Annals of Gastroenterology (2018) **31,** 115-120

Parenchyma-sparing hepatectomy (PSH) versus non-PSH for bilobar liver metastases of colorectal cancer

Lidewij Spelt, Daniel Ansari, Max Swanling, Peter Holka, Roland Andersson

Clinical Sciences Lund, Skåne University Hospital Lund and Lund University, Sweden

Abstract

Background Preoperative interventions have increased the resectability of colorectal cancer (CRC) liver metastases. This retrospective study compares outcomes after liver resection for bilobar CRC metastases between patients who underwent parenchyma-sparing hepatectomy (PSH), i.e., segmentectomies and smaller resections on both lobes, and those treated with non-PSH, i.e., hemihepatectomy plus any resection on the other lobe.

Methods A cohort of 119 patients who underwent liver resection for bilobar CRC metastases were included. Perioperative course and long-term survival were compared between 59 patients who underwent PSH and 60 patients who underwent non-PSH. Statistical analyses were done using Pearson's chi-square test, Fisher's exact test and the Mann-Whitney *U* test. Overall survival analysis was performed by the Kaplan-Meier estimator and Cox regression analysis.

Results The median number of liver metastases was 2 in patients treated with PSH and 3 in those treated with non-PSH (P<0.01). Postoperative mortality, severe complications and radicality did not differ significantly between groups. Median intraoperative bleeding was 250 mL for PSH and 600 mL for non-PSH (P<0.001). Median operation time and hospital stay were significantly shorter for PSH. Overall survival was comparable between groups, also after adjustment for covariates.

Conclusions There were no significant differences in outcome, except for differences in bleeding, operation time and postoperative stay, favoring PSH. Furthermore, minimizing resection did not influence radicality. Hence, this study supports the use of PSH for bilobar CRC liver metastases when possible.

Keywords Liver resection, colorectal cancer metastasis, parenchyma-sparing, bilobar disease

Ann Gastroenterol 2018; 31 (1): 115-120

Introduction

Within three years after the diagnosis of colorectal cancer (CRC), 29% of patients will have developed liver metastases [1]. If these can be resected, 5-year survival of up to 60% is achievable [2-4]. Curative liver resection is feasible when the metastases can be radically resected whilst sufficient liver volume can be spared [5]. The number of patients eligible for resection has expanded over time, through advances in surgical procedures and the development of multimodal treatment strategies, in which preoperative chemotherapy is used to decrease tumor burden, and portal vein embolization (PVE) is applied to increase the liver volume spared after resection [6,7].

This has also increased the possibilities for resection in the case of bilobar liver metastases. However, bilobar disease inevitably implies balancing between resecting enough liver tissue to achieve radicality and sparing enough parenchyma to prevent postoperative liver failure. When treating bilobar metastases, resection in practice often implies at least a hemihepatectomy, sacrificing one lobe entirely and sparing very little liver tissue. Previous research has shown that parenchyma-sparing surgery for CRC liver metastases can be feasible and does not compromise the outcome when compared to more extensive surgery; indeed, it may even have better results in terms of complications and overall survival [8-10]. However, in these studies most patients had only a few metastases and often merely unilobar spread. Another study, including only patients with at least four metastases and thus often with bilobar

Department of Surgery, Clinical Sciences Lund, Skåne University Hospital Lund and Lund University, Sweden

Conflict of Interest: None

Correspondence to: Lidewij Spelt, MD, PhD, Department of Surgery, Clinical Sciences Lund Skåne University Hospital Lund and Lund University, SE-221 85 Lund, Sweden,
e-mail: lidewij.spelt@med.lu.se

Received 30 May 2017; accepted 26 September 2017;
published online 26 October 2017

DOI: https://doi.org/10.20524/aog.2017.0205

spread, found no certain difference in survival based on the extent of resection [11]. The strategy of parenchyma-sparing hepatectomy (PSH) is presumably most relevant in patients with bilobar disease, where it can be hard to preserve a sufficient amount of liver parenchyma. Yet, studies show that advances are being made in the application of parenchyma-sparing liver surgery, even in patients with technically challenging tumor locations, in which intraoperative ultrasound guidance plays an important role [12,13]. Few studies have shown comparable oncological results when applying PSH compared to more extensive surgery (non-PSH) in patients with bilobar disease; whilst PSH might improve perioperative morbidity and mortality [14,15], a true consensus is lacking.

The aim of this retrospective study was to compare the perioperative course and overall survival after liver resection for bilobar CRC metastases in patients who underwent PSH, i.e., segmentectomies and minimal resections in both liver lobes, preserving liver parenchyma, and those who were treated with non-PSH, i.e., an extended hemihepatectomy or hemihepatectomy plus any resection needed on the other lobe.

Patients and methods

Patients

All cases of liver resection for bilobar CRC metastases at the Department of Surgery, Lund University Hospital, Sweden, between January 2006 and December 2014, were included in this retrospective cohort study. Patients were excluded if they had undergone previous liver resections or if tumors were deliberately left *in situ* after operation. The study population was divided into one group treated with PSH and another treated with non-PSH.

Baseline characteristics were collected, including age, sex, comorbidity, American Society of Anesthesiologists (ASA) score, TNM staging of the primary colorectal tumor, and the number and greatest size of the liver metastases. In addition, the performance of preoperative PVE and the administration of chemotherapy were noted.

Treatment

All patients in both groups underwent liver resection with curative intent. One group was treated with PSH, e.g., multiple wedge resections, atypical resections or segmentectomies on both lobes, the resection entailing in total less than four whole segments. The patients in the other group were subjected to non-PSH, defined as an extended hemihepatectomy or hemihepatectomy plus any resection needed on the other lobe.

Outcome measures

Outcome measures were intraoperative bleeding, operation time, postoperative hospital stay, radicality of resection and complications. The occurrence of severe complications was noted, implying grade III or higher as defined by the Dindo-Clavien classification system [16]. In addition, the postoperative 30- and 90-day mortality was calculated, together with the median postoperative overall survival.

Data collection

Through identification of operation codes, all patients who underwent liver resection for colorectal cancer liver metastases at the Department of Surgery, Lund University Hospital between January 2006 and December 2014, were listed. Their medical files were obtained, after which medical charts, chemotherapy files, operation records and hospital course were carefully reviewed in order to identify the selected patients and obtain all the necessary data. For long-term follow up on survival, the regional administration system was consulted for data on December 6th 2016.

The study was approved by the regional human ethics committee at Lund University.

Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY, USA). Comparisons were made using Pearson's chi-square test, Fisher's exact test and the Mann-Whitney *U* test. Two-sided P-values were used and P-values of <0.05 were considered to represent statistical significance. Predictive value for survival was analysed by logistic regression. Unadjusted overall survival analysis was performed by Cox regression and the Kaplan-Meier estimator, using the log-rank test for comparisons between groups. Overall survival adjusting for other covariates was performed using a Cox regression proportional hazards model. Factors taken into account were age, sex, the variables in which the groups differed at baseline, as well as perioperative factors previously shown to be predictors of overall survival, including the occurrence of severe complications and radicality of resection [17-19].

Results

Patients

A total of 119 patients with liver resection for bilobar CRC metastases were included. Of these, 59 underwent PSH and 60 patients underwent non-PSH. Both groups had a comparable distribution over time for operation, with 2012 and 2011 as the median years of operation in the PSH group and the non-SPH group, respectively. Patients undergoing PSH had a higher median age ($P<0.01$), but the two groups were comparable regarding sex, ASA score and

staging of their CRC (Table 1). Although the median size of the largest metastasis was comparable between groups, the median number of metastases was significantly higher in the group with non-PSH and this group also included patients who underwent preoperative PVE, whereas the group with PSH did not. Preoperative chemotherapy administration was similar in both groups, and most often entailed oxaliplatin-based treatment, followed by irinotecan-based treatment.

Perioperative outcome

The patients treated with PSH had statistically significantly less median intraoperative bleeding, a shorter operation time and a shorter postoperative stay in hospital (Table 2). Although the division among the different complication grades differed slightly between groups, with more patients having grade 0 or I after PSH and grade II being more common after non-PSH, the occurrence of severe complications was comparable. Radical resection was achieved in similar numbers in both groups.

Within the entire study population there were no perioperative deaths, yielding a total 30-day and 90-day mortality rate of 0%.

Long-term outcome

The median follow-up time was 35 months among survivors. The median overall unadjusted survival, calculated by the Kaplan-Meier method, was 39 months after PSH and 51 months after non-PSH (P=0.139). The Kaplan-Meier curve for overall survival in the two groups is presented in Fig. 1, which also shows the unadjusted overall survival using Cox regression (P=0.141).

Adjusted overall survival was calculated considering age, sex, the patient variables with significant differences or tendencies to differ between groups (ASA score, synchronous versus metachronous metastases, presence of lung metastases, number of liver metastases, size of the largest metastasis and preoperative treatment with PVE), as well as perioperative parameters including the occurrence of severe complications

Table 1 Baseline characteristics in patients undergoing PSH or non-PSH for bilobar CRC metastases

Characteristic	PSH n=59 (IQR or %)	Non-PSH n=60 (IQR or %)	P	Missing
Median age in years	69 (63-76)	65 (61-69)	<0.01	0%
Sex, male : female	35:24 (59.3% : 40.7%)	39:21 (65% : 35%)	0.573	0%
Year of liver resection	2012 (2010 -2013)	2011 (2008-2013)	0.121	0%
ASA-score				
I	2 (3.4%)	7 (11.7%)	0.092	0%
II	35 (59.3%)	39 (65%)		
III	22 (37.3%)	14 (23.3%)		
T-stage of CRC				
1	1 (1.9%)	0 (0%)	0.759	16.8%
2	3 (5.8%)	4 (8.5%)		
3	32 (61.5%)	29 (61.7%)		
4	16 (30.8%)	14 (29.8%)		
N-stage of CRC				
0	13 (24.5%)	17 (33.3%)	0.243	12.6%
1	24 (45.3%)	15 (29.4%)		
2	16 (30.2%)	19 (37.3%)		
Synchronous metastases	29 (51.8%)	38 (64.4%)	0.190	3.4%
Lung metastases	10 (17.9%)	2 (3.4%)	<0.05	4.2%
Median preoperative CEA-level in µg/L	5 (3-17)	5 (3-18)	0.824	34.5%
Median number of liver metastases	2 (2-4)	3 (2-5)	<0.01	2.5%
Median size of largest metastasis in mm	22 (15-30)	26.5 (17-40)	0.080	3.4%
Preoperative chemotherapy	40 (67.8%)	47 (78.3%)	0.220	0%
Preoperative PVE	0 (0%)	12 (20.7%)	<0.001	1.7%
Simultaneous RFA	10 (16.9%)	10 (16.7%)	1.000	0%

CRC, colorectal cancer; PSH, parenchyma-sparing hepatectomy; ASA, American Society of Anesthesiologists; IQR, interquartile range; CEA, carcinoembryonic antigen; PVE, portal vein embolization; RFA, radiofrequency ablation

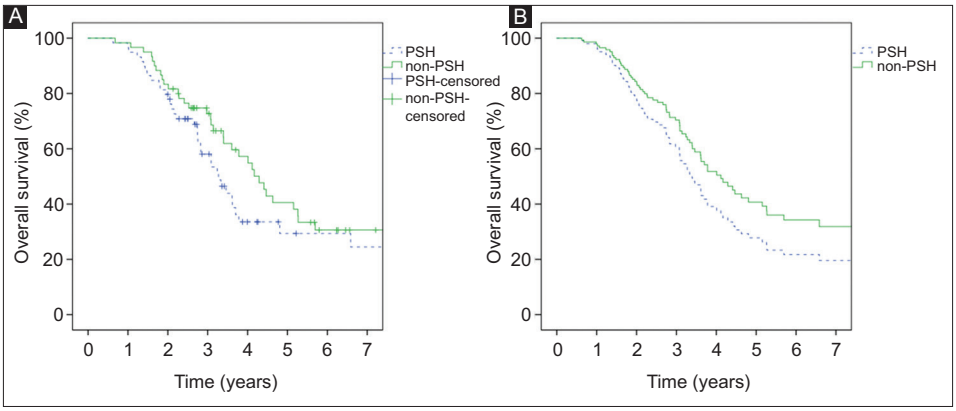

Figure 1 Unadjusted overall survival curves showing overall survival in patients undergoing parenchyma-sparing hepatectomy (PSH) or non-PSH for bilobar colorectal cancer metastases, as demonstrated by the Kaplan-Meier method (A) and unadjusted Cox regression (B)

Table 2 Perioperative outcome in patients undergoing PSH or non-PSH for bilobar CRC metastases

Perioperative outcome	PSH n=59 (IQR or %)	Non-PSH n=60 (IQR or %)	P
Median bleeding in mL	250 (200-500)	600 (400-925)	<0.001
Median operation time in hours	5h (3.75-7)	7h25 (6-8.75)	<0.001
Median postoperative stay in days	7 (7-8)	8.5 (7-12.5)	<0.01
Severe complications	4 (6.8%)	11 (18.3%)	0.095
Complication grade			
0	21 (35.6%)	14 (23.3%)	0.032
I	18 (30.5%)	9 (15.0%)	
II	16 (27.1%)	26 (43.3%)	
III	3 (5.1%)	10 (16.7%)	
IV	1 (1.7%)	1 (1.7%)	
Radical resection	52 (88.2%)	48 (80%)	0.317

CRC, colorectal cancer; PSH, parenchyma-sparing hepatectomy; IQR, interquartile range

and radicality of resection. Using Cox proportional hazards regression analysis, no statistically significant differences in survival were found when comparing patients who underwent PSH with those who underwent non-PSH (Fig. 2). Hazard ratios for extensive versus limited resection are displayed in Table 3.

Table 3 Cox multivariable regression analysis for overall survival

Overall survival	HR	95% CI for HR	P
PSH vs. non-PSH, unadjusted	1.426	0.889-2.289	0.141
PSH vs. non-PSH, adjusted for covariates[a]	1.375	0.669-2.826	0.386

[a]Adjusted for sex, age, ASA-score, synchronous metastases, lung metastases, number of liver metastases, size of the largest metastasis, PVE treatment, radicality of resection and the occurrence of severe complications

HR, hazard ratio; CI, confidence interval; PSH, parenchyma-sparing hepatectomy; ASA, American Society of Anesthesiologists

Discussion

The present study is one of few reports focusing on the influence of the extent of liver surgery on perioperative outcome and long-term survival, specifically in patients with bilobar liver metastases. An important argument against performing PSH when dealing with bilobar CRC liver metastases has been the suggestion that this might have a negative impact on radicality. Radicality, i.e., a tumor-free resection margin, is a prognostic factor for long-term survival [18,20], and some have found a higher rate of positive margins when comparing wedge resections to larger anatomical resections [21]. In the current study, however, no difference in radicality was found between groups. This finding is supported by the study of Memeo *et al*, who also compared patients with bilobar disease undergoing PSH to those undergoing non-PSH and found similar rates of radical resection [15].

The present study demonstrated differences in perioperative course when comparing both types of surgery. When the resected liver volume was limited, this was associated with a

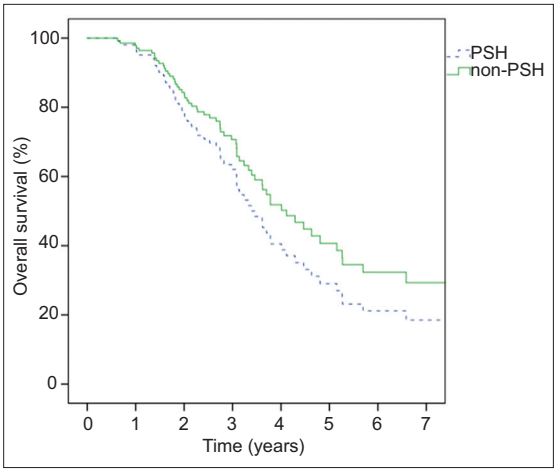

Figure 2 Adjusted overall survival curves showing overall survival in patients undergoing parenchyma-sparing hepatectomy (PSH) or non-PSH for bilobar colorectal cancer metastases, calculated through adjusted Cox regression

smaller amount of perioperative bleeding, a shorter operation time and shorter hospital stay. Also, the division amongst the different grades of complications was different. However, when the number of severe complications was considered, the groups were comparable. A favorable perioperative course after PSH was also reported by Memeo *et al*, showing fewer complications, although hospital stay was comparable in their study [15]. In the study by Gold *et al* [14], groups were separated according to different time periods and this showed that less extensive resections were performed during later periods, and were correlated with a decrease in blood loss, hospital stay and 90-day mortality over time. They also showed that extensive resections were related to a higher morbidity.

Besides the possibly favorable perioperative course, another reason to opt for PSH is the possibility of future resections in case the patient suffers from hepatic recurrence. If achievable in these cases, reresection has been shown to be beneficial [22,23], but is more likely to be ruled out in patients with a previous non-PSH and thus less remaining liver tissue.

This study showed comparable overall survival in patients treated with PSH and those who underwent non-PSH. However, one difficulty in the current study, which was a retrospective study with all its limitations, was the difference between the two study groups regarding certain aspects that may have affected outcomes. First of all, the median age was higher in the group with PSH, reported to negatively influence survival [2]. Also, this group included 10 patients who had lung metastases at the time of liver resection, whilst the group with non-PSH only contained two patients with lung metastases. Since the overall 3-year survival for patients with lung metastases from CRC is reported to be only in the range of 11-14% [24], the presence of lung metastases would thus be considered as a negative prognostic factor. Additionally, the median number of liver metastases differed between the two groups. Several studies found a higher number of liver metastases to be related to worse survival [25-27], whereas others have not judged this to be a negative predictive factor [28]. A higher number of liver metastases might also have influenced the surgeon to consider non-PSH in the first place, and the possible prognostic value of this parameter should be taken into account. To adjust for the abovementioned factors and also taking other marginally differing variables into account, an adjusted survival analysis was performed with Cox regression analysis and this still showed no statistically significant difference in survival between the two groups. This finding is in accordance with previous studies involving patients with bilobar liver metastases, also showing comparable overall survival in patients with extensive and with limited surgery [14,15]. Therefore, the presumption that PSH might negatively influence long-term outcome is contradicted.

In conclusion, when comparing the perioperative outcome and long-term survival in CRC patients who underwent PSH or non-PSH for bilobar liver metastases, our study could not demonstrate any disadvantage when using PSH. Instead, possible advantages compared to non-PSH—e.g., less intraoperative bleeding, shorter operation time and shorter hospital stay—were noted. Furthermore, minimizing the liver resection did not appear to influence radicality. Although extensive resections often are unavoidable because of tumor location and technical aspects, our findings imply that the

Summary Box

What is already known:

- The number of patients who are considered for treatment with liver resection for colorectal cancer (CRC) metastases is increasing, partly due to advances in multimodal treatment strategies that allow for larger resections to be performed
- A balance needs to be found between resecting enough liver tissue to achieve radicality and sparing enough parenchyma to prevent postoperative liver failure
- Especially in the case of bilobar liver metastases this can be a challenge, and few studies have started to compare parenchyma-sparing operation techniques with more extensive resections such as (extended) hemihepatectomies

What the new findings are:

- Outcomes in patients treated with parenchyma-sparing hepatectomy (PSH) were compared to outcomes in those treated with non-PSH, showing no difference in radicality
- The amount of intraoperative bleeding was smaller and the median operation time and hospital stay were shorter after PSH compared to non-PSH, while overall survival was comparable
- This study supports the use of PSH for bilobar CRC liver metastases, when possible

application of PSH is safe when feasible, thereby sparing liver parenchyma and facilitating possible future liver resections for local recurrences.

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