



Laparoscopic liver resection with simultaneous diaphragm resection

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Background: Liver resection or ablation remains the only curative treatment for patients with colorectal metastases. Simultaneous resection of tumors in the liver with invasion to the diaphragm is challenging and controversial. Therefore, we wanted to assess the safety of simultaneous laparoscopic liver and diaphragm resection (SLLDR) in a large single center.

Methods: Patients who underwent primary laparoscopic liver resection (LLR) for colorectal liver metastases at Oslo University Hospital between 2008 and 2019 were included in this study. Patients who underwent SLLDR (group 1) were compared to patients who underwent LLR only (group 2). Perioperative and oncologic outcomes were analyzed.

Results: A total of 467 patients were identified, of whom 12 patients needed a simultaneous diaphragm resection (group 1) while 455 underwent laparoscopic liver surgery alone (group 2). The conversion rate was 16.7% in group 1 and 2.4% in group 2 ($P=0.040$). In 10 of 12 (83.3%) cases the diaphragm resection was performed *en bloc* with the liver tumor. There was no significant difference in operative time, blood loss, resection margins, hospital stay or postoperative complications. One patient died within 30 postoperative days (0.2%) in group 2 and none in group 1. Overall survival was not statistically different between the groups.

Conclusions: In selected patients, SLLDR can be performed safely with good surgical and oncological outcomes.

Keywords: Laparoscopic hepatectomy; diaphragm resection; combined procedures; colorectal metastases

Submitted Oct 21, 2019. Accepted for publication Dec 27, 2019.

doi: 10.21037/atm.2020.01.62

View this article at: <http://dx.doi.org/10.21037/atm.2020.01.62>

Introduction

Colorectal cancer is common in the Western countries (1). The most common site of distant metastases is the liver. About half of patients diagnosed with colorectal cancer will either present with synchronous liver metastases or

subsequently develop liver metastases after definitive treatment of their primary tumor (2). For patients with isolated liver metastases, multimodal therapy involving surgery is the only potential curative treatment. Recent series have reported 5-year overall survival ranging 35–55% after liver resection for colorectal metastases combined with

adjuvant and optionally neoadjuvant chemotherapy (3).

For colorectal liver metastases invading the diaphragm, liver resection with a simultaneous diaphragm resection is required to achieve negative surgical margins. However, resection of tumors with invasion of adjacent viscera is challenging. Simultaneous liver and diaphragm resection has been reported to be associated with higher morbidity rate and worse overall survival as compared with outcomes of liver resection alone (4-7).

Additionally, the need to resect the diaphragm is often realized by the surgeon intraoperatively, as tumor invasion of the diaphragm frequently is underestimated by the preoperative radiologic work-up (7,8). Differentiation between true invasion and dense adhesions liver adherence to the diaphragm is still difficult, even with the most advanced imaging techniques (8). This emphasizes the importance of having a clear routine to deal with diaphragm resection.

Most reports on this topic refer to open liver surgery, and laparoscopic simultaneous liver and diaphragm resection is thus uncommon and may be considered controversial (4-7,9-12).

During the recent 25 years, laparoscopy has tremendously changed the practice of gastrointestinal surgery (13-16). Besides, continuous improvement in imaging and systemic treatment regimens have altered both indications, techniques and outcomes in hepatic surgery (17).

The aim of this study was to assess the safety and value of simultaneous laparoscopic liver and diaphragm resection (SLLDR) in patients with colorectal liver metastases.

Methods

Patients, management, techniques

Oslo University Hospital is a high-volume institution for laparoscopic and open liver surgery. From August 1998 to January 2019 a total number of 1,233 LLR were performed in our institution, of whom 839 were performed for colorectal liver metastases. We here report outcomes from the cohort of patients that underwent SLLDR. The protocol has been approved by the institutional review board (protocol reference number 2015/13401).

Patients who underwent primary one-stage LLR for colorectal liver metastases from January 2008 to January 2019 were identified and included in this study. Patients that required simultaneous resection of other organs except the diaphragm or combined cryo- or radiofrequency ablations

of the liver were excluded.

Patients who underwent SLLDR (group 1) were compared to patients who underwent LLR only (group 2). Standard preoperative investigations included abdominal and chest computed tomography and clinical biochemistry.

The surgical technique was described previously (18). Laparoscopic ultrasonography and presence of a range of advanced laparoscopic equipment were the prerequisites for LLR. An ultrasonic surgical aspirator, such as SonoSurg® (Olympus, Tokyo, Japan), or Selector®/CUSA® (Integra, Plainsboro, NJ, USA) and a bilobar coagulator LigaSure® (Medtronic, Minneapolis, MN, USA) were the main dissection instruments applied during the procedures.

If necessary, additional laparoscopic ports were introduced to facilitate resection of the diaphragm. A suction tip was introduced into the right pleural cavity via a laparoscopic port in all cases to evacuate pneumothorax. After diaphragm resection the defect was sutured by resorbable thread.

Postoperative analgesia consisted of a nonsteroidal anti-inflammatory drug and intravenous paracetamol. Opioids were given if additional analgesia was required. The patients were encouraged to mobilize early and resume feeding as soon as tolerated. Tumor size was measured following specimen fixation in formaldehyde during the histopathologic analyses of the resected specimens. Procedures with a resection margin ≥ 1 mm and no signs for residual tumor in the liver were considered as R0-procedures. Perioperative mortality was defined as death within 90 days or before hospital discharge.

Following diaphragm resection, patients had a plain thoracic X-ray direct postoperatively and on the first postoperative day to evaluate any residual pneumothorax.

Patients were routinely followed every 4 months up to 24 months and then every 6 months up to 60 months by outpatient visits with clinical examinations, carcinoembryonic antigen assay and imaging studies.

Statistics

Procedures were analyzed on intention to treat basis, i.e., cases converted to laparotomy were not excluded from the analyses. The data are presented as median (range), or number (percentage). To compare proportions between groups the Chi-square test or the Fisher exact test were used as appropriate. The Mann-Whitney test was used to compare continuous variables. The Life Tables and the Kaplan-Meier method were applied for survival analyses.

Table 1 Patient characteristics

Parameters	Group 1 (N=12)	Group 2 (N=455)	P value
Age (years)	66 [50–76]	69 [26–89]	0.566
ASA score	2.5 [2–3]	2 [1–4]	0.391
Female/male	4/8	187/268	0.769
BMI (kg/m ²)	26.3 [21.3–34.7]	24.8 [13.8–40.9]	0.094

Values are presented as median (range) or number. ASA, American Society of Anesthesiologists; BMI, body mass index.

Time defined survival values were presented in percentage \pm standard error. Log-rank test was applied for comparison of survival between groups. Length of survival was described as mean [95% confidence interval (CI)].

Results

A total of 467 patients fulfilled the inclusion criteria, of whom 12 patients needed a simultaneous diaphragm resection (group 1) while 455 underwent laparoscopic liver surgery alone (group 2). Patient demographic data was similar in both groups (Table 1). The median follow-up was 31 [1–128], and 26 [0–110] months for the patients in group I, and II respectively.

All patients who had intraoperative suspicion of tumor invasion of the diaphragm underwent SLLDR. Only in 3 cases (25.0%) suspicion of tumor invasion was preoperatively based on CT and/or MRI. *En bloc* technique for SLLDR was applied in 10 out of 12 cases (83.3%). Histology confirmed the diaphragm invasion of the diaphragm in 9 cases (75.0%), including in all three cases of preoperative suspicion based on preoperative imaging. In both cases of SLLDR where *en bloc* techniques were not applied, histology confirmed that there was no tumor invasion of the diaphragm. Details of cases in the group 1 are summarized in Table 2. Overview of types of liver resections in the group 2 are presented in Table 3.

Two patients (16.7%) in group 1 were converted to open surgery, three additional patients were converted to hand-assisted laparoscopic surgery (HALS), whereas 11 patients (2.4%) were converted to laparotomy in group 2 (P=0.040) (Table 4).

Operative time and blood loss were similar in two groups. One patient in group 2 died within 30 days (severe bleeding from the right hepatic vein, expired in a multiorgan failure postoperatively), there was no mortality in group 1. The median tumor size (largest tumor) was 22 [8–40] mm in

group 1 and 21 [3–110] mm in group 2 (P=0.977). The rate of R0 resections was 91.7% and 77.8% in groups 1 and 2 respectively (P=0.508). There was no statistical difference in the rate of postoperative complications and postoperative stay between the groups (Table 4).

Six out of 12 patients in group 1 developed recurrences, including both hepatic and extrahepatic recurrences in five cases and recurrence in the lungs only in one case. Carcinomatosis developed in one case. There was no statistical difference between the groups in regard to overall survival rates (Table 5, Figure 1). Five-year actuarial overall survival was 58% and 49%, and mean overall survival was 89 (95% CI: 54–124) and 66 (95% CI: 61–71) months respectively.

Discussion

Laparoscopic liver resection has been proven a good alternative to open liver resection for patients with colorectal liver metastases (14,15). A number of recent comparative studies, meta-analyses and two randomized trials have shown benefits of LLR over open liver resection in terms of perioperative outcomes, especially less morbidity and shorter hospital stay and equivalent oncologic outcomes (14–16,19).

In the present series we showed the technical feasibility, safety and efficacy of diaphragm resection during laparoscopic liver surgery. This is reflected in median operative time, blood loss, postoperative hospital stay and rate of postoperative morbidity compiling 125 minutes, 100 mL, 2.5 days and 8.3%—data that corresponds to LLR without diaphragm resection in our series. Diaphragm resection was performed without compromising oncologic outcomes, with a R0 resection rate of 92% and 5-year overall survival of 58%.

Irrespective to the operative approach, the impact of diaphragm invasion is sparsely studied. Only few small

Table 2 Review of cases of simultaneous laparoscopic liver and diaphragm resection

Case N/type of resections	Preoperative suspicion of ingrowth in the diaphragm	Conversion	En bloc resection	Number of liver resections	Histology proved ingrowth	R status	Operative time, min	Blood loss, mL
1/segment 4	No	No	No	1	No	R0	113	<50
2/segment 8	Yes	No	Yes	1	Yes	R0	116	200
3/segment 7	No	HALS	Yes	1	Yes	R0	210	100
4/segment 2+3	No	No	No	2	No	R0	105	<50
5/segment 4+7+8	No	No	Yes	5	Yes	R0	Not available	300
6/segment 6	Yes	No	Yes	1	Yes	R0	93	<50
7/segment 5/6+6/7	No	Yes	Yes	2	Yes	R0	125	<50
8/segment 6/7	No	No	Yes	1	No	R0	116	<50
9/segment 5/6+7	No	No	Yes	2	Yes	R0	162	300
10/segment 7	Yes	HALS	Yes	2	Yes	R1	200	600
11/several segments affected	No	Yes	Yes	6	Yes	R0	195	<50
12/segment 7	No	HALS	Yes	1	Yes	R0	153	1,200

HALS, hand-assisted laparoscopic surgery.

Table 3 Overview of type of liver resections in the group 2

Type of resections	Group I (N=455)
Left lateral sectionectomy	30
Left lateral sectionectomy and atypical resection(s)	17
Left formal hemihepatectomy	8
Left formal hemihepatectomy and atypical resection(s)	4
Atypical resection(s), left lobe	93
Right formal hemihepatectomy	22
Right formal hemihepatectomy and atypical resection(s)	3
Anatomic segmentectomy 1 and atypical resection	1
Anatomic segmentectomy 4b	1
Anatomic segmentectomy 6–7 and atypical resections	1
Atypical resection(s), right lobe	199
Atypical resection(s), both lobes	76

Table 4 Surgical outcomes

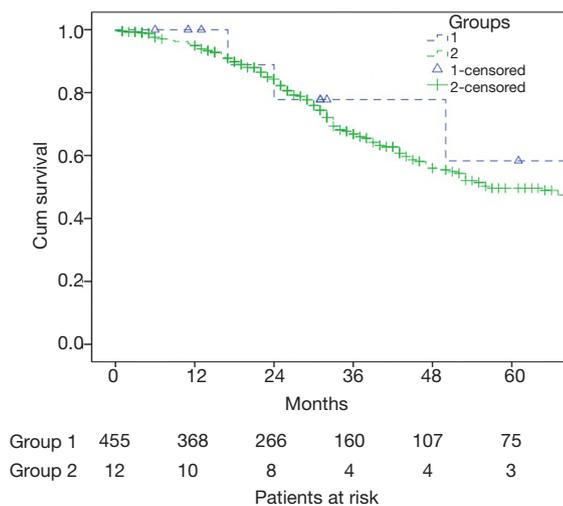
Parameters	Group 1 (N=12)	Group 2 (N=455)	P value
Intraoperative parameters			
Conversions	2 (16.7)	11 (2.4)	0.040
Operative time, min	125 [93–210]	119 [21–430]	0.300
Blood loss, mL	100 [<50–1,200]	200 [<50–4,400]	0.412
Postoperative parameters			
Postoperative complications	1 (8.3)	81 (17.8)	0.347
Postoperative stay, days	2.5 [1–14]	2 [1–35]	0.430

Values are presented as median [range] or number (percentage).

Table 5 Overall survival

Variable	Group 1 (N=12)	Group 2 (N=455)	P value
Mean survival, months	89 [54–124]	66 [61–71]	0.491
1-year overall survival rate, %	100	95±1	
3-year overall survival rate, %	78±14	67±3	
5-year overall survival rate, %	58±20	49±3	

Values are presented as mean [95% confidence interval] or number ± standard error.

**Figure 1** Kaplan-Meier survival curves.

series and one multicenter database study have analyzed specifically the surgical results of simultaneous liver and diaphragm resection (4-7,9-12).

Some authors advocated blunt dissection to avoid unnecessary resection of the diaphragm, based on a low rate of reported true invasion to the diaphragm (20,21).

In contrast, we applied *en bloc* techniques in 10 of the 12 SLLDR (83.3%). *En bloc* techniques was applied in all cases of dense adhesions of the liver to the diaphragm to avoid both tumoral rupture and bleeding due to parenchymal tear. R0 resection was obtained in 9 cases (90%) of *en bloc* SLLDR. Histology confirmed the tumor invasion to diaphragm in 9 cases (90%) of *en bloc* SLLDR. Thus, we suggest to perform diaphragm resection using an *en bloc* technique when a liver tumor is adhesive to the diaphragm, to avoid tumor rupture. In the two cases where *en bloc* resection was deemed unnecessary, histology confirmed the absence of tumor invasion.

It has been argued that in spite of improvements in imaging techniques, a reliable modality for preoperative diagnostics of tumor invasion to the diaphragm still does not exist (8). In our series imaging modalities showed only 33 % of sensitivity to diagnose a tumor invasion to the diaphragm (preoperative radiologic suspicion in 3 out of 9 cases of histologically confirmed invasion), but 100% of specificity (all cases of preoperative radiologic suspicion were confirmed by histologic report). This underlines the importance of intraoperative diagnostics including intraoperative laparoscopic ultrasonography (22).

Technically, there are several challenging factors which have precluded surgeons from diaphragm resection during laparoscopic liver surgery. Tumors located in posterosuperior segments are more likely to grow into the diaphragm, and tumors in these segments are considered to be technically challenging (23,24). Patients with tumors in posterosuperior segments are still reserved for open liver resection in many institutions worldwide, although many leading hepatobiliary centers routinely perform LLR in these tumor locations (25,26).

However, SLLDR is technically more challenging to the surgeon than LLR only. This was reflected in a significantly higher rate of conversions to laparotomy in the group of SLLDR, 16.7% (2 cases) versus 2.4% in the group of LLR. Extensive adhesions were present in these two cases necessitating the conversions. There were also 3 (25%) additional cases of conversions to HALS. In all these three cases tumors were localized in the segment 7. We found HALS to be useful especially when performing diaphragm resection as it improves exposure and eases the closure of the defect in the diaphragm (27).

Development of pneumothorax might complicate good operative exposure. Different techniques can be applied to deal with this challenge. A transthoracic catheter may be utilized to evacuate the carbon dioxide from the pleural cavity, this allows retaining the diaphragm in a concave position (12). In our series, we have not considered this maneuver since the pneumothorax could be managed by placement of suction tip into the right pleural cavity. Some surgeons routinely apply a transthoracic trocar to improve surgical exposure when approaching tumors in the posterosuperior segments (28-32). In case of intraoperative finding that requires diaphragm resection this trocar port may be utilized for external suction of pneumothorax. We neither apply a transthoracic catheter or a transthoracic trocar, nor place thoracic drain and the end of the operation. In our experience, the residual pneumothorax dissolves rapidly and is usually not identifiable on the second postoperative day. It is possible that the routine use of a transthoracic trocar may prevent conversion to HALS. Interestingly, Lainas and colleagues reported a similar (14.3%) rate of conversions to open surgery in a series of seven patients undergoing SLLDR (12).

We consider the relatively high conversion rate in the SLLDR group as acceptable, as oncologic principles must prevail over the surgeon's ambition to treat every patient with minimally invasive techniques. In view of the technical complexity of SLLDR, this procedure probably should be

limited to expert centers.

Our study has several limitations. Most importantly, the number of patients in group 1 is low, so type 2 error may be present. The retrospective design is also a limitation, and there might be a selection bias where patients needing more complex diaphragm resections were operated with open liver resection. Further studies on this topic are required.

Conclusions

SLLDR can be performed safely with good short- and long-term outcomes in patients with colorectal liver metastases. We recommend *en bloc* resection when a liver tumor invades the diaphragm, and we find hand-assisted laparoscopic surgery useful in difficult cases.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: AMK serves as an unpaid editorial board member of Annals of Translational Medicine from Dec 2018 to Nov 2020. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol has been approved by the institutional review board (protocol reference number 2015/13401).

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Cite this article as: Kazaryan AM, Aghayan DL, Fretland ÅA, Semikov VI, Shulutko AM, Edwin B. Laparoscopic liver resection with simultaneous diaphragm resection. *Ann Transl Med* 2020;8(5):214. doi: 10.21037/atm.2020.01.62