research article

Laparoscopic parenchyma-sparing liver resection for colorectal metastases

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Background. Laparoscopic liver resection (LLR) of colorectal liver metastases (CLM) is increasingly performed in specialized centers. While there is a trend towards a parenchyma-sparing strategy in multimodal treatment for CLM, its role is yet unclear. In this study we present short- and long-term outcomes of laparoscopic parenchyma-sparing liver resection (LPSLR) at a single center.

Patients and methods. LLR were performed in 951 procedures between August 1998 and March 2017 at Oslo University Hospital, Oslo, Norway. Patients who primarily underwent LPSLR for CLM were included in the study. LPSLR was defined as non-anatomic hence the patients who underwent hemihepatectomy and sectionectomy were excluded. Perioperative and oncologic outcomes were analyzed. The Accordion classification was used to grade postoperative complications. The median follow-up was 40 months.

Results. 296 patients underwent primary LPSLR for CLM. A single specimen was resected in 204 cases, multiple resections were performed in 92 cases. 5 laparoscopic operations were converted to open. The median operative time was 134 minutes, blood loss was 200 ml and hospital stay was 3 days. There was no 90-day mortality in this study. The postoperative complication rate was 14.5%. 189 patients developed disease recurrence. Recurrence in the liver occurred in 146 patients (49%), of whom 85 patients underwent repeated surgical treatment (liver resection [n = 69], ablation [n = 14] and liver transplantation [n = 2]). Five-year overall survival was 48%, median overall survival was 56 months.

Conclusions. LPSLR of CLM can be performed safely with the good surgical and oncological results. The technique facilitates repeated surgical treatment, which may improve survival for patients with CLM.

Key words: laparoscopic parenchyma-sparing liver resection; colorectal cancer; liver metastases; survival

Introduction

Colorectal cancer is the third most common cancer worldwide.[1] Liver resection is considered the only curative treatment for colorectal liver metastases (CLM), with postoperative 5-year survival rates of 30–58%.[2-5] Parenchyma-sparing liver resection (PSLR) has, in many centers, become an essential part of multimodal treatment of CLM. The parenchyma-sparing approach allows radical resection with maximum preservation of liver parenchyma, thereby decreasing the risk of postoperative liver failure and facilitating repeated resections in the case of liver recurrence.[6-13]

Laparoscopic liver resection (LLR) has progressively developed during the past two decades and the advantages are well-known.[14-20] Our experience in LLR has been reported previously.[18,21-27] The

short- and long-term outcomes after laparoscopic parenchyma-sparing liver resection (LPSLR) for CLM have been minimally reported in the literature.[28-30] In this study we report short and long-term outcomes after 18 years of LPSLR for CLM in a single center.

Patients and methods

Rikshospitalet is the tertiary referral center for hepato-pancreato-biliary surgery for the South-Eastern Regional Health Authority in Norway. Between August 1998 and March 2017, LLRs were performed in 951 procedures. Of these, patients who primarily underwent LPSLR for CLM between August 1998 and March 2016 were identified from the continuously updated database and included in the study. Patients who previously underwent open liver resections were excluded from the study. LPSLR was defined as non-anatomic laparoscopic liver resections. In one case LPSLR was performed in a patient with a transplanted liver. Patients who underwent hemihepatectomy or sectionectomy were excluded, as were patients with planned two-stage procedures. Data were collected from Electronic Health Records. The study was performed in accordance with the Declaration of Helsinki, and all patients signed informed consent for the procedures.

Standard preoperative investigations included contrast-enhanced X-ray computed tomography (CT) scans of the thorax and abdomen, clinical biochemistry, magnetic resonance imaging (MRI) of the liver (if required) and positron emission tomography (PET) scan (if required).

Synchronous CLM was defined as liver metastases detected within 12 months of diagnosis of the primary CRC, otherwise metastases were defined as metachronous.

The surgical technique for LLR at our centre has been described previously.[18,21] Laparoscopic ultrasonography and advanced laparoscopic equipment were preconditions. The main dissection instruments were LigaSure® (Covidien, Mansfield, MA, USA), Thunderbeat® (Olympus, Tokyo, Japan) or Cayman® (B.Braun, Melsungen, Germany), sometimes assisted by ultrasonic aspirators, mainly CUSA® (Integra, Cincinnati, OH, USA), SonoSurg aspirator® (Olympus, Tokyo, Japan) and Söring aspirator® (Söring, Quickborn, Germany). Ultrasonic dissectors, as Sonicision® (Covidien, Mansfield, MA, USA) or Harmonic Scalpel® (Ethicon, Sommerville, NJ, USA) were mostly used to achieve a superficial parenchymal transection. Surgical clips and the LigaSure® were used in small and medium-sized vessel transections, whereas the Endo-GIA®(Covidien, Inc.) was applied for transection of major vessels.

Non-steroidal anti-inflammatory drugs and intravenous paracetamol were used for postoperative analgesia. Opioids were given if required. Patients were encouraged to mobilize early and resume oral intake as soon as tolerated.

Tumor size was measured following specimen fixation in formaldehyde during the histopathologic analyses of resected specimens. The distance from the tumor to the resection margin was measured macroscopically and microscopically after fixation. All resection margins were assessed microscopically with regard to tumor tissue, a resection margin of less than 1 mm was defined as positive (R1). In cases where multiple resections were performed, the narrowest resection margin was recorded.

Postoperative complications were categorized in accordance to the Accordion classification.[31,32]

Patients were treated with neoadjuvant and adjuvant chemotherapy following national guidelines. The data are presented as median (range) and/or number (percentage). Overall survival was estimated from liver resection until death and recurrence-free survival was estimated from liver resection until the first registered recurrence of the disease or progression in cases with extrahepatic metastases. Survival probabilities were calculated using the Kaplan–Meier method. SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA: IBM corp) was used for statistical analysis.

Results

Perioperative data

Between August 1998 and March 2016, a total of 296 patients underwent LPSLR as the primary surgical treatment for CLM at Oslo University Hospital. Baseline characteristics are summarized in Table 1. Resection of solitary metastases was performed in 204 patients (69%), multiple resections were performed in the remaining 92 patients (31%). Two concomitant liver resections were performed in 66 cases, three resections in 12 cases, four resections in 12 cases, five and seven resections in the two remaining cases. In total, 432 liver specimens were resected in 296 procedures. Median resection margin was 3 mm (range 0 to 30 mm). The total

TABLE 1. Patient characteristics (N = 296)

Age, years, median (range)	66 (29–89)
Gender (female/male)	110/186
BMI, kg, median, (range)	25 (16–42)
ASA score	2 (1–3)
Synchronous/metachronous	224/72
Neoadjuvant chemotherapy yes/no/no information	122/168/6
Preoperative CEA, median (range)	12 (1–498)
Extrahepatic disease at the time of liver resection, n (%)	21 (7.1)
Liver involvement (unilobar/bilobar)	233/63

ASA = American Society of Anestesiology; BMI = body mass index; CEA = carcino-embryonic antigen

TABLE 2. Intraoperative details and postoperative complications

Operative time, min, median (range)	134 (20-373)
Blood loss, ml, median (range)	200 (<50-4000)
No. of resected specimens pr. procedure, 1/ 2/ 3/ 4/ 5/ 7 Total	204/ 66/ 12/ 12/ 1/ 1 432
Total No. of removed lesions	448
Max diameter of lesions, mm, median d (range)	22 (4-80)
Resection margin, R0 / R1 (n=294) Median, mm (range)	239 / 55 3 (0-30)
Conversion to open access, n (%)	5 (1.7)
Combination with RFA or cryoablation, n (%)	20 (6.7)
Simultaneous resection with primary, n (%)	11 (3.7)
Postoperative complications, Accordion, n (%) Grade 2 / Grade 3 / Grade 4 / Grade 5	43 (14.5) 19/ 14/ 8/ 2
Postoperative hospital stay, days, median (range)	3 (1-35)

RFA = Radiofrequency ablation

TABLE 3. Long-term outcomes

Disease recurrence, n (%)	189 (64)
Liver recurrence, n (%)	146 (49.3)
Isolated liver recurrence, n (%)	75 (25.3)
Recurrence in resection bed, n (%)	7 (2.3)
Repeat liver resection, n (%)	69 (23.3)
Secondary RFA, n (%)	14 (4.7)
Median overall survival, months (95% confidential interval)	56 (46-66)
3-year overall survival rate, %	68
5-year overall survival rate, %	48
3-year recurrence-free survival rate, %	36
5-year recurrence-free survival rate, %	34

RFA = Radiofrequency ablation

number of removed lesions was 448 and the median diameter was 22 mm (range: 4 to 80 mm). The resected tumors were located in all liver segments (Table 2).

Five procedures (1.7%) were converted to open surgery. The reason for conversion was hemorrhage (n = 3), unfavorable location of tumor (n = 1) and small intestine perforation (n = 1). In 20 cases LPSLR was combined with ablation (n = 18) or cryoablation (n = 2). 11 patients underwent synchronous resections for colorectal cancer. Median operative time was 134 min (20–373), while median blood loss was 200 ml (<50–4000). Postoperative complications developed in 43 patients (14.5%) and were graded according to the expanded Accordion classification (Table 2). The median hospital stay was 3 days (range: 1–35). There was no 90-day mortality in this study. Perioperative adverse events are described in Table 2.

Long-term outcomes

Median observation time was 40 months (4 to 191). Twenty-one patients had extrahepatic metastases (16 with lung metastases, two with metastases on the peritoneum, two with the metastases in the brain and the lungs, and one with metastasis in the spine) at the time of liver resection.

Disease recurrence or progression of extrahepatic metastases occurred in 189 (64%) patients on a median follow-up of 6 months. Recurrence in the liver occurred in 146 (49.3%) patients with a median follow-up of 6 months, including 7 patients (2.3%) who experienced local recurrence. Isolated hepatic recurrences developed in 75 patients. The most common sites of recurrence were liver, lungs, peritoneum and brain. A total of 69 patients underwent repeated liver resections, of whom 43 had laparoscopic and 26 had open resections. Additionally, 14 patients underwent secondary radiofrequency ablation and two patients had liver transplantation for liver recurrences (Table 3).

Median overall survival was 56 months One-, three- and five-year overall survival rates were 97%, 68% and 48%, respectively (Figure 1).

One-, three- and five-year recurrence-free survival was 50%, 36% and 34%, while the median recurrence-free survival was 12 months (Table 3).

Discussion

In this study, we report a single center experience of LPSLR for CLM. In 1960's and 1970's the major-

ity of patients with CLM (70–80%) were never candidates for resection, but nowadays a large portion of patients undergo surgery due to significant improvements in preoperative investigations, surgical techniques, anesthesia, chemotherapy regimens and the expansion of resectability criteria.[4,5] Based on oncologic reasoning at that time, hemihepatectomies were considered the only curative option in patients with CLM. Nevertheless, over the years, PSLR has increasingly been used for CLM.[6,33] There are two main reasons for this: the evolution of the concept of resectability and the increased knowledge on tumor biology.[34,35]

Over the past decades, the concept of tumor resectability in CLM has changed significantly. While in the 1970s, resection was considered only in patients with solitary liver metastasis, nowadays resection of CLM is considered regardless of tumor size and number, provided that a resection with negative margins is possible, that stable disease can be achieved, that the remaining parenchyma is sufficient to prevent liver failure, and that there is no unresectable extrahepatic disease.[36]

There are two known mechanisms for hepatic spread of colorectal cancer: metastasis from the primary tumor, and metastasis from other existing metastases. In contrast to hepatocellular carcinoma, tumor cells from CLM do not migrate into intrahepatic portal branches to form secondary intrahepatic metastases. Instead, intrahepatic lymphatic invasion can be responsible for ''remetastasis'' from liver metastases and may be a prognostic factor for CLM.[37-42]

PSLR is an essential part of multimodal treatment of CLM, as it avoids unnecessary removal of normal parenchyma and is associated with less surgical stress, fewer postoperative complications and feasibility of future resections.[6,33,43]

LLR is becoming an important alternative to conventional open surgery. In this study we included patients who primarily underwent LPSLR for CLM. All resections aimed to achieve complete tumor resection and to preserve as much liver parenchyma as possible. We report both perioperative and long-term oncologic outcomes. Five patients (1.7%) were converted to open surgery in our series, which is a lower conversion rate than reported for both minor and major laparoscopic hepatectomies by other groups.[16,28,29,44] Postoperative complications developed in 43 cases (14.5%) and the median postoperative length of stay was 3 days. Perioperative outcomes in this study are consistent with earlier reported surgical results after open and laparoscopic PSLR for CLM.[7,9-12,28,29]
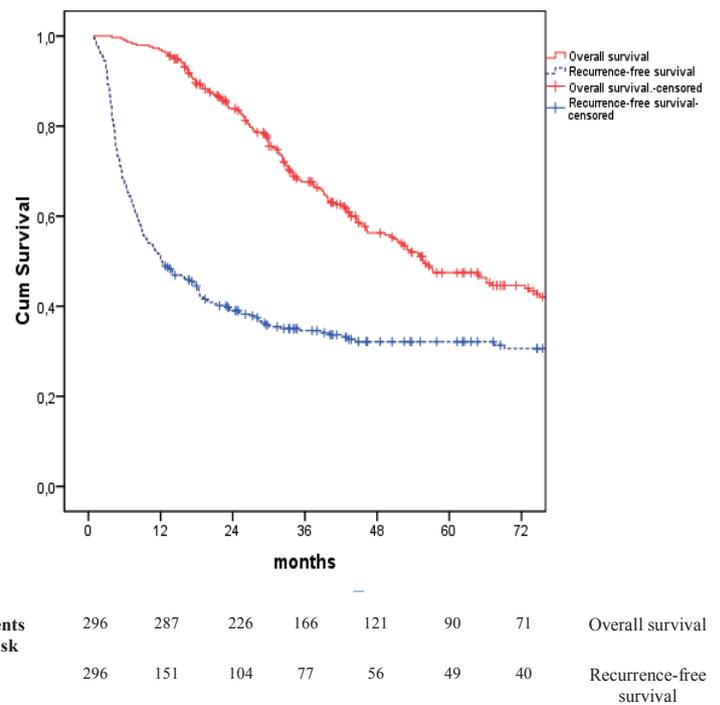

FIGURE 1. Kaplan-Meier survival curves.

Previous studies have indicated that survival rates were higher in patients with resection margins larger than 10 mm compared to those with the resection margins less than 10 mm.[45,46] Other studies have opposed these findings and indicate that predicted margins of less than 10 mm should not be an exclusion criteria for resection in these patients.[40,47] Moreover, recently two large studies suggested that a one mm cancer free margin can be considered oncologically adequate for resection of CLM.[27,48]

In the present study, isolated hepatic recurrence developed in 75 cases, for which repeated hepatectomy was performed in 68% (51 of 75) (18 open, 33 laparoscopic). Local recurrence developed in seven patients (2.3%), five following R1 resection (9%) and two following R0 resection (0.8%). The relatively low number of local recurrences after R1 resections can be explained by the use of energy-based surgical instruments for parenchyma transection, that induce thermal damage to the surrounding tissue and thus create an additional zone of tissue necrosis. As a result, the true resection margins may be several millimeters wider than those estimated by the pathologist.

In our study liver recurrences were frequently resectable. A total of 69 repeat liver resections (51 with isolated liver recurrence and 18 with extrahepatic resectable metastases) were performed.

Tanaka *et al.*[49] showed that minor resections may offer a long-term survival advantage compared to a major resection in patients with multiple CLM. In our study 80 patients received solely multiple LPSLR, and the five-year survival for this group was 44%.

In the study published in 2014, Evrard *et al.*[50] combined PSLR with RFA in 288 patients, five-year overall survival was 37%, compared to 39% for the 18 patients that underwent resection combined with local ablation in our study.

These outcomes demonstrate that multiple simultaneous LPSLRs are feasible and may be preferred over single major resection in a substantial portion of patients. In patients with additional unfavorable located lesions, PSLR can be combined with local ablation avoiding formal resections with acceptable oncological results. In addition, the patients with formal resections compared with parenchyma-sparing technique have reduced chance of further surgical treatment.[6]

Alvarez *et al.*[6] showed in a systematic review that five-year overall survival rates varied from 27% to 60% for anatomic and from 29% to 61% for non-anatomic liver resection, compared to 48% in our study.

In conclusion, outcomes after laparoscopic parenchyma-sparing liver resection are comparable to those after open major and minor hepatectomy. In centers with sufficient expertise, this may be a good treatment option for patients with CLM.

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