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ORIGINAL ARTICLE

Laparoscopic hepatectomy for colorectal liver metastases located in all segments of the liver

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Summary

Purpose: *Laparoscopic hepatectomy is not a well-established treatment modality for colorectal liver metastases. Moreover, most reports have been limited to tumors in the anterolateral segments (segments 2, 3, 4b, 5, and 6). We evaluated the short- and long-term outcomes after laparoscopic hepatectomy for colorectal liver metastases located in all segments, including tumors located in the posterosuperior segments (segments 1, 4a, 7, and 8).*

Methods: *TThis retrospective study included 102 patients who underwent laparoscopic hepatectomy for colorectal liver metastases with radical intent between January 2009 and January 2016. The patients were divided into two groups (anterolateral and posterosuperior group) according to tumor location. The clinical and follow-up data of the two groups were retrospectively reviewed.*

Results: *TThere was no 30-day postoperative mortality. Most of the postoperative 30-day complications were classified as minor complications (Clavien–Dindo classification). There was no difference in clinicopathologic characteristics between the two groups. Although posterosuperior group patients had significantly longer operative time (p=0.008) and postoperative hospital stay duration (p=0.041), as well as a greater blood loss (p=0.012), there was no significant difference in rate and severity of postoperative complications (p=0.314 and 1.000 respectively). During a median follow-up period of 41 months, the 5-year overall survival (OS) (p=0.449), and disease-free survival (DFS) (p=0.370) was no significant difference between the two groups.*

Conclusions*: Laparoscopic hepatectomy for colorectal liver metastases located in all segments of the liver can be safely performed in selected patients, with acceptable postoperative morbidity and oncologic results.*

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

Introduction

Due to improved laparoscopic instruments and skills, the technical difficulty of laparoscopic hepatectomy is slowly gaining ground [1-4]. An increasing number of reports on laparoscopic hepatectomy have documented outcomes comparable to those of open hepatectomy [5-12]. The applicability of laparoscopic hepatectomy is currently expanding in terms of indications and extent of resection. Nonetheless, there have been few reports on the use of laparoscopic hepatectomy for colorectal liver metastases [12-17]. Although some reports have shown encouraging surgical and oncologic results, laparoscopic hepatectomy for colorectal liver metastases is still challenging

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due to technological difficulties. Moreover, tumor location also limits the applicability of laparoscopic hepatectomy for colorectal liver metastases. Most reported cases have had peripheral lesions located in the anterolateral segments (Couinaud segments 2, 3, 4b, 5, and 6) [12-17].

More recently, the limitations of laparoscopic hepatectomy because of lesion location are being gradually overcome. Laparoscopic hepatectomy has reportedly been used for lesions located in the posterosuperior segments (Couinaud segments 1, 4a, 7, and 8) [18,19]. However, there has been no report on the surgical and oncologic outcomes after laparoscopic hepatectomy for colorectal liver metastases in the posterosuperior segments. In this study, we analyzed our experience with laparoscopic hepatectomy for colorectal liver metastases located in all liver segments and evaluated the surgical and oncologic outcomes according to tumor location (anterolateral or posterosuperior segments).

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.

Between January 2009 and January 2016, laparoscopic hepatectomies for colorectal liver metastases were performed with radical intent in 102 consecutive patients at our institution. Inclusion criteria were as follows: 1) hepatectomy with radical intent; 2) no other operations; and 3) complete patient data. Exclusion criteria were as follows: 1) palliative hepatectomy; and 2) incomplete patient data. An intent-to-treat analysis that included the conversion cases was used in this study. Abdominal computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) have been crucial preoperative diagnostic tools in identifying the number, location, and size of liver metastases. Intraoperative US during laparoscopic hepatectomy was performed in all cases. These preoperative and intraoperative radiological examinations delineated the location and multiplicity of the tumors and their anatomical relation with the major vascular structures. Laparoscopic hepatectomy was applied regardless of tumor location unless the tumor was larger than 5 cm, had invaded or was close to the main portal pedicle or major hepatic veins, or was located in the suprahepatic junction adjacent to the major hepatic veins. Non-anatomical hepatectomy involving removal of fewer than two segments was usually performed for patients with peripherally located tumors. Major hepatectomy was considered when the tumor was deeply located and the remaining liver function was expected to be adequate. The operative technique for laparoscopic hepatectomy has been described elsewhere [12].

To evaluate the surgical and oncologic outcomes after laparoscopic hepatectomy for colorectal liver metastases with radical intent according to tumor location, the patients were divided into two groups according to the location of the removed tumors. The clinical data of the two groups was retrospectively analyzed: anterolateral group (n=69) included patients with a lesion in the anterolateral segments (Couinaud segments 2, 3, 4b, 5, and 6), and posterosuperior group (n=33) included the patients with a lesion in the posterosuperior segments (Couinaud segments 1, 4a, 7, and 8). The two groups were compared in terms of baseline data, surgical outcomes, 30-day postoperative mortality and morbidity, and survival outcomes. We graded 30-day postoperative morbidity, which included major and minor complications, according to the Clavien–Dindo classification, as previously reported [20]. Major complications were defined as grades 3, 4, and 5. Minor complications were classified as grades 1 and 2 [21-25].

After hepatectomy for colorectal liver metastases, the patients received adjuvant therapy following colorectal cancer treatment guidelines. The follow-up protocol included abdominal imaging and measurement of serum tumor markers every six months. Recurrences were documented radiographically and confirmed histologically, when feasible. OS was assessed from the date of hepatectomy until date of the last follow-up or death from any cause. DFS was calculated from the date of the hepatectomy until the date of cancer recurrence or death from any cause. Data analysis was closed on August 1, 2016.

Statistics

All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed using t-test and presented as mean ± standard deviation when the variables followed a normal distribution. Data following non-normal distribution were compared using Wilcoxon 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 chi-square 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

The clinical and pathologic characteristics of the two patient groups are presented in Table 1. There were no differences between the two groups in terms of clinicopathologic characteristics. Non-anatomical hepatectomy was commonly applied in the anterolateral group and anatomical hepatectomy in the posterosuperior group (p=0.000). Most patients had a single metastasis, but 10 patients had multiple metastases. Multiple metastases were treated by laparoscopic hepatectomy alone in 6 patients and by concurrent intraoperative radiofrequency ablation and hepaetectomy in 4 patients.

During surgery, conversion to open hepatectomy was necessary in 6 patients. Two patients in the anterolateral group needed conversion due to bleeding, while 4 patients in posterosuperior group needed conversion due to bleeding (n=1), due to inadequate margin (n=1) and poor localization of the tumor (n=2). The operative time was significantly longer for posterosuperior group than for anterolateral group. Blood loss was greater in the posterosuperior group than in the anterolateral group (p=0.012) and the rate of periop-

Table 1. Comparison of clinical and pathological characteristics of the two groups

Characteristics	*Anterolateral group (n=69)*	*Posterosuperior group (n=33)*	*p value*
Age, years (range)	59 (48-69)	62 (39-71)	0.548
Gender (Male:Female)	45:24	23:10	0.653
Initial pathological stage (7th)			0.975
I	14	5	
II	25	15	
III	30	13	
Disease-free interval (months)			0.655
<36	45	23	
≥36	24	10	
Preoperative CEA level (ng/ml)			0.430
<5	22	8	
≥5	47	25	
Tumor number			0.868
Single	62	30	
Multiple	7	3	
Surgical procedure			0.000
Nonanatomical hepatectomy	54	12	
Anatomical hepatectomy	15	21	
Postoperative adjuvant therapy			0.191
Yes	28	9	
No	41	24	

Table 2. Comparison of short-term outcomes of the two groups

Outcomes	*Anterolateral group (n=69)*	*Posterosuperior group (n=33)*	*p value*
Conversion	2	4	0.161
Operative time, min (range)	180 (150-230)	210 (170-300)	0.008
Blood loss, ml (range)	250 (190-440)	300 (180-500)	0.012
Blood transfusion	10	7	0.394
Postoperative hospital stay, days (range)	9 (5-18)	15 (13-32)	0.041
Patients with postoperative complications	11	8	0.314
Patients with major complications	2	1	1.000
Highest grade of complications			
Grade 1	6	4	0.851
Grade 2	5	4	0.661
Grade 3	2	1	1.000
Grade 4	0	0	-

Table 3. Univariate Cox regression analysis of overall survival

Variables	*5-year overall survival*	*p value*
Age, years		0.088
<65	61	
≥65	54	
Gender		0.255
Male	58	
Female	51	
ASA score		0.220
I-II	60	
III	54	
Initial pathological stage		0.008
I-II	74	
III	48	
Disease-free interval, months		0.012
≥36	69	
<36	48	
Preoperative CEA level, ng/ml		0.258
<5	58	
≥5	54	
Tumor number		0.091
Single	61	
Multiple	54	
Tumor location		0.449
Anterolateral (segments 2, 3, 4b, 5, and 6)	58	
Posterosuperior (segments 1, 4a, 7, and 8)	55	
Surgical procedure		0.185
Nonanatomical hepatectomy	58	
Anatomical hepatectomy	55	
Postoperative adjuvant therapy		0.080
Yes	62	
No	55	

Table 4. Multivariate Cox regression analysis of overall survival

Variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Age, years			
<65	1.00		0.188
≥65	1.69	0.87-1.98	
Primary tumor pathological stage			0.018
I-II	1.00		
III	2.02	1.55-3.82	
Disease-free interval, months			0.028
≥36	1.00		
<36	1.71	1.17-3.02	
Postoperative adjuvant therapy			
Yes	1.00		
No	1.21	0.57-1.88	0.258
Tumor number			
Single	1.00		
Multiple	1.49	0.84-1.80	0.125

Table 5. Univariate Cox regression analysis of disease-free survival

Variables	*5-year disease free survival*	*p value*
Age, years		0.200
<65	42	
≥65	34	
Gender		0.187
Male	42	
Female	37	
ASA score		0.458
I-II	43	
III	35	
Initial pathological stage		0.001
I-II	61	
III	23	
Disease-free interval, months		0.009
≥36	51	
<36	32	
Preoperative CEA level, ng/ml		0.148
<5	42	
≥5	34	
Tumor number		0.081
Single	52	
Multiple	38	
Tumor location		0.370
Anterolateral (segments 2, 3, 4b, 5, and 6)	42	
Posterosuperior (segments 1, 4a, 7, and 8)	37	
Surgical procedure		0.209
Nonanatomical hepatectomy	45	
Anatomical hepatectomy	38	
Postoperative adjuvant therapy		0.139
Yes	46	
No	35	

erative blood transfusion was similar between the two groups.

There was no 30-day postoperative mortality in either group. Most of postoperative 30-day complications were classified as minor (Clavien–Dindo classification). There was no significant difference in the rate and severity of 30-day postoperative complications between the two groups. The postoperative hospital stay was significantly longer for the posterosuperior group than for the anterolateral group.

During a median follow-up period of 41 months, recurrence was detected in 32 patients (19 patients in the anterolateral group and 12 patients in the posterosuperior group). There was no difference in the recurrence rate between the two groups (p=0.365). The 5-year OS and DFS rates were 58 and 42% in the anterolateral group, and 55 and 37% in the posterosuperior group. There was no statistically significant difference in OS

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

Variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Primary tumor pathological stage			0.010
I-II	1.00		
III	1.87	1.24-2.90	
Disease-free interval, months			0.028
≥36	1.00		
<36	1.87	1.54-3.38	
Tumor number			
Single	1.00		0.201
Multiple	1.24	0.57-1.55	

and DFS rates between the two groups (p=0.449 and 0.370, respectively). Tumor location was not a significant predictor of OS or DFS in univariate and multivariate analyses. Significant predictors of worse OS or DFS were higher primary tumor pathological stage and shorter disease-free interval.

Discussion

Previous reports on laparoscopic hepatectomy for colorectal liver metastases with radical intent have shown better surgical outcomes and similar oncologic outcomes comparable to those of open hepatectomy [12-17]. However, unlike the selection of patients for open hepatectomy, which is determined by tumor location and liver function reserve, selection of patients for laparoscopic hepatectomy has been limited by tumor location in addition to the above-mentioned factors. Currently, colorectal liver metastases located in the anterolateral segments are considered suitable for laparoscopic approach with respect to technical feasibility [12-17]. We successfully performed laparoscopic right posterior sectionectomy for liver tumor in segments 6 and 7 in 2007. Since then, we have not restricted the application of laparoscopic hepatectomy for colorectal liver metastases according to tumor location unless the tumor is close to the hilum or the main hepatic veins. Laparoscopic hepatectomy has been performed for liver tumor located in all liver segments, including the posterosuperior segments. The present study was designed to evaluate the surgical and oncologic outcomes of laparoscopic hepatectomy for colorectal liver metastases on all segments. We were able to successfully perform laparoscopic hepatectomy in most of the included patients with 18.6% postoperative 30-day morbidity rate, and the 5-year OS and DFS rates were 56 and 40%, respectively. In addition, it was demonstrated that patients with colorectal liver metastases in the posterosuperior and anterolateral segments have comparable outcomes. Although the posterosuperior group of patients had longer operative time and postoperative hospital stay and greater blood loss, these differences in early clinical outcome did not affect the postoperative morbidity or oncologic results.

However, laparoscopic hepatectomy for colorectal liver metastases in the posterosuperior segments is still more technically demanding than laparoscopic hepatectomy for anterolateral segments [12-

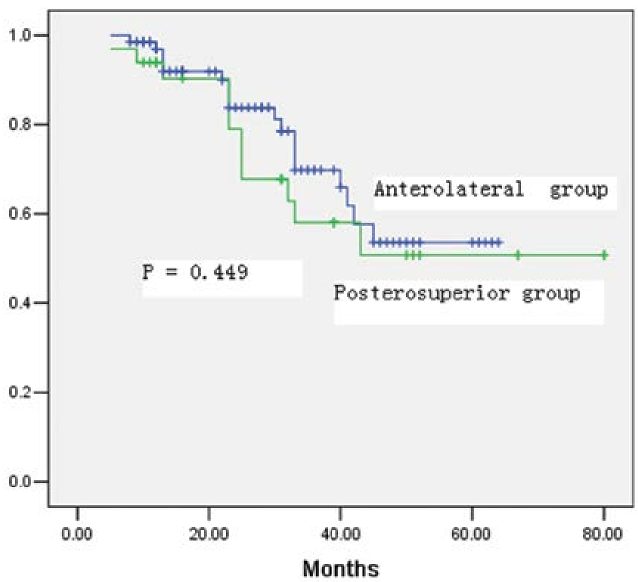

Figure 1. Comparison of overall survival according to tumor location.

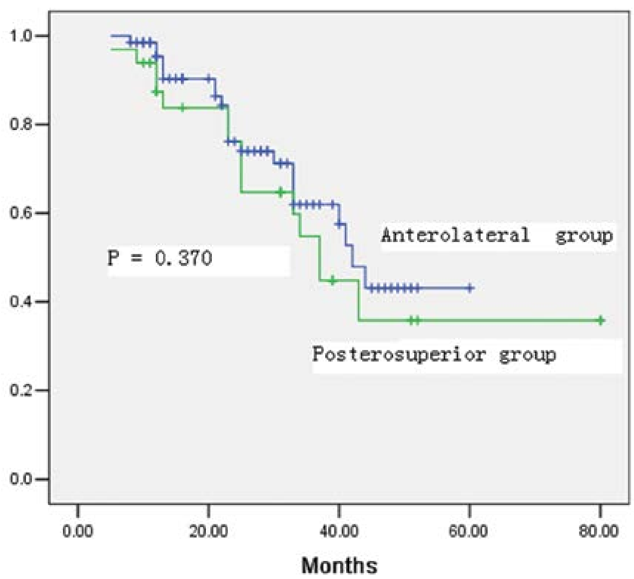

Figure 2. Comparison of disease-free survival according to tumor location.

17]. A minor liver resection in the posterosuperior segments is not as easy as that in the anterolateral segments because of the difficulty in exposing the deeply located tumors and the narrow surgical field [26-29]. Unless the tumor is superficially located, anatomical resection, such as hemihepatectomy or right posterior sectionectomy, could be more appropriate to obtain adequate tumor-free resection margins if these patients have sufficient remaining hepatic reserve [26-29]. For this reason, anatomical resection was performed more frequently in the posterosuperior group than in the anterolateral group. Although there was no difference in tumor-free resection margin between the two groups, 4 patients in the posterosuperior group needed conversion to open laparotomy because of inadequate resection margins or poor tumor localization. Although the routine use of intraoperative US helps avoid these problems, there is still the possibility of suboptimal tumor-free margins in the deep tissues. Therefore, when selecting laparoscopic hepatectomy for colorectal liver metastases in the posterosuperior segments, more caution should be given to obtaining safe deep margins.

Although hepatectomy with radical intent is the most efficient method in treating colorectal liver metastases, there exists the risk of postoperative liver failure [1-5]. For this reason, nonsurgical treatments, such as radiofrequency ablation, have been widely used, owing to their advantage of minimal invasiveness. In particular, radiofrequency ablation has shown similar therapeutic effectiveness to hepatectomy for colorectal liver metastases in selected cases [30]. However, radiofrequency ablation has a high recurrence rate and a high risk of subcapsular tumor seeding [31-33]. Therefore, laparoscopic hepatectomy could be a good therapeutic option for colorectal liver metastases considering that it has therapeutic effects similar to those of open liver resection, and laparoscopic hepatectomy had better surgical outcomes compared with open liver resection.

This advantage of laparoscopic hepatectomy for colorectal liver metastases is considered to be extended to multiple liver tumors. However, reports on the laparoscopic approach for treating multiple liver tumors are rare. In this study, patients with multiple metastases, accounting for about 9.8% of the total number of patients, were managed by laparoscopic hepatectomy alone or in combination with laparoscopic radiofrequency ablation. This study presents the possible therapeutic role of laparoscopic hepatectomy in the treatment of multiple metastases; however, selecting the optimal treatment for multiple metastases is still inconclusive. If metastases are located peripherally, then limited liver resection can be performed for each tumor, and if tumors are located in the same segment or in the hemiliver and liver function reserve is good, then resection that includes all tumors can be chosen. If tumors are deeply located and liver function reserve is not sufficient for liver resection, then laparoscopic radiofrequency ablation can additionally be applied.

Some limitations of this study have to be acknowledged. First, this was a retrospective, single-center study. This limitation should be taken into account when interpreting the results. Another limitation was the small sample of patients participating in this study. Thus, future studies should be conducted, with increased sample sizes for more reliable results.

In conclusion, this study shows that laparoscopic hepatectomy can be safely performed in selected patients with colorectal liver metastases in all segments of the liver with acceptable postoperative morbidity and oncologic results. Our results suggest that the limitation of laparoscopic hepatectomy application according to tumor location for treatment of colorectal liver metastases will be overcome with further accumulation of experience and technical advances.

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Conflict of interests

The authors declare no confict of interests.

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