

Good results after repeated resection for colorectal liver metastases

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ABSTRACT

INTRODUCTION: Our study aim was to evaluate the perioperative events, postoperative events and survival after a second liver resection due to colorectal liver metastases (CLM), compared with a matched control group that had only undergone primary liver resection due to CLM.

MATERIAL AND METHODS: Retrospective review of charts from patients having undergone a second liver resection due to CLM. A control group was identified by selecting the first liver resection due to CLM occurring after a second resection due to CLM. Twenty-four patients were hereby included in both the primary resection group (PRG) and the second resection group (SRG). The groups were compared statistically with regard to demographics, primary tumour and hepatic involvement.

RESULTS: No significant differences between the groups were noted in terms of perioperative events, although there was a trend towards PRG resections involving more liver segments than SRG resections ($p = 0.08$). The rate of postoperative surgical complications was 17.4% in the PRG and 4% in the SRG ($p = 0.18$). The admission time was 10.6 days in the PRG and 8.4 days in the SRG ($p = 0.71$). 30-day mortality was 4% in the PRG and 0% in the SRG ($p = 0.41$). The five-year survival was 36% in the PRG and 42% in the SRG ($p = 0.17$).

CONCLUSION: This study shows that a second hepatic resection due to recurrent CLM is safe and feasible. It also shows that patients undergoing a second liver resection due to CLM have five-year survival rates comparable to those of patients who have only undergone one hepatic resection due to CLM.

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The liver is the most prevalent target organ for distant metastases from colorectal cancer [1]. Without treatment, the median survival in colorectal cancer complicated by liver metastases is 6-12 months [2]. It is well-established that the treatment of choice for resectable colorectal liver metastases (CLM) is surgery [1] where the reported five-year survival rates are around 40% [3]. Unfortunately, up to 70% of patients will develop recurrence of the disease after a liver resection. However, in 30% of the cases, recurrent metastases will be isolated to the liver [3], which makes these patients potential candidates for repeated liver resection. In the past dec-

ade, reports have revealed that repeat hepatic resection in selected patients with recurrent CLM enjoys a long-term survival comparable to that of patients undergoing primary hepatic resection for CLM [1, 3, 4].

Most of the newer and larger studies of repeat hepatic resections have focused on survival and on finding predictors of long-term survival [1, 3, 4]. The majority of these studies compared results after the second liver resection with historical control groups.

In the present study, we evaluated the peri- and postoperative events and long-term survival of patients who underwent a second liver resection due to recurrent CLM, and these results were compared with those of a matched group of patients who only underwent primary liver resection due to CLM.

MATERIAL AND METHODS

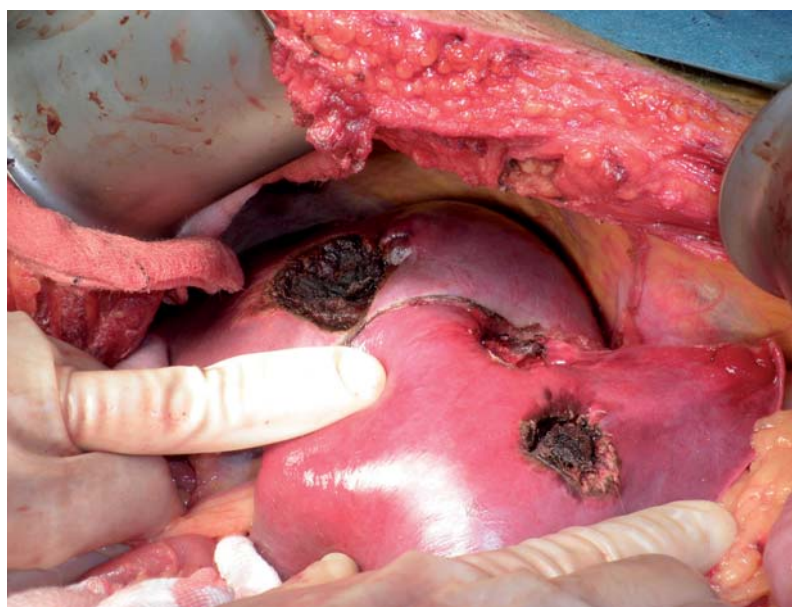
The data in this study were collected by retrospective review of files from patients who underwent liver resection due to recurrent CLM.

We collected data regarding patient demographics (gender, age, American Society of Anaesthesiologists classification (ASA classification)), primary tumour (colon or rectal carcinoma, Duke's classification), hepatic in-

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Liver with resection cavities after local resection for colorectal liver metastases.

involvement (number and size of metastases and whether the involvement was uni- or bilobular), perioperative events (number of segments involved in liver resection, preoperative ultrasound, intravenous infusions, radio-frequency ablation, macro- and microscopical radical resection (R0)), postoperative events (intensive care unit (ICU) stay, admission time and medical/surgical complications, 30-day mortality) and survival.

All surgical complications were noted and our primary focus was on:

- Bile leakage requiring endoscopic or surgical intervention
- Postoperative bleeding requiring surgical intervention
- Wound infection/rupture needing surgical intervention
- Intra-abdominal abscesses requiring percutaneous ultrasound drainage or reoperation
- Liver insufficiency as defined by the “50-50” criteria [5].

Medical complications were defined as complications needing medical treatment, i.e. pneumonia, respiratory distress, renal dysfunction, etc.

We unfortunately had no access to data regarding oncological treatment of these patients. The standard oncological regimen was adjuvant FOLFOX supplemented by biological target therapy depending on tumour biology.

Patients were identified from our Unit’s liver database in the period from 1 January 1996 to 1 February 2010. The exclusion criteria were: Non-CLM-related liver resection, primary liver resection for CLM, only radio-frequency ablation treatment of CLM and presence of extrahepatic disease. Twenty-four patients who had undergone a second liver resection were thus identified for inclusion into the study.

We further identified a control group of 24 patients matched over time and in terms of preoperative data who had undergone only primary liver resection due to CLM in order to be able to compare the perioperative events, postoperative events and survival.

Over the course of the long inclusion period, the approach to metastatic liver surgery changed markedly. The major current focus in liver surgery is on what is left behind. The important factors are: Free margins, sufficient future liver remnant (20% in “liver healthy” individuals and 30-40% in patients with liver disease, i.e. cirrhosis), sufficient in- and outflow and biliary drainage of remnant liver segments. In addition to the above mentioned, considerable technical advances have been made in liver surgery owing, among others, to new transaction techniques, increased use of the Glissonian

approach, increased use of non-anatomical/liver-sparing resections, portal vein embolization/ligation, two-stage procedure and hanging manoeuvre. To avoid bias over time due to the above-mentioned factors, the patients in the control group were identified by chronologically selecting the first occurring primary liver resection after a repeat liver resection due to CLM.

To ensure that the two groups were similar with regard to demographics, primary tumour and hepatic involvement, a statistical comparison was made.

Preoperative evaluation

Our Department serves the eastern part of Denmark and acts as a tertiary hepatobiliary referral centre. Patients are referred to our department when the colorectal cancer is complicated by liver metastases. The standard workup for these patients is a triphase thoracoabdominal computed tomography (CT) to evaluate the possibility of curative-intent surgery. In the presence of diagnostic uncertainty, the standard workup is supplemented by positron emission tomography-CT, magnetic resonance imaging or diagnostic laparoscopy. All decisions are made on a multi disciplinary team conference.

Statistics

Statistical analysis was carried out using SPSS version 17.0. Both nominal and categorical variables were collected in this study. Non-parametric tests were utilized to compare data on demographics, primary tumour, hepatic involvement, perioperative events and postoperative events.

Regarding the binomial variables, Fisher’s exact test was applied, and the Mann-Whitney test was used for nominal variables. The level of significance was set at $p = 0.05$

Survival plots were conducted using the Kaplan-Meier function. Comparison of the Kaplan-Meier plots was done by applying the log-rank test.

Trial registration: not relevant.

RESULTS

An overview of the results is shown in **Table 1**.

Demographics

There were no statistically significant differences between the two groups regarding the proportion of males, age distribution and preoperative ASA score (Table 1).

Primary tumour

A total of 62.5% of the primary tumours had colonic origin in the primary resection group (PRG), while the

corresponding share was 64% in the second resection group (SRG) ($p = 1$). The proportion of Dukes B tumours was 65% versus 12.5% ($p = 0.25$). 35% of the colorectal cancers in the PRG were Dukes C compared with 87.5% in the SRG ($p = 0.25$).

Hepatic involvement

The average number of metastases was 2.13 in the PRG versus 2.06 in the SRG ($p = 0.88$), the average diameter of the largest metastasis was 3.3 cm in the PRG versus 2.1 cm in the SRG ($p = 0.63$). Hepatic involvement was unilobular in 78% of the cases in the SRG versus 86% in the PRG ($p = 0.7$).

Perioperative events

The mean number of segments involved in the surgical procedures was 2.6 in the PRG versus 1.9 in the SRG ($p = 0.08$), the total number of Saline-Adenosine-Glucose-Mannitol erythrocyte (SAG-M) infusions used perioperatively was 2.6 versus 2 ($p = 0.75$), the number of freshly frozen plasma infusions was 1.13 versus 0.42 ($p = 0.9$), and the number of thrombocyte concentrate infusions was 0.4 versus 0.1 ($p = 0.95$). Macro- and microscopical radical resection (R0) was accomplished in 87.5% versus 92% ($p = 0.67$).

Postoperative events

Postoperatively, 0.13% of the patients in the PRG were admitted to the intensive care unit (ICU) compared with 0% in the SRG ($p = 0.15$). Total admission time was 10.6 days in the PRG versus 8.4 days in the SRG ($p = 0.71$).

The rate of medical complications in the PRG was 8.7% compared with 20% in the SRG ($p = 0.42$).

The medical complications in the SRG consisted of four cases of pneumonia and one case of urinary tract infection. Complications were easily treated with relevant antibiotics and did not prolong the hospital stay. Surgical complications occurred in 17.4% in the PRG and 4% in the SRG ($p = 0.18$). In the SRG, only one patient had surgical complications in the form of bile leakage which was treated successfully with endoscopic retrograde cholangiography (ERC) and stent. In the PRG, there were two cases of bile leakage which were both successfully treated with ERC, papillotomy and stent. Furthermore, there was one case of postoperative bleeding which needed immediate reoperation and, finally, one case of a subphrenic abscess which required percutaneous ultrasound-guided drainage. Liver insufficiency did not occur in any of the two groups.

The 30-day mortality was 4% in the PRG compared with 0% in the SRG ($p = 0.4$). The patient who died in the PRG was one of the patients who had bile leakage. The patient in question was never discharged from the ICU,

primarily due to respiratory distress, and died due to a stress ulcer 28 days after liver resection.

Survival

The survival plot (**Figure 1**) shows the comparison of the two groups (PRG and SRG). The starting point of the PRG curve is the primary liver resection, and the starting point of the SRG curve is the second liver resection. Regarding five-year survival, the rate in the SRG was 42% compared with 36% in the PRG; however, this difference was not statistically significant ($p = 0.4$).

DISCUSSION

The present study has shown that a second liver resection for colorectal liver metastases is feasible and safe.



TABLE 1

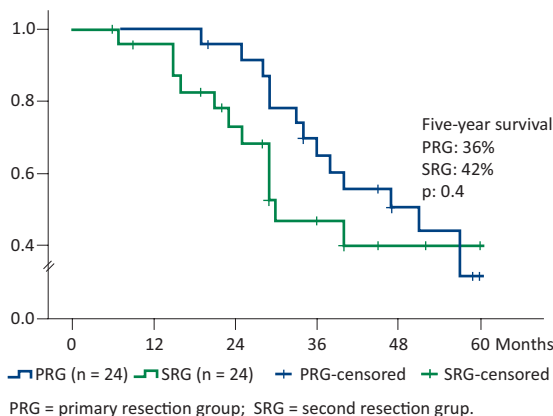
Results of the comparative statistical analyses between the primary resection group and the second resection group. The Mann-Whitney test was used for the nominal variables and Fisher's exact test was used for dichotomous variables. For further specifications of complications, please see the Results section.

	Primary resection group (n = 24)	Second resection group (n = 24)	p value
<i>Demographics</i>			
Male, %	62.3	52	0.57
Age, years, mean	65.1	61.7	0.38
ASA 1, %	18	12	0.69
ASA 2, %	73	56	0.36
ASA 3, %	9	32	0.08
ASA 4, %	0	0	
<i>Primary tumour</i>			
Colon, %	62.5	64	1
Rectum, %	37.5	36	1
Duke B, %	65	12.5	0.25
Duke C, %	35	87.5	0.25
<i>Hepatic involvement</i>			
Metastases, n, mean	2.13	2.06	0.88
Size of metastases, cm, mean	3.3	3.1	0.63
Unilobular involvement, %	78	86	0.7
Bilobular involvement, %	22	14	0.7
<i>Perioperative events</i>			
Segments involved in liver resection, n, mean	2.6	1.9	0.08
Peroperative ultrasound, %	100	100	1
Erythrocyte infusions, n, mean	2.63	2.04	0.75
Fresh frozen plasma infusions, n, mean	1.13	0.42	0.9
Thrombocyte infusions, n, mean	0.35	0.08	0.95
Radiofrequency ablation, %	16.7	12	0.7
R0, n, mean	87.5	92	0.67
<i>Postoperative events</i>			
ICU stay, days, mean	10.6	8.4	0.71
Admission time, days, mean	10.6	8.4	0.71
Surgical complications, %	17.4	4	0.18
Medical complications, %	8.7	20	0.42
30-day mortality, %	4	0	0.41

ASA = American Society of Anesthesiologists classification; ICU = intensive care unit; R0 = macro- and microscopical radical resection.

FIGURE 1

Kaplan-Meier plot showing the five-year survival curves for the primary and the second resection group. The starting point of the primary resection group curve was primary liver resection. The starting point for the second resection group curve was second liver resection.



Furthermore, the long-term survival after a second resection was equal to that observed for patients who had only undergone one liver resection. In the assessment of long-term survival, it is important to note that both the PRG and SRG were highly selected patient groups. It is also important to keep in mind that not all patients experience recurrent CLMs that allow curative intent surgery. Unfortunately, we are not able to give a precise estimate of the proportion of patients who were not available for curative intent surgery or of the number of patients deemed inoperable on the operating table because we only registered patients who had undergone liver surgery in the liver database.

Repeat resection has been reported to be more technically challenging than primary resection due to adhesions, hypertrophy and anatomical variations of the remnant liver [4]. However, this theoretical challenge was not reflected in a significant difference in peri- and postoperative events between the primary and the second resection group. Actually, there was a trend towards a lower rate of surgical complications in the SRG. This was also reflected in a shorter length of hospital stay in this group. The rate of postoperative surgical complications in the SRG was 4% (one case of bile leakage). Other studies have reported complications differently which impedes direct comparison, but Pessaux et al. reported a 2.4% prevalence of surgical complications [4].

The 30-day mortality in the SRG was 0% compared with 4% in the PRG. Our Unit has previously reported a 30-day mortality of 1.4% after primary liver resection [6]. The discrepancy between the two studies was most likely explained by the difference in sample sizes be-

tween the studies. The mortality rate in the present study was comparable to those observed in other high-volume hepatobiliary units [7].

There was no difference in long-term survival between the two groups (estimated five-year survival 36% (PRG) versus 42% (SRG)). The reported five-year survival after repeated liver resection in the present series is comparable to survival rates reported in other series published Pessaux et al [4, 8, 9].

The main weakness of this study was the relatively small sample size which meant that the statistical power was low. This underlines the need for a national Danish liver database, which will provide a stronger basis for future studies on this subject. The strength of this study, on the other hand, was its use of a matched control group selected to avoid any time bias.

CONCLUSION

The present study confirms that repeated resection for colorectal liver metastasis is worthwhile and does offer a fair long-term survival in these very sick patients without increasing their risk of postoperative complications. The study also underlines the importance of a sufficient surveillance programme after primary resection. Finally, it shows that our results are comparable with those of other high volume hepatobiliary centres.

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CONFLICTS OF INTEREST: none

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