

# Short- and long-term outcomes of laparoscopic hepatectomy for colorectal liver metastases in elderly patients

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**Purpose:** This study aimed to evaluate the short- and long-term outcomes of laparoscopic hepatectomy (LH) for colorectal liver metastases (CRLM) in elderly patients.

**Patients and methods:** Between January 2009 and January 2016, LH was performed for 241 consecutive patients who were  $\geq 60$  years old and had CRLM. Based on their age at the LH, the patients were divided into an elderly group ( $\geq 70$  years old, 78 patients) and a middle-aged group (60–69 years old, 163 patients). The short- and long-term outcomes were compared between the two groups.

**Results:** Compared to the middle-aged group, the elderly group had higher values for Charlson comorbidity index, proportion of preoperative chemotherapy, and American Society of Anesthesiologists score. No other significant differences were observed in the preoperative characteristics. The elderly group had a higher conversion rate, compared to the middle-aged group, although no significant differences were observed in the surgical procedures, surgical times, intraoperative blood losses, numbers and severities of postoperative 90-day complications, postoperative 90-day mortality rates, pathology results, and other short-term outcomes. Long-term follow-up revealed similar rates of recurrence, disease-free survival, and overall survival in the two groups. Multivariable analysis revealed that age did not independently predict overall survival or disease-free survival.

**Conclusion:** Similar short- and long-term outcomes were observed after LH for CRLM in elderly and middle-aged patients. Thus, advanced age is not a contraindication for LH treatment in this setting.

**Keywords:** laparoscopic hepatectomy, minimally invasive surgery, colorectal liver metastases, surgical oncology

## Introduction

The westernization of Chinese lifestyle has created recent trends toward decreased physical activity, increased life expectancy, and an increased incidence of colorectal cancer.<sup>1</sup> Studies have demonstrated that approximately one-half of colorectal cancers develop liver metastases, and surgical resection is the primary treatment for colorectal liver metastases (CRLM).<sup>2–4</sup> A large number of studies have revealed that the 5-year overall survival rate is 30%–60% among patients who undergo radical resection for CRLM, and good long-term survival can be achieved using open hepatectomy for CRLM.<sup>5–7</sup> However, ~70% of patients with CRLM are  $\geq 65$  years old when they seek treatment, and elderly patients may be less able to tolerate hepatectomy (versus younger patients), which has led some surgeons to reject hepatectomy for elderly patients.<sup>5–8</sup>

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The first reported laparoscopic hepatectomy (LH) was performed in 1992,<sup>9</sup> and a growing number of reports have described LH treatment for CRLM.<sup>10–15</sup> Compared to open hepatectomy, LH for CRLM leads to lesser intraoperative blood loss, shorter hospital stays, similar or lower incidences of complications, and similar long-term outcomes.<sup>10–15</sup> However, the previous studies have not included large numbers of elderly patients, and only a few English reports have described LH treatment for CRLM.<sup>16–19</sup> Furthermore, there is a lack of studies comparing short- and long-term outcomes of LH treatment between elderly and middle-aged patients with CRLM. Therefore, the present study aimed to compare the short- and long-term outcomes of LH treatment among elderly and middle-aged patients with CRLM.

## Patients and methods

This study complied with the Declaration of Helsinki rules. This retrospective research was approved by the Ethics Committee of First Hospital, JiLin University. The need for informed consent from all patients was waived because this was a retrospective study. All data had no personal identifiers and were kept confidential.

Between January 2009 and January 2016, 241 consecutive patients underwent LH treatment for CRLM and were considered eligible for this retrospective study. The inclusion criteria were as follows: 1) the patient was undergoing their first hepatectomy, 2) the patient had undergone radical resection of colorectal cancer, and 3) complete clinical and follow-up data were available for the patient. The exclusion criteria were as follows: 1) repeat hepatectomy and 2) palliative hepatectomy. Based on their age at the LH, the patients were divided into an elderly group ( $\geq 70$  years old, 78 patients) and a middle-aged group (60–69 years old, 163 patients). The location, number, diameter, and operability of liver metastatic lesions were preoperatively confirmed in all patients using tumor biomarkers, abdominal computed tomography or magnetic resonance imaging, and other examinations. Positron emission tomography–computed tomography was performed as needed. Lung function tests, electrocardiography, echocardiography, and other examinations were performed to determine the patients' preoperative cardiopulmonary function. All patients were operated using the totally laparoscopic technique, and intraoperative ultrasonography was performed in all cases. The LH was performed according to a previous report.<sup>19</sup> All LHs were carried out by the surgeon Dr Zhenhua Kang. Before this study, he had successfully completed 50 LH surgeries.

The Clavien–Dindo criteria were used to classify the severity of postoperative 90-day complications. Minor complications were defined as grades I–II and major complications as grades III–V. Postoperative 90-day mortality was defined as any death from oncological or non-oncological causes within 90 days after surgery.

After the patients were discharged, follow-ups were performed at outpatient clinics, the patient's house, community health service centers, and other locations. The follow-ups were performed every 3 months during the first year after surgery, every 4 months during the second year, every 6 months during the third year, and annually thereafter. Patients were referred for in-hospital treatment if tumor recurrence was suspected at any time. The follow-up rate was 100%, as all patients lived near our hospital, and the last follow-up was performed on May 31, 2017.

All the statistical analyses were performed using SPSS, Version 14.0 (SPSS Inc., Chicago, IL, USA). Normally distributed variables were analyzed by Student's *t*-tests and presented as mean and SD. Non-normally distributed variables were analyzed by Mann–Whitney *U* test and presented as medians and ranges. Differences between semiquantitative results were analyzed by Mann–Whitney *U* tests. Differences between qualitative results were analyzed by chi-square or Fisher's exact tests, as appropriate. Survival rates were analyzed by the Kaplan–Meier method, and differences between the two groups were analyzed by log-rank test. Multivariable Cox regression analysis was performed to identify the factors predictive of poor disease-free survival and overall survival by using both forward and backward stepwise selection. Explanatory variables with univariate *P* values  $\leq 0.100$  were included in the multivariable analysis. The results are reported as hazard ratios with 95% CIs. A level of 5% was set as the criterion for statistical significance.

## Results

The patients' general preoperative characteristics are shown in Table 1. Compared to the middle-aged group, the elderly group had significantly higher values for Charlson comorbidity index, proportion of preoperative chemotherapy, and the American Society of Anesthesiologists score. No other significant differences were observed in the other preoperative characteristics (e.g., gender, body mass index, TNM stage, pre-LH carcinoembryonic antigen levels, and location of liver metastases).

The patients' short-term prognoses are shown in Table 2. Both groups underwent similar surgical procedures, with

most patients undergoing wedge resection or sectionectomy and a few patients undergoing left lateral sectionectomy. No significant inter-group differences were observed in the surgical times, intraoperative blood losses, intraoperative and postoperative blood transfusion rates, or incidences and

severities of postoperative complications. The elderly group had a higher rate of conversion to open hepatectomy, and conversion in both groups was primarily related to bleeding. There were no intraoperative deaths in either group, although one patient in the elderly group died within 90 days because of liver failure and one patient in the middle-aged group died after 2 months because of metastasis to the central nervous system. Both groups had similar pathology results.

**Table 1** Baseline characteristics of the two groups

Characteristic	Middle-aged group (n=163)	Elderly group (n=78)	P-value
Age (years)	67 (60–69)	74 (70–78)	0.000
Gender			0.616
Male	114	57	
Female	49	21	
Charlson comorbidity index			0.027
≤2	130	52	
>2	33	26	
BMI (kg/m <sup>2</sup> )	22 (18–26)	21 (17–25)	0.221
Largest tumor size (cm)	3 (1–5)	2 (1–4)	0.128
Tumor number	2 (1–4)	2 (1–3)	0.200
Tumor laterality			0.584
Left	98	44	
Right	65	34	
Preoperative CEA level			0.357
<5 ng/mL	65	36	
≥5 ng/mL	98	42	
Preoperative chemotherapy	118	69	0.005
Initial colorectal cancer TNM stage			0.271
I	29	18	
II	50	25	
III	84	35	
ASA score			0.000
I	92	21	
II	42	33	
III	29	24	

**Abbreviations:** ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen.

The median follow-ups for the elderly and middle-aged groups were 31 and 34 months, respectively, and this difference was not statistically significant ( $P=0.387$ ). During the follow-ups, 32 patients in the elderly group died because of recurrence ( $n=29$ ), ischemic stroke ( $n=1$ ), hemorrhagic stroke ( $n=1$ ), and sudden cardiac death ( $n=1$ ), as shown in Table 3. Fifty-three patients in the middle-aged group died because of recurrence ( $n=48$ ) and non-cancer-related diseases ( $n=5$ ). There were no significant inter-group differences in the recurrence locations, median time to recurrence, or other factors (Table 3).

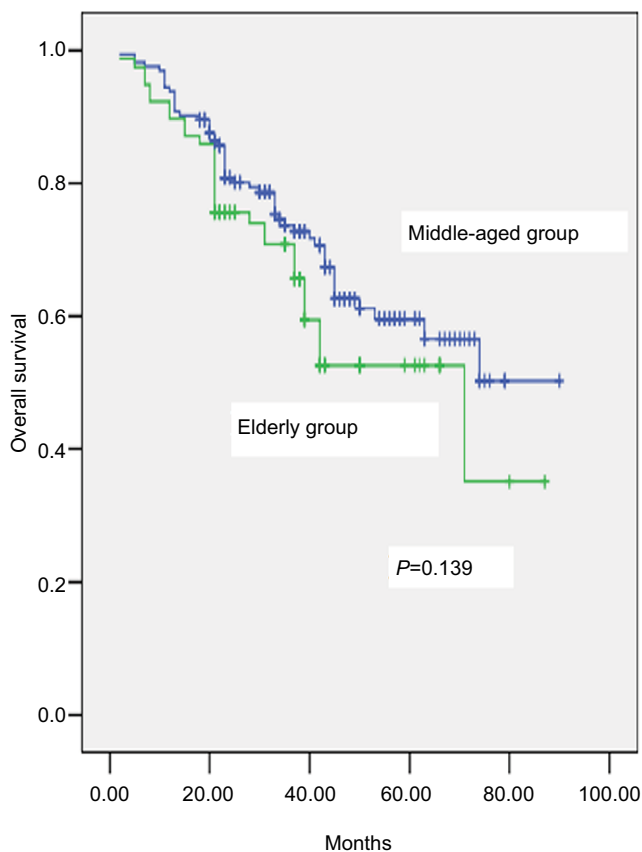
The 5-year overall survival rates for the elderly and middle-aged groups were 52% and 59%, respectively, and this difference was not statistically significant ( $P=0.139$ ; Figure 1). Multivariable analyses revealed that TNM stage, disease-free interval, and number of metastases independently predicted overall survival (Tables 4 and 5). The 5-year disease-free survival rates for the elderly and middle-aged groups were 45% and 49%, respectively, and this difference was not statistically significant ( $P=0.090$ ; Figure 2). Multivariable analyses revealed that disease-free interval and preoperative carcinoembryonic antigen levels independently predicted disease-free survival (Tables 6 and 7). Age did not independently predict overall or disease-free survival.

**Table 2** Short-term outcomes of the two groups

Outcome	Middle-aged group (n=163)	Elderly group (n=78)	P-value
Surgical procedure			0.576
Left lateral sectionectomy	11	7	
Sectionectomy	51	28	
Wedge resection	101	43	
Operative time (min)	190 (150–290)	180 (160–260)	0.210
Estimated blood loss (mL)	240 (160–410)	260 (180–430)	0.218
Conversion to open surgery	2	6	0.025
Blood transfusion	9	4	0.899
Patients with postoperative 90-day complications	38	21	0.542
Patients with postoperative 90-day major complications	9	5	1.000
Postoperative hospital stay (days)	9 (7–23)	10 (7–32)	0.128
Postoperative 90-day mortality	1	1	1.000
Residual tumor (R0/R1/R2)	163/0/0	78/0/0	1.000
Margin distance (mm)	10 (5–25)	11 (6–28)	0.521

**Table 3** The follow-up data of the two groups

Outcome	Middle-aged group (n=163)	Elderly group (n=78)	P-value
Tumor recurrence, n	66	41	0.078
Liver	32	21	0.201
Extrahepatic	25	14	0.607
Both	9	6	0.713
Time to recurrence (median, months)	22 (2–45)	18 (2–42)	0.090
Mortality	53	32	0.196
Died of cancer	48	29	0.228
Died of non-cancer-related diseases	5	3	1.000



**Figure 1** Comparison of overall survival rate between elderly and middle-aged groups ( $P=0.139$ ).

**Table 4** Univariate Kaplan–Meier analysis of overall survival

Variable	Five-year overall survival	P-value
Age		0.139
60–69 years	59	
≥70 years	52	
Gender		0.201
Male	58	
Female	54	
Charlson comorbidity index		0.087
≤2	61	
>2	52	
ASA score		0.351
I–II	59	
III	54	
Preoperative CEA level		0.106
<5 ng/mL	61	
≥5 ng/mL	49	
TNM stage of colorectal cancer		0.007
I–II	68	
III	43	
Disease-free interval		0.011
<12 months	42	
≥12 months	67	
Tumor number		0.024
<3	59	
≥3	48	
Tumor laterality		0.547
Left	56	
Right	51	

**Abbreviations:** ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

## Discussion

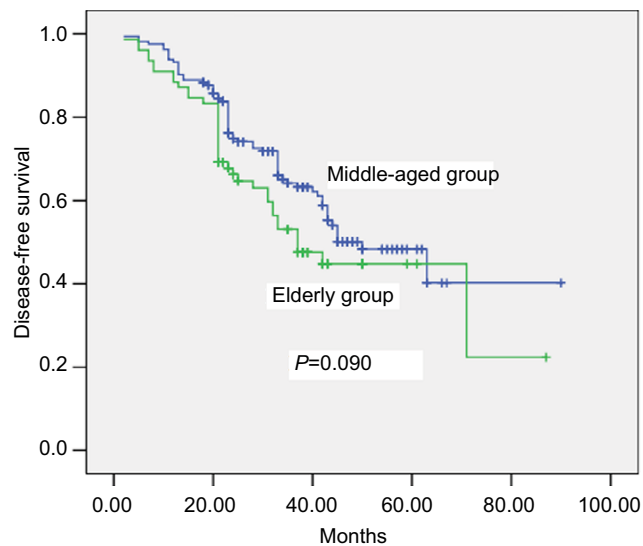
Increasing life expectancy is leading to a rise in the surgical treatment of elderly patients with CRLM, and surgical resection of liver metastases is considered safe for these patients. However, elderly individuals have more comorbidities and less cardiopulmonary functional reserve, compared to younger patients, and elderly patients experience relatively high rates of postoperative complications and mortality.<sup>5–8</sup> These factors explain the relatively small proportion of elderly patients in the present study, as well as their higher

Charlson comorbidity index and American Society of Anesthesiologists score, compared to middle-aged patients. Interestingly, the patients and their families expressed concern regarding the surgery and a desire for non-surgical CRLM treatments.

The liver receives an abundant supply of blood from the hepatic artery and portal vein, and bleeding is common during open hepatectomy.<sup>20–23</sup> However, it is difficult to control any bleeding and replicate some of the open procedures during LH, which can necessitate conversion to open hepatectomy

**Table 5** Cox proportional hazards model for overall survival

Variable	Hazard ratio (95% CI)	P-value
Charlson comorbidity index ≤2 versus >2	1.205 (0.651–1.558)	0.128
TNM stage of colorectal cancer I–II versus III	1.981 (1.258–3.854)	0.021
Disease-free interval ≥12 versus <12 months	1.610 (1.378–2.873)	0.015
Tumor number <3 versus ≥3	1.500 (1.258–1.870)	0.041

**Figure 2** Comparison of disease-free survival rates between elderly and middle-aged groups ( $P=0.090$ ).

in up to 12% of cases.<sup>10–15</sup> In the present study, the conversion rate among elderly patients was higher than that among middle-aged patients (7% versus 1%, respectively), and bleeding was the overwhelming reason for conversion to open hepatectomy. These findings may be related to the deterioration of physiological mechanisms (e.g., vascular elasticity) and coagulation function in elderly patients, which makes it difficult to control intraoperative bleeding.<sup>24–26</sup> Thus, only open hepatectomy can ensure patient safety. Although we did not detect any obvious differences in the preoperative platelet counts and coagulation test results, coagulation is a very complicated process that may not be completely described using clinical platelet counts and coagulation tests.

The current guidelines categorize LH based on the extent and complexity as minor hepatectomy, major hepatectomy, and difficult hepatectomy.<sup>27</sup> Only minor hepatectomy was performed in the present study, and previous reports have also confirmed that LH generally involves minor hepatectomy,<sup>5–8</sup> with a few reports showing major and difficult hepatectomy. This is likely because major and difficult hepatectomies are

**Table 6** Univariate Kaplan–Meier analysis of disease-free survival

Variable	Five-year overall survival	P-value
Age		0.090
60–69 years	49	
≥70 years	45	
Gender		0.210
Male	51	
Female	46	
Charlson comorbidity index		0.089
≤2	52	
>2	44	
ASA score		0.181
I–II	51	
III	45	
Preoperative CEA level		0.021
<5 ng/mL	58	
≥5 ng/mL	41	
TNM stage of colorectal cancer		0.032
I–II	54	
III	46	
Disease-free interval		0.008
<12 months	39	
≥12 months	59	
Tumor number		0.128
<3	51	
≥3	44	
Tumor laterality		0.224
Left	52	
Right	44	

**Abbreviations:** ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; TNM, tumor-node-metastasis.

**Table 7** Cox proportional hazards model for disease-free survival

Variables	Hazard ratio (95% CI)	P-value
Age 60–69 versus ≥70 years	1.328 (0.544–1.698)	0.210
Charlson comorbidity index ≤2 versus >2	1.187 (0.749–1.584)	0.267
TNM stage of colorectal cancer I–II versus III	1.415 (0.879–1.874)	0.089
Disease-free interval ≥12 versus <12 months	1.874 (1.215–2.001)	0.036
Preoperative CEA level <5 versus ≥5 ng/mL	1.740 (1.418–2.108)	0.028

**Abbreviation:** CEA, carcinoembryonic antigen; TNM, tumor-node-metastasis.

inherently difficult to perform using the open approach, and the laparoscopic approach further complicates the surgery. Thus, patients who require major or difficult hepatectomy for CRLM may not be able to benefit from the advantages of laparoscopic surgery. Nevertheless, recent reports have indicated that laparoscopic major and difficult hepatectomy is safe and feasible,<sup>28–31</sup> and our hospital began performing laparoscopic major and difficult hepatectomy in June 2016, based on the accumulated experience with LH. We hope to

generate additional data to examine the utility of laparoscopic major and difficult hepatectomy in future studies.

Relatively few elderly patients with CRLM undergo LH because of concerns among surgeons that elderly patients may not be able to tolerate pneumoperitoneum, which can lead to higher intraperitoneal pressure and CO<sub>2</sub> retention in the blood. These factors can theoretically lead to cardiopulmonary complications, although none of the elderly patients in the present study experienced severe cardiopulmonary complications. Three elderly patients experienced minor lung infections, based on the Clavien–Dindo criteria,<sup>32–35</sup> although they recovered fully after treatment using intravenous antibiotics.

Previous studies have revealed 5-year overall survival rates of 48%–61% and 5-year disease-free survival rates of 43%–58% among elderly patients who underwent hepatectomy for CRLM.<sup>36–38</sup> We observed similar outcomes among our elderly patients, and their outcomes were comparable to those of the middle-aged patients. The predominant cause of death among elderly patients was tumor recurrence, with relatively few deaths caused by non-oncological diseases. Therefore, LH appears to be beneficial when indicated for elderly patients with CRLM and to provide good long-term survival, compared to the outcomes for middle-aged patients. Moreover, elderly patients with CRLM have an extremely poor prognosis after receiving non-surgical treatments.

The present study has two important limitations. First, the retrospective design is associated with known risks of bias, and a prospective randomized controlled trial is needed to confirm that LH is safe and effective for elderly patients with CRLM. Second, we only examined data from a single center with a small sample size, and it is possible that our findings may not generalize to other centers and/or patient groups. The fact that the study failed to find statistical significance between the two groups in survival may be due to the small sample size.

## Conclusion

The present study results indicate that LH was not associated with elevated rates of postoperative complications or mortality among elderly patients with CRLM, and that their long-term outcomes were comparable to those of middle-aged patients. Therefore, advanced age is not a contraindication for LH treatment of CRLM.

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## Disclosure

The authors report no conflicts of interest in this work.

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