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ORIGINAL ARTICLE

Laparoscopic versus open hepatectomy for elderly patients with liver metastases from colorectal cancer

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Summary

Purpose: *To date, it is unclear whether laparoscopic hepatectomy (LH) is a suitable treatment for elderly patients (aged ≥65 years) with liver metastases from colorectal cancer. The aim of the present study was to clarify the value of LH in the elderly using the propensity score matching method.*

Methods: *Data from 385 elderly patients who underwent hepatectomy for liver metastases from colorectal cancer at our institution between January 2008 and January 2016 were prospectively collected. Propensity score matching was applied at a ratio of 1:1 to compare LH and open hepatectomy (OH) groups. The short- and long-term outcomes were compared between the matched groups.*

Results: *The LH group had significantly less blood loss than the OH group. The postoperative length of hospital stay was shorter in the LH group than in the OH group; however, no significant intergroup differences were found in morbidity and mortality. Furthermore, the 5-year overall (OS) and disease-free survival (DFS) rates were similar between the two groups.*

Conclusion: *LH for elderly patients with liver metastases from colorectal cancer was feasible and safe with acceptable oncologic outcomes. Therefore, patient age alone should not be considered as a contraindication when deciding between LH and OH as treatment options.*

Key words*: colorectal cancer liver metastases, hepatectomy, minimally invasive surgery, laparoscopy, survival*

Introduction

The World Health Organization defines an "elderly" or older person as an individual aged ≥65 years. During the last two decades, life expectancy has doubled, and the elderly population is constantly increasing. Approximately 50% of cancer incidence and 80% of cancer-related mortality occur in individuals aged ≥65 years [1].

In China, death due to liver metastases from colorectal cancer is increasing in elderly patients [2-4], but objective indicators for the selection of surgical options have not been established [5]. Previous studies have reported a high incidence of comorbid diseases, postoperative morbidity, and mortality in elderly patients who have undergone OH for liver metastases from colorectal cancer [5-10]. For these reasons, minimized surgical trauma is recommended for such patients [11-13]. Therefore, the comparative effectiveness between laparoscopic and open approaches to hepatectomy in elderly patients with liver metastases from colorectal cancer needs to be investigated.

Since the first reported LH for liver neoplasm in the 1990s, many reports have demonstrated the clinical advantages of LH over OH [14-18]. With advances in instruments and increasing surgical skills, LH is increasingly being used by some surgeons for the treatment of primary and metastatic liver cancer. However, most reports do not include

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a sufficiently longer follow-up period to compare patients who underwent LH with those who underwent OH [14-20]. Moreover, the suitability of LH for the treatment of elderly patients with liver metastases from colorectal cancer has not been previously analyzed.

In this study, we analyzed the short- and long-term outcomes for elderly patients with liver metastases from colorectal cancer after LH and OH using the propensity score matching method.

Methods

This study complied with the rules of the Declaration of Helsinki and was approved by the local ethics committee. The need for informed consent from all patients was waived because the study design was retrospective and not prospective.

Patients were selected from the prospective database of our institution between January 2008 and January 2016. The inclusion criteria were as follows: (1) age ≥65 years, (2) primary colorectal cancer controlled, (3) radical hepatectomy being the primary treatment, (4) no other metastases, and (5) R0 resection performed according to the pathologic reports.

Abdominal computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography have been crucial preoperative diagnostic tools for identifying the number, location, and size of the liver metastases. The indications for LH at our institution were lesions less than 5 cm in diameter and located in the peripheral segments of the liver and larger tumor lesions located in the left lateral section and not invading major vessels. Primary colorectal cancer stage was determined according to the pathologic classification of the Union Internationale Contre le Cancer/American Joint Committee on Cancer, 7th edition [21]. Adjuvant therapy was applied according to the colorectal cancer treatment guideline [22].

LH has been the preferred approach for most metastatic origin liver cancers since 2008. The indications for LH at our institution were lesions less than 5 cm in diameter and located in the peripheral segments of the liver and larger tumor lesions located in the left lateral section and not invading major vessels. OH was reserved for cases that were deemed not suitable for LH. However, some patients had the option to choose OH regardless of being suitable for LH because the mechanical stapler used for LH was not covered by the medical insurance system. The techniques for LH or OH have been reported elsewhere [23].

Definitions

Postoperative morbidity and mortality were defined as complications and death, respectively, within 30 days after hepatectomy. Postoperative complications were grouped according to the Clavien–Dindo classification, which simplified the definition of postoperative complications and graded the severity of these events. The details of the Clavien–Dindo classification have been previously reported. Major complications were defined as grades 3, 4, and 5, whereas minor complications were classified as grades 1 and 2 [24].

Follow-up

All patients were regularly followed for at least 3 years after hepatectomy. Follow-up investigations were scheduled at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and then annually until the death of the patient. Recurrence was radiographically documented and histologically confirmed, if feasible. Data analysis was closed on February 1, 2016. OS rate was assessed from the date of hepatectomy until the last follow-up or death from any cause. DFS rate was calculated from the date of hepatectomy until the date of cancer recurrence or death from any cause.

Propensity score matching

The propensity score method attempts to construct a randomized experiment-like situation in which the treatment groups are comparable for the observed prognostic factors. We performed a one-to-one matching analysis between the LH and OH groups based on the estimated propensity scores of each patient. The propensity scores were estimated using a logistic regression model and the following covariates: age, gender, tumor size, location, and surgical procedure.

Statistics

For variables following normal distribution, data were presented as mean and standard deviation and analyzed by Student's *t* test. For data following a non-normal distribution, results were expressed as median and range and compared by Wilcoxon test. Differences in semiquantitative results were analyzed by Mann–Whitney *U* test. Differences in qualitative results were analyzed by x^2 test or Fisher exact test, as appropriate. The survival rates were generated using the Kaplan–Meier method and compared with the log-rank test. Univariate analyses were performed to identify the prognostic variables related to survival. Univariate variables with probability values <0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. All p values were two-sided and the threshold for significance was $p<0.05$. All statistical analyses were conducted using SPSS version 13.0 software (SPSS Inc., Chicago, IL).

Results

A total of 385 patients who underwent LH or OH for liver metastases from colorectal cancer at

Table 1. Demographic and clinical data of patients undergoing LH or OH

Data	*LH (N=79)*	*OH (N=79)*	*p value*
Age, years (range)	69 (65-75)	68 (65-76)	0.580
Sex (male:female)	58:21	53:26	0.384
Tumor size, cm (range)	2.9 (2.2-4.8)	3.3 (2.9-4.7)	0.409
Tumor laterality			0.421
Left	48	43	
Right	31	36	
Surgical procedure			0.533
Left lateral sectionectomy	32	27	
Sectionectomy	19	25	
Wedge resection	28	27	
Preoperative CEA level (ng/ml)			0.259
<5	29	36	
≥5	50	43	
ASA score			0.380
I	54	59	
II	25	20	
Comorbidities			0.704
Hypertension	15	9	
Diabetes Mellitus	5	6	
Stable angina	3	1	
Atrial fibrillation	1	2	
Interstitial lung disease	1	1	
Initial colorectal cancer pathological stage			0.443
I	14	19	
II	29	27	
III	36	33	

CEA: carcinoembryonic antigen, LH: laparoscopic hepatectomy, OH: open hepatectomy

Table 2. Short-term outcomes of LH and OH

Outcomes	*LH (N=79)*	*OH (N=79)*	*p value*
Operative time, min (range)	200 (150-230)	160 (140-240)	0.002
Blood loss, ml (range)	250 (160-420)	351 (150-200)	0.013
Postoperative stay, days (range)	10 (8-25)	13 (10-32)	0.008
Postoperative adjuvant therapy			
Yes	48	38	0.110
No	31	41	0.110

LH: laparoscopic hepatectomy, OH: open hepatectomy

our institution between January 2008 and January 2016 were included in the analysis. Using one-to-one propensity score matching, 79 pairs of LH and OH patients were selected for the final analysis.

Table 1 shows the demographics of the propensity score-matched patients. After propensity score matching, the patient distributions were carefully balanced between the LH and OH groups.

Table 2 provides the details of the short-term outcomes for the two groups. The LH group had a significantly longer operation time. Estimated blood loss and postoperative stay in the LH group were significantly less than that in the OH group (p=0.013 and 0.008, respectively). Table 3 summarizes the postoperative complications in the two groups. There were no significant differences in complications between the two groups. However, major complications tended to be more common in the OH group than in the LH group. There was no mortality.

The median follow-up period was 43 months (range 1–96). The 5-year OS rate was 51%. Kaplan–Meier plots show the 5-year OS rates according to the operative approach. No significant differences in 5-year OS were found between the two approaches (p=0.276) (Figure 1). Univariate analysis revealed that primary tumor pathological stage, disease-free interval, and tumor size were associated with 5-year OS. Multivariate analysis

Table 3. Postoperative morbidity of LH and OH

Morbidity	*LH (N=79) N*	*OH (N=79) N*	*p value*
Overall complications	14	19	0.328
Major complications			
Intraabdominal bleeding	1	1	
Bile leakage	0	3	
Hepatic insufficiency	1	0	
Minor complications			
Intraabdominal abscess	3	4	
Hepatic insufficiency	3	4	
Postoperative ascites	4	5	
Bile leakage	2	2	

showed that disease-free interval was a significant predictor of OS (Table 4). Moreover, the operative approach was not a predictor of 5-year OS.

The 5-year DFS rate was 42% and was not significantly different between the two approaches (p=0.492) (Figure 2). Univariate analysis revealed that primary tumor pathologic stage, disease-free interval, and carcinoembryonic antigen (CEA) level before hepatectomy were associated with 5-year DFS. Multivariate analysis showed that disease-free interval was a significant predictor of DFS (Table 5). Moreover, the operative approach was not a predictor of 5-year DFS.

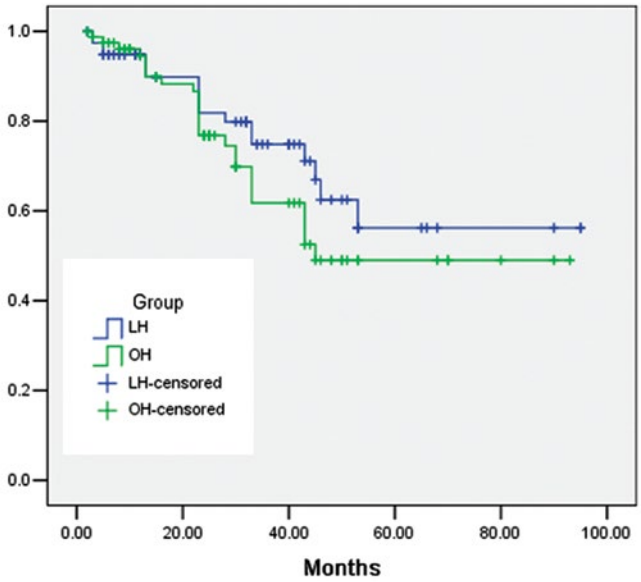

Figure 1. Kaplan–Meier overall survival estimates for patients who underwent laparoscopic hepatectomy and open hepatectomy (p=0.276).

Discussion

Over the next decade, the number of elderly people with liver metastases from colorectal cancer will increase with the increase in the number of the geriatric population [5]. Radical hepatectomy is one of the most important curative modalities for the treatment of liver metastases from colorectal cancer [25,26]. However, many elderly patients have more comorbidities and decreased functional reserves. Based on these reasons, some authors have suggested that non-surgical treatment such as chemotherapy and radiofrequency ablation should be considered for this patient population to reduce operative mortality. To date, some studies have demonstrated the benefits of LH for benign and malignant liver tumors [14-20]; these benefits include better cosmetic effect, less pain, less blood loss, shorter hospital stay, and faster recovery compared with OH [14-20]. When considering the trauma induced by hepatectomy, LH may be optimal for minimizing surgical trauma in elderly patients. Case series and comparative studies of LH procedures in the elderly have been published, but most of these studies were focused on short-term outcomes [17-19].

Table 4. Univariate and multivariate analysis of overall survival

		Univariate analysis			*Multivariate analysis*	
Factors	*OR*	*95% CI*	*p value*	*OR*	*95% CI*	*p value*
Sex (male vs female)	0.899	0.541-1.269	0.329			
CEA (≥5 vs <5 ng/ml)	1.358	0.410-1.840	0.215			
Co-morbidities (yes vs no)	1.158	0.654-1.369	0.258			
Tumor laterality (left vs right)	0.787	0.549-1.684	0.320			
Primary tumor pathological stage						
Stage II vs stage I	2.215	1.515-2.595	0.032	1.236	0.879-1.720	0.098
Stage III vs stage I	3.598	2.358-3.960	0.012	2.369	0.902-2.698	0.060
Disease-free interval (<36 vs≥36 months)	4.540	2.580-5.230	0.002	2.987	2.012-6.980	0.009
Tumor size (≥2.5 vs <2.5 cm)	1.987	1.320-2.014	0.040	1.230	1.158-1.980	0.090

Table 5. Univariate and multivariate analysis of disease-free survival

		Univariate analysis			*Multivariate analysis*	
Factors	*OR*	*95% CI*	*p value*	*OR*	*95% CI*	*p value*
Sex (male vs female)	0.586	0.456-1.362	0.849			
CEA (≥5 vs <5 ng/ml)	1.870	1.158-1.980	0.038	1.503	0.851-1.980	0.128
Co-morbidities (yes vs no)	1.208	0.602-1.403	0.188			
Tumor laterality (left vs right)	1.360	0.650-1.580	0.406			
Primary tumor pathological stage						
Stage II vs stage I	1.894	1.305-2.025	0.042	1.103	0.655-1.889	0.189
Stage III vs stage I	2.036	1.658 -2.541	0.010	2.023	0.778-2.360	0.093
Disease-free interval (<36 vs ≥36 months)	3.026	1.895-4.663	0.010	2.950	1.895-3.562	0.010
Tumor size (≥2.5 vs <2.5 cm)	1.025	0.840-1.586	0.156			

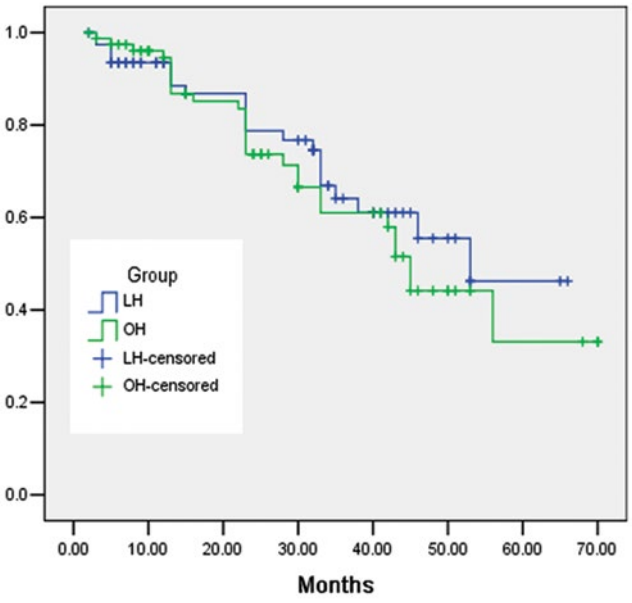

Figure 2. Kaplan–Meier disease-free survival estimates for patients who underwent laparoscopic hepatectomy and open hepatectomy (p=0.492).

Previous studies have indicated that blood loss was associated with morbidity after hepatectomy [27-29]; therefore, blood loss should be minimized using careful operative techniques. Using the laparoscopic approach in our patients, we observed a significant decrease in blood loss compared with the open procedure. In addition, the results of this study significantly favored LH in terms of the length of hospital stay. These results were consistent with the reports of available literature [14-20]. A significant benefit of LH was not observed with regard to the incidence of major complications, although we observed a tendency that favored LH. Additional studies will be required to validate our results.

A major concern in performing LH for liver metastases from colorectal cancer is the long-term survival of patients. Although the oncological outcomes of LH were comparable with those associated with OH, most of the studies excluded elderly patients [14-20]. The suitability of LH in terms of long-term survival outcomes in elderly patients with liver metastases form colorectal cancer remains unclear. Our results indicated that the long-term survival outcomes such as 5-year OS and 5-year DFS in elderly patients who underwent LH were comparable with those of patients who underwent OH [30-35]. Therefore, LH may be feasible for long-term oncological outcomes in elderly patients with liver metastases from colorectal cancer. In addition, our findings suggested that disease-free interval, primary tumor pathological stage, tumor size, and CEA level were prognostic factors in elderly patients with liver metastases from colorectal cancer after hepatectomy. However, multivariate analysis revealed that disease-free interval was the only independent prognostic factor; this is similar to the results of previous studies on the prognostic factors for survival after resection of liver metastases of colorectal cancer [36,37].

To the best of our knowledge, the present study was the first in the English literature that evaluated the surgical and oncological outcomes of LH in elderly patients with liver metastases from colorectal cancer using the propensity score matching method. However, we recognize that our study has several limitations. First, this was not a randomized controlled trial and inherent selection bias may have existed even after adjusting by propensity score matching. Second, this was a single-center Asian study; therefore, our results

may not be directly applicable to Western populations. However, despite these limitations and considering the increased cost of multi-center randomized clinical trials, more investigators are now conducting observational studies such as the present study. We believe that this study could serve as a useful background research for future multi-center randomized clinical trials that aim to investigate LH in elderly patients with liver metastases from colorectal cancer.

In summary, LH was a safe and effective treatment for colorectal cancer liver metastases in the elderly. Advanced age alone should not be considered a contraindication when deciding between LH and OH. However, well-designed multi-center randomized clinical trials will be necessary to make a definitive statement on the efficacy of LH in elderly patients with liver metastases from colorectal cancer.

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Conflict of interests

The authors declare no confict of interests.

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