the two groups. Four and seven patients in the elderly and non-elderly groups, respectively, were converted to open surgery. The reason of conversion was difficult-to-control bleeding. No patient died during surgery and within 30 postoperative days.

**Table 1.** Comparison of preoperative clinical characteristics between the two groups

| *Characteristics* | *Non-elderly group (n=97) n (%)* | *Elderly group (n=48) n (%)* | *p value* |
|---|---|---|---|
| Age, years, median (range) | 54 (35-69) | 72 (70-75) | 0.000 |
| Sex | | | 0.487 |
| Male | 61 (63) | 33 (69) | |
| Female | 36 (37) | 15 (31) | |
| BMI (kg/m²), median (range) | 20 (17-24) | 22 (18-25) | 0.548 |
| Charlson comorbidity index | | | 0.0017 |
| < 3 | 86 (89) | 35 (73) | |
| ≥ 3 | 11 (11) | 13 (27) | |
| ASA score | | | 0.039 |
| I | 75 (77) | 30 (63) | |
| II | 19 (20) | 12 (25) | |
| III | 3 (3) | 6 (12) | |
| ICG retention at 15 min (%), median (range) | 23 (11-33) | 22 (10-35) | 0.254 |
| Hepatitis B virus | 68 (70) | 15 (31) | 0.00 |
| Hepatitis C virus | 12 (12) | 9 (19) | 0.304 |
| Negative for both HBsAg and HCV antibody | 17 (18) | 24 (50) | 0.000 |
| Liver cirrhosis | 61 (63) | 21 (44) | 0.029 |
| Tumor location | | | 0.962 |
| Right lobe | 38 (39) | 19 (40) | |
| Left lobe | 59 (61) | 29 (60) | |
| CLIP stage | | | 0.214 |
| CLIP 0 | 68 (70) | 39 (81) | |
| CLIP 1 | 20 (21) | 4 (8) | |
| CLIP 2 | 9 (9) | 5 (10) | |
| JLS stage | | | 0.662 |
| JLS 0 | 59 (61) | 31 (65) | |
| JLS 1 | 38 (39) | 17 (35) | |

ICG: indocyanine green, ASA: American Society of Anesthesiologists, JLS: Japanese Integrated Staging, CLIP: Cancer of the Liver Italian Program, TNM: tumor, node and metastasis

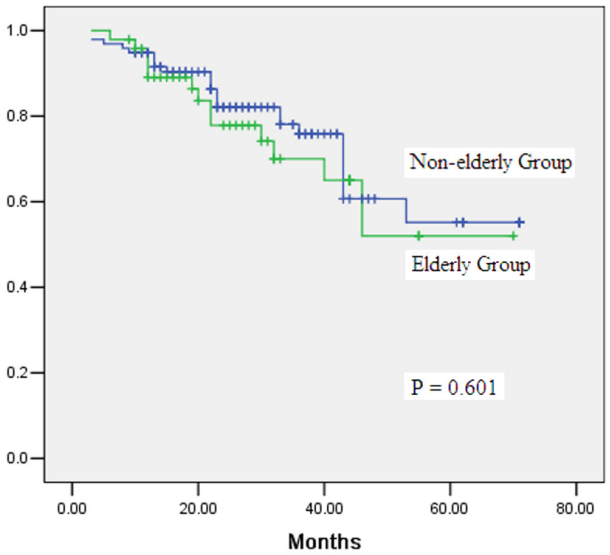


**Figure 1.** Comparison of overall survival according to age.

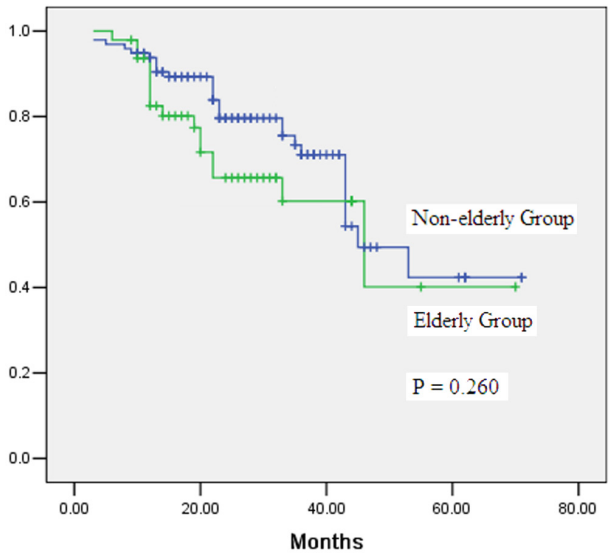


**Figure 2.** Comparison of disease-free survival according to age.

There was no significant difference in the pathological results between the two groups (Table 3).

The median follow-up time in the elderly and non-elderly groups was 37 and 40 months, respectively, and the difference was not statistically significant. Up to the last follow-up, 14 patients died in the elderly group, of whom 12 died of tumor recurrence and two of non-neoplastic causes. Moreover, 23 patients died in the non-elderly group, of whom 19 died of tumor recurrence and 4 of non-neoplastic causes (Table 4). The 5-year OS of patients in the elderly and non-elderly groups were 52 and 55%, respectively, and the difference was not statistically significant (Figure 1, p=0.601). Multivariate analysis indicated that tumor differentiation status and tumor numbers were independent predictors of OS (Table 5).

Furthermore, 14 and 23 patients had tumor recurrence in the elderly and non-elderly groups, respectively. The most common locations of recurrence were intrahepatic locations. For the treatment of tumor recurrence, the most commonly method used was transcatheter arterial chemoembolization (TACE) (Table 4). The 5-year DFS of the elderly and non-elderly groups were 40 and 42%, respectively, and the difference was not statistically significant (Figure 2, p=0.260). Multivariate analysis showed that tumor lesion numbers and alpha fetoprotein (AFP) were independent predictors of DFS (Table 6). Age was not an independent predictor of OS and DFS.

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

| *Data* | *Non-elderly group (n=97) n (%)* | *Elderly group (n=48) n (%)* | *p value* |
|---|---|---|---|
| Type of resection | | | 0.915 |
| Left lateral sectionectomy | 38 (39) | 18 (38) | |
| Segmentectomy | 30 (31) | 14 (27) | |
| Partial resection | 29 (30) | 16 (33) | |
| Converted to open surgery | 7 (7) | 4 (8) | 1.000 |
| Operative time min, median (range) | 170 (140-250) | 160 (130-280) | 0.428 |
| Blood loss, ml, median (range) | 220 (170-400) | 230 (180-410) | 0.250 |
| Length of hospital stay, days, median (range) | 10 (7-18) | 12 (8-21) | 0.120 |
| Mortality within 30 days postoperative | 0 | 0 | - |
| Overall complications | 14 (14) | 9 (19) | 0.503 |
| Major complications | 10 (10) | 7 (15) | 0.829 |
| Minor complications | 4 (4) | 2 (4) | |
| Intraabdominal bleeding | 2 (2) | 1 (2) | 1.000 |
| Liver failure | 2 (2) | 1 (2) | 1.000 |
| Pleural effussion | 4 (4) | 3 (6) | 0.880 |
| Postoperative ascites | 2 (2) | 2 (4) | 0.850 |
| Ileus | 3 (3) | 2 (4) | 1.000 |

**Table 3.** Comparison of pathological data between laparoscopy and open group

| *Data* | *Non-elderly group (n=97)* | *Elderly group (n=48)* | *p value* |
|---|---|---|---|
| Histology | | | 0.166 |
| Well differentiated | 32 | 14 | |
| Moderately differentiated | 36 | 12 | |
| Poorly differentiated | 29 | 22 | |
| Surgical margin size (cm) | 2 (0.4-1.0) | 3 (0.3-0.9) | 0.540 |
| Surgical margin status (R0/R1/R2) | 97/0/0 | 48/0/0 | 1.000 |
| Pathological TNM stage | | | 0.650 |
| I | 63 | 33 | |
| II | 34 | 15 | |

**Table 4.** Follow-up and tumor recurrence data

| *Data* | *Non-elderly group (n=97)* | *Elderly group (n=48)* | *p value* |
|---|---|---|---|
| Cause of death | 23 | 14 | 0.478 |
| Tumor recurrence | 19 | 12 | |
| Not related to cancer | 4 | 2 | |
| Tumor recurrence | 23 | 14 | 0.478 |
| Time to first recurrence, median, months (range) | 24 (3-45) | 21 (6-33) | 0.258 |
| Main treatment for recurrence | | | 0.928 |
| Transcatheter arterial chemoembolization | 10 | 5 | |
| Systemic chemotherapy | 4 | 3 | |
| Radiofrequency ablation | 3 | 3 | |
| Repeat hepatectomy | 3 | 2 | |
| Supportive care only | 3 | 1 | |

**Table 5.** Multivariate Cox regression analysis of overall survial

| *Regression variables* | *Adjusted hazard ratio* | *95%CI* | *p value* |
|---|---|---|---|
| Tumor differentiation | | | |
| Well differentiated | 1.00 | | |
| Moderately differentiated | 1.23 | 0.87-1.58 | 0.102 |
| Poorly differentiated | 2.58 | 1.54-2.98 | 0.021 |
| Tumor numbers | | | |
| 1 | 1.00 | 0.58-1.20 | 0.235 |
| 2 | 1.18 | 1.38-4.30 | 0.012 |
| ≥3 | 2.02 | | |

**Table 6.** Multivariate Cox regression analysis of disease-free survival

| *Regression variables* | *Adjusted hazard ratio* | *95%CI* | *p value* |
|---|---|---|---|
| Tumor numbers | | | |
| 1 | 1.00 | | |
| 2 | 1.35 | 0.78-1.57 | 0.079 |
| ≥3 | 2.04 | 1.69-3.05 | 0.039 |
| AFP (ng/ml) | | | |
| <400 | 1.00 | | 0.025 |
| ≥400 | 2.54 | 1.37-2.99 | |

AFP: alpha fetoprotein

## Discussion

Since Reich's first report of using LH to treat benign liver tumors in 1991 [31], LH has been rapidly developed. Many studies have shown the minimal invasiveness of LH as well as the similarity of treatment outcomes compared with open surgery [32-35]. Despite the lack of evidence in randomized controlled trials, LH has been widely used in large medical centers [32-35]. The number of elderly patients with HCC is gradually increasing, and open hepatectomy presents a higher surgical risk for this patient group [9-12]. In recent years, LH has been gradually carried out in elderly patients with HCC [36-42], and studies indicate that LH can achieve lower complications, less blood loss, and shorter hospital stay than open hepatectomy [36-42]. Thus, LH is safe and feasible in elderly patients with HCC. However, these studies have treated HCC and liver metastatic tumors as similar diseases, and only a

few have examined their long-term outcomes. We searched through databases, including PubMed, EMBASE and Chemical Abstracts, and found that the present study is the first English language article on short- and long-term outcomes of LH in elderly patients with HCC. The results show that performing LH to treat HCC in elderly patients can achieve short- and long-term outcomes similar to those in non-elderly patients.

The staging of malignant tumors is of great significance in determining tumor stage, providing treatment recommendations and assessing prognosis [43,44]. In all common malignancies, such as lung, gastric and colorectal cancers, the American Joint Committee on Cancer (AJCC) TNM staging system is used. However, HCC has no an academically recognized staging system compared with other common malignancies. The reason is that most patients with HCC have a liver disease background, and the staging system should consider not only the tumor but also the liver function. Currently, more than 10 staging systems for HCC have been reported, and each has its advantages and disadvantages. In this study, we used the four commonly used staging systems, namely, TNM, Japanese Integrated Staging (JLS), and Cancer of the Liver Italian Program (CLIP), to compare tumor staging between the two groups [45,46], and the results showed that the tumor staging of the two groups was similar.

In this study, for the preoperative clinical data, the HBsAg positive rate and incidence of cirrhosis in the elderly group were lower than those in the non-elderly group, and the HCV antibody positive rate was similar to that in the non-elderly group, which is consistent with a previous report by East Asian researchers [9-12]. Most HBV infections occur in children, which later lead to cirrhosis and liver cancer. Given that the overall prognosis of HCC is poor, these patients hardly live up to 70 years; this phenomenon is caused by the lower HBV infection rate in the middle-aged and elderly patients with HCC. The rate of patients without hepatitis virus infection in the elderly group is higher than that in the non-elderly group because the occurrence of HCC in elderly patients is related to non-viral infection factors, such as alcoholic and non-alcoholic fatty liver diseases [9-12].

Regarding the difficulty of the operation, LH can be divided into minor, major and difficult hepatectomies [14-16]. In this study, all patients were subjected to minor hepatectomy, which is less challenging than the major and difficult hepatectomy. However, LH is only used to perform minor hepatectomy. Patients with HCC who require either major or difficult hepatectomy cannot take advantage of the minimal invasiveness of LH. Since 2017, with the accumulation of experience in LH, our hospital has also been performing major and difficult hepatectomies. Short-term outcomes are satisfactory, but long-term outcomes remain to be further followed-up.

In previous studies, the 5-year survival rate in elderly patients with HCC treated with open hepatectomy ranged between 41 and 64%, and long-term outcomes were similar to those of non-elderly patients [9-12]. Based on our thorough literature search, at present, there are no English-language studies on long-term survival rates of elderly patients with HCC treated with LH. In this study, the 5-year OS of the elderly group was 52%, which is similar to previous results of open hepatectomy [9-12]. This finding indicates that for elderly patients with HCC, as long as there are indications of LH, LH should be highly recommended, and the long-term prognosis is similar to that of non-elderly patients. At present, in China, the life expectancy of the elderly population is increasing, thus, old age is not a contraindication to LH.

However, this study has several limitations. First, it was based on a single-center retrospective analysis, not on prospective randomized analysis. Second, the sample size was small, and the follow-up period was not very long. These limitations should be considered when interpreting our study results. In the future, a multicenter prospective randomized controlled study with longer follow-up period is necessary to validate the safety of LH for elderly patients with HCC.

## Conclusions

This study showed that LH in elderly patients with HCC can achieve short- and long-term outcomes similar to those in non-elderly patients. Old age is not a contraindication to LH for elderly patients with HCC.

## Conflict of interests

The authors declare no conflict of interests.

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