



Parenchymal-sparing hepatectomy for colorectal liver metastases reduces postoperative morbidity while maintaining equivalent oncologic outcomes compared to non-parenchymal-sparing resection

Andreas Andreou¹, Severin Gloor¹, Julia Inglin, Claudine Di Pietro Martinelli, Vanessa Banz, Anja Lachenmayer, Corina Kim-Fuchs, Daniel Candinas, Guido Beldi^{*}

From the Department of Visceral Surgery und Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

ARTICLE INFO

Keywords:

Colorectal liver metastases
Parenchymal-sparing resection
Tumor burden score

ABSTRACT

Background: Modern chemotherapy and repeat hepatectomy allow to tailor the surgical strategies for the treatment of colorectal liver metastases (CRLM). This study addresses the hypothesis that parenchymal-sparing hepatectomy reduces postoperative complications while ensuring similar oncologic outcomes compared to the standardized non-parenchymal-sparing procedures.

Methods: Clinicopathological data of patients who underwent liver resection for CRLM between 2012 and 2019 at a hepatobiliary center in Switzerland were assessed. Patients were stratified according to the tumor burden score [$TBS^2 = (\text{maximum tumor diameter in cm})^2 + (\text{number of lesions})^2$] and were dichotomized in a lower and a higher tumor burden cohort according to the median TBS. Postoperative outcomes, overall survival (OS) and recurrence-free survival (RFS) of patients following parenchymal-sparing resection (PSR) for CRLM were compared with those of patients undergoing non-PSR.

Results: During the study period, 153 patients underwent liver resection for CRLM with curative intent. PSR was performed in 79 patients with $TBS < 4.5$, and in 42 patients with $TBS \geq 4.5$. Perioperative chemotherapy was administered in equal rates in both groups (PSR vs. non-PSR) both in $TBS \geq 4.5$ and $TBS < 4.5$. In patients with lower tumor burden ($TBS < 4.5$), PSR was associated with lower overall complication rate (15.2% vs. 46.2%, $p = 0.009$), a trend for lower major complication rate (8.9% vs. 23.1%, $p = 0.123$), and shorter length of hospital stay (5 vs. 9 days, $p = 0.006$) in comparison to non-PSR. For $TBS < 4.5$, PSR resulted in equivalent 5-year OS (48% vs. 39%, $p = 0.479$) and equivalent 5-year RFS rates (44% vs. 29%, $p = 0.184$) compared to non-PSR. For $TBS \geq 4.5$, PSR resulted in lower postoperative complication rate (33.3% vs. 63.2%, $p = 0.031$), a trend for lower major complication rate (23.8% vs. 42.2%, $p = 0.150$), lower length of hospital stay (6 vs. 9 days, $p = 0.005$), equivalent 5-year OS (29% vs. 22%, $p = 0.314$), and equivalent 5-year RFS rates (29% vs. 18%, $p = 0.156$) compared to non-PSR. Among all patients treated with PSR, patients undergoing minimal-invasive hepatectomy had equivalent 5-year OS (42% vs. 37%, $p = 0.261$) and equivalent 5-year RFS (34% vs. 34%, $p = 0.613$) rates compared to patients undergoing open hepatectomy.

Conclusions: PSR for CRLM is associated with lower postoperative morbidity, shorter length of hospital stay, and equivalent oncologic outcomes compared to non-PSR, independently of tumor burden. Our findings suggest that minimal-invasive PSR should be considered as the preferred method for the treatment of curatively resectable CRLM, if allowed by tumor size and location.

1. Introduction

Patients with colorectal liver metastases (CRLM) are regularly

evaluated for curatively-intended hepatectomy and 5-year overall survival (OS) rates between 55% and 60% can be achieved, if resection of the entire tumor burden is feasible combined with perioperative

^{*} Corresponding author. Department of Visceral Surgery und Medicine, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010, Bern, Switzerland.

E-mail address: guido.beldi@insel.ch (G. Beldi).

¹ Equal contribution as first author.

<https://doi.org/10.1016/j.suronc.2021.101631>

Received 14 March 2021; Received in revised form 14 June 2021; Accepted 6 July 2021

Available online 10 July 2021

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Table 1
Comparison of patient characteristics between patients who underwent PSR vs. non-PSR for CRLM.

Variable	TBS <4.5		TBS ≥4.5		<i>p</i> ¹	<i>p</i> ²
	non-PSR	PSR	non-PSR	PSR		
	(n = 13)	(n = 79)	(n = 19)	(n = 42)		
Gender, n (%)					0.744	0.028
Female	4 (31)	28 (35)	3 (16)	19 (45)		
Male	9 (69)	51 (65)	16 (84)	23 (55)		
Age, years, median (range)	61 (30–79)	62 (36–84)	70 (52–82)	64 (26–83)	0.897	0.021
Age >65 years, n (%)	6 (46)	36 (46)	13 (68)	19 (45)	0.969	0.096
BMI, kg/m ² , median (range)	22 (18–30)	26 (13–40)	27 (17–33)	24 (18–38)	0.237	0.060
BMI >30 kg/m ² , n (%)	0 (0)	13 (17)	5 (26)	6 (14)	0.116	0.262
ASA physical status, n (%)					0.684	0.108
1	0 (0)	0 (0)	0 (0)	0 (0)		
2	3 (23)	26 (33)	4 (21)	15 (36)		
3	10 (77)	49 (62)	13 (69)	27 (64)		
4	0 (0)	4 (5)	2 (10)	0 (0)		
Diabetes, n (%)	0 (0)	11 (14)	4 (21)	4 (10)	0.154	0.221
Cardiovascular disease, n (%)	2 (23)	30 (38)	10 (53)	14 (33)	0.302	0.156
Pulmonary disease, n (%)	2 (15)	9 (11)	3 (16)	3 (7)	0.683	0.298
Renal disease, n (%)	0 (0)	9 (11)	4 (21)	2 (5)	0.203	0.050

TBS, Tumor Burden Score; CRLM, colorectal liver metastases; BMI, body mass index; ASA, American Society of Anesthesiologists.

*p*¹ TBS <4.5: non-PSR vs. PSR.

*p*² TBS ≥4.5: non-PSR vs. PSR.

systemic therapy [1]. Modern criteria for technical resectability include the ability to perform resection with tumor-free margins (R0) while maintaining sufficient future liver remnant (FLR) to avoid postoperative liver failure [2,3]. Systemic therapy regimens with modern cytotoxic and biologic agents [4] may downstage primary unresectable CLRM and enable curative-intended resection. Developments in interventional radiology such as portal vein embolization (PVE) may result in significant hypertrophy of the FLR thus making extended resections possible [5]. Modern surgical techniques including two-stage hepatectomy [6] and ALPPS procedure (Associating Liver Partition and Portal Vein Ligation) [7] provided liver surgeons with further tools to perform anatomic hepatectomy for patients with advanced disease.

More recently, the concept of parenchymal-sparing resection (PSR) has been proposed to achieve complete removal of the entire tumor burden in patients with multiple and/or bilateral CLRM without risking insufficient FLR and subsequent liver failure [8,9]. PSR may be particularly beneficial for patients treated with systemic therapy before surgery because of chemotherapy-associated liver disease. In particular, neoadjuvant treatment with oxaliplatin-based regimens has been associated with chemotherapy-induced hepatic injury known as sinusoidal obstruction syndrome (SOS) [10]. SOS correlated with an increased risk for postoperative complications including liver failure and bleeding [11]. PSR may also be a more effective method to increase technical resectability among patients with extended disease since alternative methods such as portal-vein embolization (PVE) with two-stage hepatectomy and ALLPS procedure have been associated with tumor progression [6] and increased postoperative morbidity [12]. Moreover, PSR can be favorably performed by laparoscopic techniques enhancing its benefits concerning less invasiveness and accelerated recovery after surgery [13,14].

PSR has potentially several advantages regarding the oncological outcome following hepatectomy for CRLM. In case of recurrent disease in approximately 45% of patients undergoing hepatectomy for CRLM [15], repeat hepatectomy may significantly prolong survival [16]. Hence, these patients may benefit on the long-term, if PSR has been performed in the first place, sparing as much liver tissue for re-resection as possible. On the other hand, several concerns have been raised whether PSR increases positive surgical margin rates and the risk for tumor recurrence [17,18].

Previous studies have evaluated PSR for CRLM, however, these studies were either lacking a comparison group [19], or included groups with significant differences in regards to the tumor burden [20], or compared only selected subgroups of patients such as those with solitary [21], bilateral [22], or deep-placed CRLM [23].

Therefore, the aim of our study was to compare the postoperative outcomes and long-term survivals of patients undergoing PSR with those of patients undergoing non-PSR in the entire cohort of consecutive patients treated in our center for CRLM after stratifying them according to their tumor burden using the previously described tumor burden score (TBS) [24].

2. Methods

2.1. Patient inclusion criteria

Clinicopathological data of 153 consecutive patients who underwent hepatectomy for CRLM between 2012 and 2019 at the Department of Visceral Surgery and Medicine at the Inselspital Bern were collected following approval from the Ethics Commission of the Canton of Bern (2018–01576).

Patients were included in the study if curative-intended resection was performed. This was defined as the ability to remove all radiologically evident tumor. Exclusion criteria were patient age <18 years and concomitant microwave ablation.

2.2. Preoperative assessment

All patients underwent standardized multidisciplinary evaluation before surgery including medical history, physical examination, serum laboratory tests, and an anesthesia evaluation. Triphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with liver-specific contrast agents was performed for tumor-staging. The multimodal treatment concept consisting of perioperative systemic therapy and hepatectomy was defined within the framework of our weekly interdisciplinary tumor board meetings.

2.3. Surgical procedure

Following laparotomy or laparoscopy, the peritoneal cavity was examined to exclude undetected peritoneal tumor spread. Intraoperative ultrasound examination of the liver was routinely performed to confirm the exact location of CRLM and guide resection by taking into consideration the relation of liver lesions to portal pedicles and hepatic veins. The aim of surgical treatment was to remove all radiologically evident disease while preserving sufficient FLR. The surgical strategy concerning the type of resection (PSR vs. non-PSR) was individually designed depending of the location and extent of the tumor burden as well the administration of preoperative chemotherapy, health status of the patient, and previous operations. In the most recent years, laparoscopic resections combined with PSR were increasingly and preferably performed, during the establishment of minimal-invasive surgery in our department.

Parenchymal transections were performed with or without total or selective hepatic vascular exclusion combining cavitron ultrasonic surgical aspirator (CUSA®; Valleylab Boulder, CO, USA), surgical energy devices such as Harmonic Ace® (Ethicon Inc. Somerville, NJ, USA) in

Table 2

Comparison of tumor and treatment characteristics between patients who underwent PSR vs. non-PSR for CRLM.

Variable	TBS <4.5		TBS ≥4.5		<i>p</i> ¹	<i>p</i> ²
	non-PSR	PSR	non-PSR	PSR		
	(n = 13)	(n = 79)	(n = 19)	(n = 42)		
Location of primary, n (%)					0.680	0.893
Colon	9 (69)	59 (75)	13 (68)	28 (67)		
Rectum	4 (31)	20 (25)	6 (32)	14 (33)		
Synchronous CRLM, n (%)	9 (69)	45 (57)	11 (58)	24 (57)	0.408	0.957
Tumor burden score, median (range)	3.6 (2.4–4.3)	3.0 (1.0–4.4)	6.8 (4.5–18.5)	6.8 (4.5–17.9)	0.120	0.846
CRLM location, n (%)					0.900	0.957
Superficial	10 (77)	62 (78)	8 (42)	18 (43)		
Deep	3 (23)	17 (22)	11 (58)	24 (57)		
Solitary CRLM, n (%)	8 (62)	43 (54)	7 (37)	14 (33)	0.635	0.791
Bilateral CRLM, n (%)	5 (39)	24 (30)	6 (32)	22 (52)	0.561	0.131
Preoperative chemotherapy, n (%)	10 (77)	62 (79)	13 (68)	33 (79)	0.900	0.398
T stage of primary, n (%)					0.032	0.392
1	1 (8)	2 (2)	1 (5)	2 (5)		
2	2 (15)	4 (5)	3 (16)	4 (9)		
3	9 (69)	48 (61)	12 (63)	23 (55)		
4	1 (8)	25 (32)	3 (16)	13 (31)		
N stage of primary, n (%)					0.503	0.532
0	6 (46)	27 (34)	6 (32)	19 (45)		
1	4 (31)	31 (39)	9 (47)	14 (33)		
2	3 (23)	21 (27)	4 (21)	9 (22)		
Poor tumor differentiation of primary (G3), n (%)	2 (15)	7 (9)	0 (0)	3 (7)	0.376	0.735
Minimal-invasive hepatectomy, n (%)	4 (31)	36 (46)	2 (11)	8 (19)	0.321	0.009
Positive resection margins, n (%)	1 (8)	10 (13)	4 (21)	8 (19)	0.604	0.892
Surgical technique, n (%)					<0.001	<0.001
Right hepatectomy	8 (62)	0 (0)	13 (69)	0 (0)		
Extended right Hepatectomy	0 (0)	0 (0)	1 (5)	0 (0)		
Left hepatectomy	5 (38)	0 (0)	5 (26)	0 (0)		
Bisegmentectomy + wedge-resection	0 (0)	1 (1)	0 (0)	2 (5)		
Segmentectomy + wedge-resection	0 (0)	2 (3)	0 (0)	1 (2)		
Bisegmentectomy	0 (0)	14 (17)	0 (0)	10 (24)		
Segmentectomy	0 (0)	2 (3)	0 (0)	0 (0)		
Wedge-resection	0 (0)	60 (76)	0 (0)	29 (69)		
Duration of operation, minutes, median (range)	267 (71–366)	149 (28–499)	176 (75–820)	171 (75–565)	0.001	0.709
Postoperative chemotherapy, n (%)	3 (23)	10 (13)	4 (21)	4 (10)	0.379	0.568

TBS, Tumor Burden Score; CRLM, colorectal liver metastases; OH, open hepatectomy; MIH, minimal-invasive hepatectomy.

*p*¹ TBS <4.5: non-PSR vs. PSR.*p*² TBS ≥4.5: non-PSR vs. PSR.

case of laparoscopic procedures, and vascular stapler (Endo GIA™ Medtronic; Dublin, Ireland).

PSR included wedge resections, segmentectomies and bisegmentectomies. Non-PSR was defined as resection of 3 or more contiguous liver segments according to the Couinaud classification [25].

2.4. Postoperative management

Patients were admitted postoperatively to an intermediate care unit or directly to the surgical ward depending on the extent of resection and medical preconditions of the patient. Patients were closely monitored for postoperative complications including intra-abdominal bleeding and liver failure [26]. Postoperative complications within 90 days after surgery were graded according to the classification of Clavien and Dindo [27]. Major postoperative morbidity was defined as any complication ≥3a grade and postoperative mortality as grade 5. All patients were discussed following surgery at the interdisciplinary tumor board meeting and recommendations regarding postoperative treatment or tumor surveillance were made. Oncologic follow-up after hepatectomy included cross-sectional imaging (CT or MRI) and tumor marker testing (carcinoembryonic antigen) every 3 months in the first two years and every 12 months after that.

2.5. Histological evaluation

Histological assessment by experienced pathologists was routinely

performed to confirm the diagnosis and extent of CRLM in the resected specimens and evaluate the resection margin status. R0 was defined as a surgical margin of ≥1 mm free of malignant cells [2].

2.6. Statistical analysis

In order to minimize the effect of tumor extent on the comparisons between the two techniques, patients were stratified according to their tumor burden using the recently introduced TBS [$TBS^2 = (\text{maximum tumor diameter in cm})^2 + (\text{number of lesions})^2$] [24] and were dichotomized by the median TBS in a lower and a higher tumor burden cohort. Tumor diameter and number were measured during histologic evaluation. PSR was compared with non-PSR in each tumor burden cohort regarding postoperative morbidity, postoperative mortality, OS, and recurrence-free survival (RFS). Additionally, groups were compared according to patient- and tumor-related characteristics as well as surgery-associated variables. Among patients undergoing PSR, oncologic outcomes were also compared according to the surgical technique performed (minimal-invasive vs. open hepatectomy).

Quantitative and qualitative variables were expressed as median (range) and frequency (percentage). Comparisons between groups were analyzed with the chi-square or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables, as appropriate. Using the Kaplan-Meier method, OS was calculated from the date of resection to the date of death or last follow-up and RFS was calculated from the date of resection to the date of first recurrence or last follow-up.

Table 3
Comparison of outcomes between patients who underwent PSR vs. non-PSR for CRLM.

Variable	TBS <4.5		TBS ≥4.5		p ¹	p ²
	non-PSR	PSR	non-PSR	PSR		
	(n = 13)	(n = 79)	(n = 19)	(n = 42)		
Length of ICU stay, days, median (range)	2 (0–3)	2 (0–9)	2 (0–9)	2 (0–4)	0.672	0.197
Length of hospital stay, days, median (range)	9 (2–13)	5 (2–37)	9 (4–34)	6 (2–50)	0.006	0.005
90-day complications, n (%)	6 (46)	12 (15)	12 (63)	14 (33)	0.009	0.031
90-day major complications, n (%)	3 (23)	7 (9)	8 (42)	10 (24)	0.129	0.150
90-day mortality, n (%)	0 (0)	0 (0)	1 (5)	1 (2)	1.000	0.562
Postoperative liver failure, n (%)	0	0	1 (5)	0	1.000	0.127
Postoperative bleeding, n (%)	1 (8)	2 (3)	1 (5)	2 (5)	0.548	0.898
Need for transfusion, n (%)	4 (31)	8 (10)	6 (32)	8 (19)	0.042	0.285
Wound infection, n (%)	1 (8)	3 (4)	2 (11)	5 (12)	0.526	0.877
Organ/space infection, n (%)	1 (8)	0	2 (10.5)	1 (2.4)	0.014	0.177
Urinary tract infection, n (%)	0	1 (1)	0	0	0.685	1.000
Pneumonia, n (%)	0	0	1 (5)	0	1.000	0.137
Intrahepatic recurrence, n (%)	7 (54)	32 (41)	9 (47)	20 (48)	0.263	0.568
Repeat hepatectomy for patients with intrahepatic recurrence, n (%)	4 (57)	18 (56)	4 (44)	10 (50)	0.722	1.000
Microwave ablation for patients with intrahepatic recurrence, n (%)	3 (43)	9 (28)	2 (22)	3 (15)	0.548	0.534

TBS, Tumor Burden Score; CRLM, colorectal liver metastases; ICU, intensive care unit.

p¹ TBS <4.5: non-PSR vs. PSR.

p² TBS ≥4.5: non-PSR vs. PSR.

Table 4
Univariate and multivariate analysis of factors associated with postoperative complications following hepatectomy for CRLM in the entire study cohort.

Variable	Postoperative complications (n = 44)	No postoperative complications (n = 109)	UV	MV ^a	
			p	p	OR (95% CI)
Age >65 years, n (%)	23 (52)	51 (47)	0.540		
Male gender, n (%)	32 (73)	67 (62)	0.189		
BMI >30 kg/m ² , n (%)	8 (18)	16 (15)	0.591		
ASA-Score ≥3, n (%)	32 (73)	73 (67)	0.489		
Primary tumor located in colon, n (%)	31 (71)	78 (72)	0.892		
Earlier abdominal operation, n (%)	38 (86)	101 (93)	0.223		
Solitary tumor, n (%)	15 (34)	57 (52)	0.042	0.152	0.6 (0.2–1.2)
Synchronous CRLM, n (%)	29 (66)	60 (55)	0.219		
TBS ≥4.5, n (%)	26 (59)	35 (32)	0.002	0.081	2.0 (0.9–4.5)
Deep tumor location, n (%)	20 (46)	35 (32)	0.121		
Bilateral tumor, n (%)	19 (43)	38 (35)	0.337		
Minimal-invasive hepatectomy, n (%)	10 (23)	51 (47)	0.006	0.035	0.4 (0.2–0.9)
Parenchymal sparing resection, n (%)	26 (59)	95 (87)	<0.001	0.011	3.2 (1.3–7.8)
Neoadjuvant chemotherapy, n (%)	33 (75)	85 (78)	0.692		
Adjuvant chemotherapy, n (%)	6 (14)	20 (18)	0.484		

^a Logistic regression multivariate analysis (MV) included all variables with p < 0.05 in univariate analysis (UV). TBS, Tumor Burden Score; CRLM, colorectal liver metastases; BMI, body mass index; ASA, American Society of Anesthesiologists.

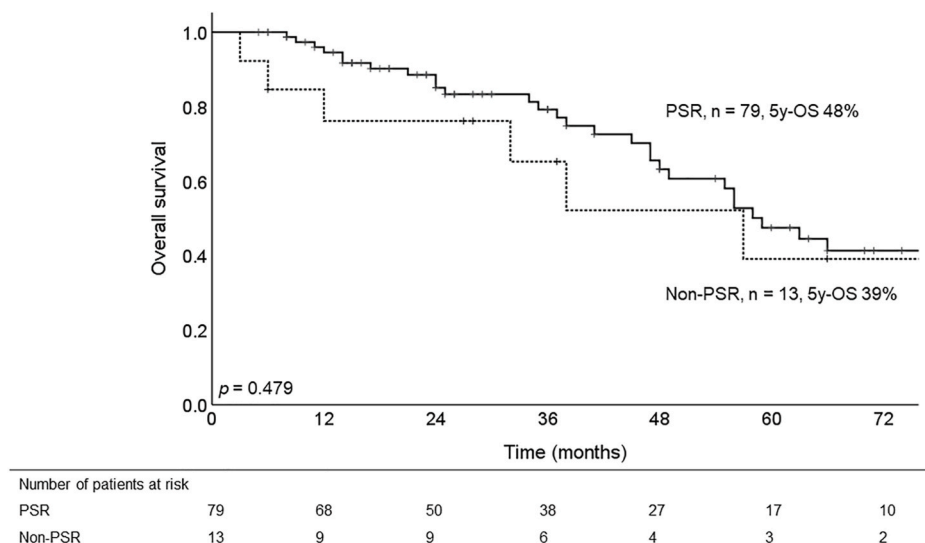


Fig. 1. Overall survival of patients with TBS <4.5 who underwent PSR vs. non-PSR for CRLM.

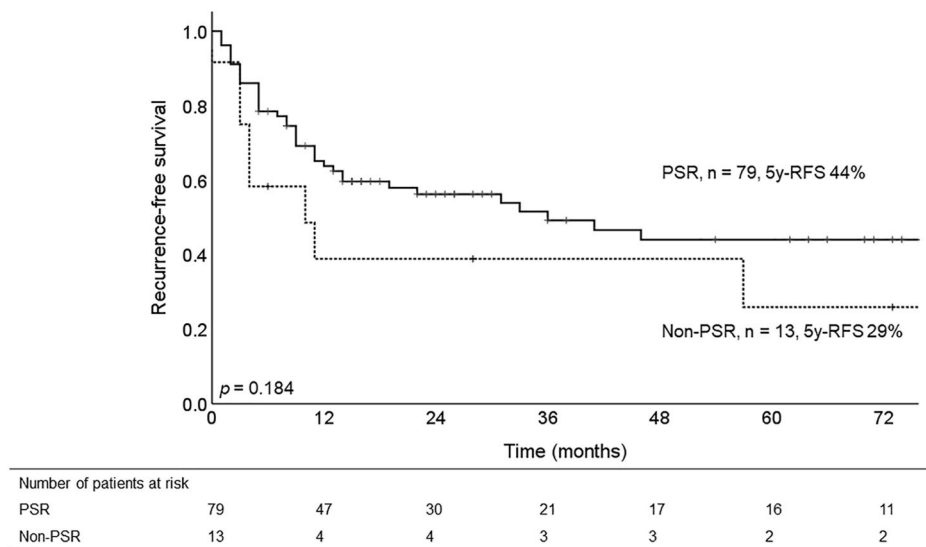


Fig. 2. Recurrence-free survival of patients with TBS <4.5 who underwent PSR vs. non-PSR for CRLM.

Multivariate analysis of factors associated with postoperative complications in the entire cohort was performed using a logistic regression model with backward elimination. Multivariate analysis was also performed to identify factors that are independently associated with OS in the entire cohort using a Cox regression model with backward elimination.

$P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Statistics version 25 (IBM, Armonk, New York, USA).

3. Results

3.1. Patient characteristics

During the study period, 153 patients underwent curative-intended liver resection for CRLM. TBS was calculated for every patient and the median TBS of 4.5 was used to stratify patients in a lower (TBS <4.5) and a higher tumor burden (TBS ≥4.5) cohort. In the TBS <4.5 cohort, 13 patients and 79 patients underwent non-PSR and PSR, respectively. Among patients with TBS ≥4.5, 19 patients were treated with non-PSR and 42 patients with PSR. Comparisons of clinicopathological

characteristics following PSR vs. non-PSR in the two tumor burden cohorts are summarized in Table 1.

Both in the TBS <4.5 and the TBS ≥4.5 cohorts, patients undergoing PSR were comparable with patients undergoing non-PSR in regards to age >65 years, BMI, American Society of Anesthesiologists (ASA) status, comorbidities (metabolic, cardiovascular, pulmonary, renal) (Table 1), tumor stage of primary, bilateral CRLM location, and CRLM tumor burden (Table 2). The distribution of superficially- and deep-placed CRLM (located >30 mm from the liver surface) [28] was equivalent between PSR and non-PSR, irrespective of the tumor burden. Additionally, perioperative chemotherapy was administered in equal rates in both groups (PSR vs. non-PSR) both in TBS <4.5 and TBS ≥4.5. There was no difference in the implementation of minimal-invasive techniques between PSR and non-PSR in the TBS <4.5 cohort (45.6% vs. 30.1, $p = 0.321$). However, more patients with TBS ≥4.5 underwent minimal-invasive PSR than minimal-invasive non-PSR (19% vs. 10%, $p = 0.009$) (Table 2).

3.2. Postoperative outcomes

In patients with TBS <4.5 (Table 3), PSR was associated with lower

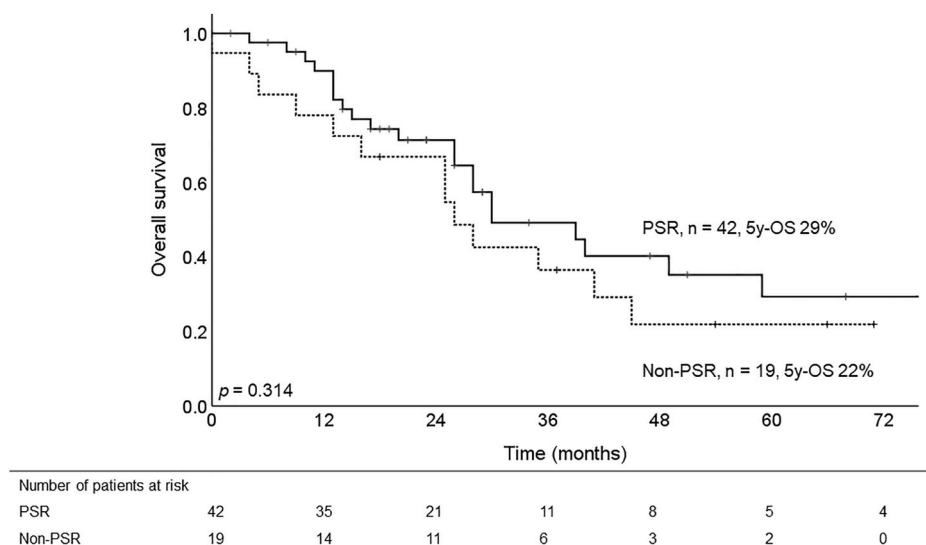


Fig. 3. Overall survival of patients with TBS ≥4.5 who underwent PSR vs. non-PSR for CRLM.

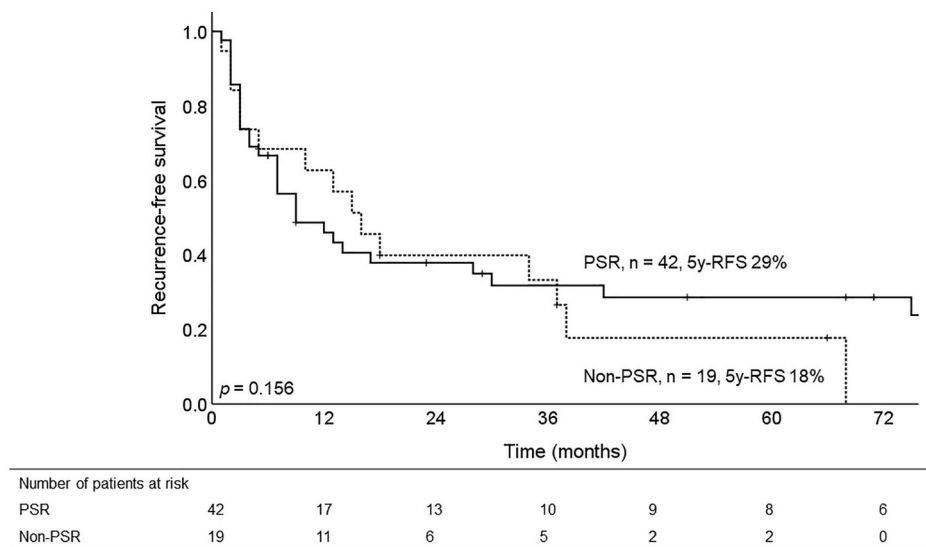


Fig. 4. Recurrence-free survival of patients with TBS ≥ 4.5 who underwent PSR vs. non-PSR for CRLM.

overall complication rate (15.2% vs. 46.2%, $p = 0.009$), a trend for lower major complication rate (8.9% vs. 23.1%, $p = 0.129$), and shorter length of hospital stay (5 vs. 9 days, $p = 0.006$) in comparison to non-PSR. Postoperative liver failure (0% vs. 0% $p = 1.0$) was comparable between the two techniques and there was a trend for less postoperative bleeding after PSR (non-PSR: 8% vs. PSR: 3% $p = 0.548$). There was no postoperative mortality, neither following PSR nor after non-PSR. No difference was found between PSR and non-PSR regarding positive resection margin status ($p = 0.604$).

Among patients with TBS ≥ 4.5 (Table 3), PSR resulted in lower postoperative complication rate (33.3% vs. 63.2%, $p = 0.031$), a trend for lower major complication rate (23.8% vs. 42.2%, $p = 0.150$), and lower length of hospital stay (6 vs. 9 days, $p = 0.005$). Postoperative liver failure (non-PSR: 5% vs. PSR: 0% $p = 0.127$) and postoperative bleeding (non-PSR: 5% vs. PSR: 3%, $p = 0.898$) did not significantly differ between non-PSR and PSR. Postoperative mortality was comparable between the two groups (non-PSR: 5% vs. PSR: 2%, $p = 0.562$). The R1 resection status was not significantly different between PSR and non-PSR. TBS ≥ 4.5 was associated with higher positive resection margin rates than TBS < 4.5 , even though statistical significance was not reached (19.7% vs. 10.9%, $p = 0.235$).

Multivariate analysis for predictors of postoperative complications in the entire study cohort confirmed that PSR was independently associated with lower postoperative morbidity (Table 4).

3.3. Oncologic outcomes

After a median follow-up time of 55 months, among patients with TBS < 4.5 , PSR resulted in equivalent 5-year OS (48% vs. 39%, $p = 0.479$, Fig. 1) and equivalent 5-year RFS rates (44% vs. 29%, $p = 0.184$, Fig. 2) compared to non-PSR.

In patients with TBS ≥ 4.5 , PSR was associated with 5-year OS (29% vs. 22%, $p = 0.314$, Figs. 3) and 5-year RFS rates (29% vs. 18%, $p = 0.156$, Fig. 4) comparable to those after non-PSR.

Intrahepatic recurrence developed in equal rates following PSR and non-PSR both in patients with TBS < 4.5 ($p = 0.263$) and patients with TBS ≥ 4.5 ($p = 0.568$). Repeat hepatectomy rate and microwave ablation rate for intrahepatic recurrence did not differ between PSR and non-PSR in both TBS groups (Table 3).

Multivariate analysis for factors associated with OS in the entire study cohort showed that TBS ≥ 4.5 was an independent predictor for worse OS, thus indicating that dichotomization of patients according to

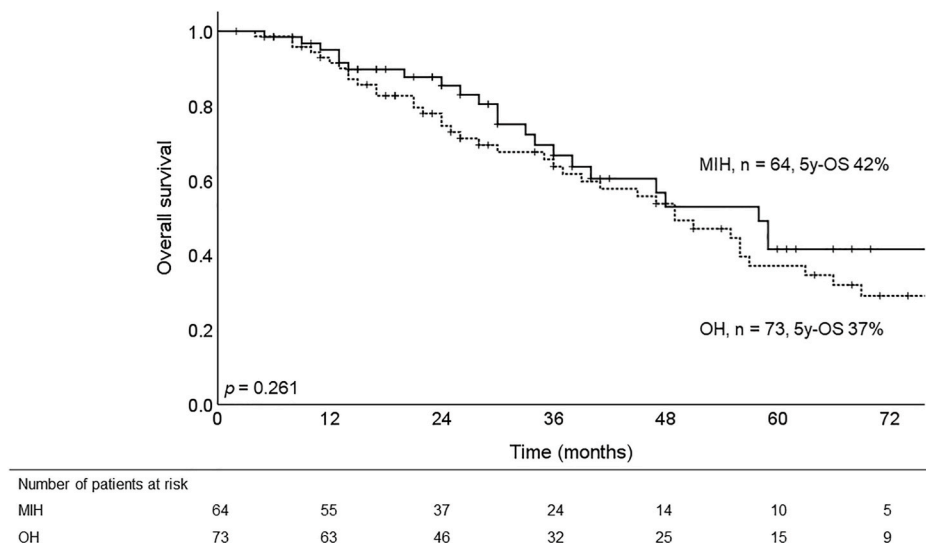


Fig. 5. Overall survival of patients with PSR who underwent open vs. minimal-invasive hepatectomy for CRLM.

Table 5
Univariate and multivariate analysis of factors associated with overall survival following hepatectomy for CRLM in the entire study cohort.

Variable	%	Median survival (months)	UV		MV ^a
			p	p	HR (95% CI)
Age, n (%)			0.491		
>65 years	52.3	41			
≤65 years	47.7	45			
Gender, n (%)			0.078		
Female	27.3	NR			
Male	72.7	39			
BMI, n (%)			0.594		
>30 kg/m ²	18.2	41			
≤30 kg/m ²	81.8	45			
ASA-Score, n (%)			0.205		
≥3	72.7	39			
<3	27.3	NR			
Primary tumor location, n (%)			0.384		
Colon	70.5	45			
Rectum	29.5	35			
Earlier abdominal operation, n (%)			0.759		
Yes	86.4	39			
No	13.6	41			
Number of CRLM, n (%)			0.127		
Solitary	34.1	NR			
Multiple	65.9	39			
Sequence of CRLM, n (%)			0.324		
Synchronous	65.9	45			
Metachronous	34.1	35			
Tumor burden score, n (%)			0.004	0.007	4.1 (1.5–11.3)
≥4.5	59.1	26			
<4.5	40.9	57			
CRLM location, n (%)			0.917		
Deep	45.5	41			
Superficial	54.5	39			
Bilateral tumor, n (%)			0.814		
Yes	43.2	45			
No	56.8	41			
Surgical approach, n (%)			0.139		
MIH	22.7	NR			
OH	77.3	39			
Resection technique, n (%)			0.642		
PSR	59.1	37			
Non-PSR	40.9	45			
Neoadjuvant chemotherapy, n (%)			0.733		
Yes	75.0	39			
No	25.0	41			
Adjuvant chemotherapy, n (%)			0.794		
Yes	13.6	20			
No	86.4	41			

^a Cox regression multivariate analysis (MV) included all variables with $p < 0.05$ in univariate analysis (UV). TBS, Tumor Burden Score; CRLM, colorectal liver metastases; OH, open hepatectomy; MIH, minimal-invasive hepatectomy; PSR, parenchymal-sparing resection; BMI, body mass index; ASA, American Society of Anesthesiologists.

the median TBS (4.5) was adequate for minimizing the effect of tumor extent on the comparison of outcomes between the two surgical techniques (PSR vs. non-PSR). There was no significant difference between PSR and non-PSR regarding long-term survival in the entire cohort as well (Table 5).

Among all patients treated with PSR, patients who underwent minimal-invasive hepatectomy had equivalent 5-year OS (42% vs. 37%, $p = 0.261$, Fig. 5) and equivalent 5-year RFS rates (34% vs. 34%, $p = 0.613$, Fig. 6) compared to patients treated with open hepatectomy.

4. Discussion

In our current study with 153 consecutive patients treated with curative-intended hepatectomy for CRLM, the postoperative and oncologic outcomes following PSR were compared with those following non-PSR. To increase the comparability of the patient groups, patients were stratified according to the TBS in a low and a high tumor burden cohort. We showed that in both tumor burden groups, PSR was associated with lower postoperative morbidity rates, whereas long-term survivals were equivalent.

Previous studies have compared the oncologic outcomes between PSR and non-PSR for CRLM underlining the concern that PSR may be less radical and therefore responsible for higher recurrence rates and worse overall survivals [29,30]. Whereas older studies predating the era of modern chemotherapy showed higher R1 resection rates and worse OS following PSR [29], recent studies indicated that PSR is not inferior to the non-PSR regarding oncologic outcomes [17,31]. Our study confirmed that favorable OS and RFS can be achieved when performing PSR, comparable to those after non-PSR, regardless of the tumor burden extent defined by the TBS. The oncological radicalness (R0) of PSR in our practice was similarly adequate as non-PSR both in patients with lower tumor burden ($p = 0.604$) and patients with extended disease ($p = 0.892$). Several studies have reported on equal R0 resection margin rates between PSR and non-PSR both for open liver surgery [20–22] and minimal-invasive hepatectomy [17]. Routine intraoperative ultrasound monitoring during liver parenchyma transection to identify the exact proximity of liver lesions to neighboring vascular structures and define the resection limits [32] as well the use of advanced energy devices and high-definition optics in laparoscopic surgery [19] have contributed to these results.

Comparable R1 rates between the two techniques have been related to similar intrahepatic recurrence rates in previous studies [23]. Intrahepatic recurrence rates were also not different between PSR and non-PSR in our study regardless of the tumor burden. However, according to a recent study from our group [18], this finding may not be associated with the R1 status and therefore with the surgical technique, as R1 may be rather a surrogate factor for unfavorable disease without influencing the development of recurrence at the intrahepatic resection margin. The advantage of PSR over non-PSR in case of intrahepatic recurrence is however, the higher possibility to perform repeat hepatectomy [17], without running the risk to suffering postoperative liver failure due to insufficient liver remnant. In our study, we did not find a difference regarding the rates of repeat hepatectomy of ablation performed following PSR of non-PSR, probably due to the relative low patient numbers in each group. Nevertheless, in other studies repeat hepatectomy [16,33] or ablation [34] for recurrent CRLM has been previously associated with better overall survivals compared to chemotherapy or best supportive care and therefore PSR may further improve oncologic outcome in the current era of increasing response to modern systemic therapy and repeated liver-directed therapies for CRLM acknowledged as a chronic disease.

Another finding of our study were the better postoperative results following PSR compared to non-PSR. PSR was associated with lower overall postoperative morbidity, a trend for lower major postoperative morbidity, and shorter length of hospital stay in both tumor burden groups (TBS ≥4.5 and TBS <4.5). Multivariate analysis for predictors of postoperative morbidity in the entire study cohort confirmed that PSR was significantly associated with less postoperative complications, independently of the tumor burden. These results are in concordance with previous studies confirming that PSR is a feasible and safe technique [35,36] not only for patients with solitary lesions [21] but also for patients with multiple [17], bilobar [22], and deep-placed [23] CRLM. Postoperative liver failure which remains the main cause for post-hepatectomy mortality [37] occurred equally frequently after PSR and non-PSR in our study. Thus, postoperative mortality did not differ between the groups independently of the tumor burden.

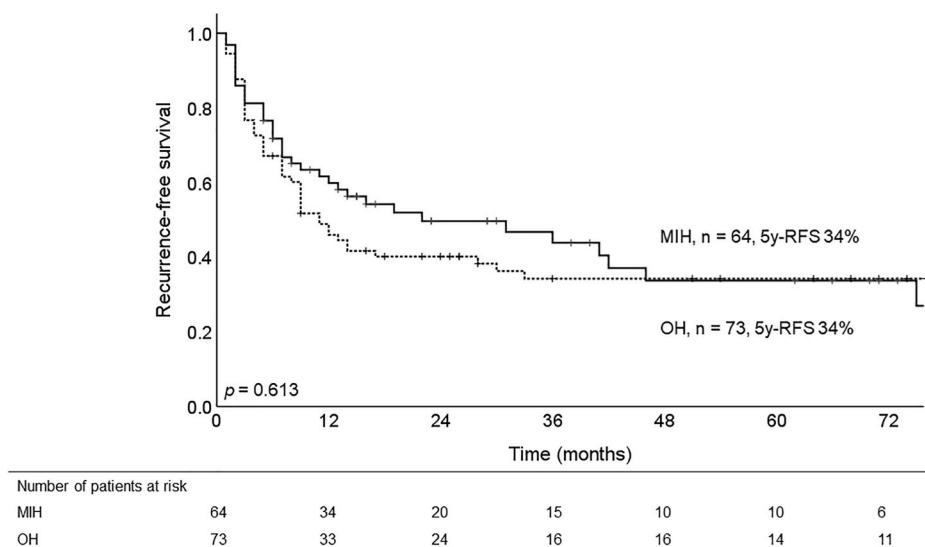


Fig. 6. Recurrence-free survival of patients with PSR who underwent open vs. minimal-invasive hepatectomy for CRLM.

Improved postoperative outcomes combined with equivalent oncologic outcomes may render PSR as the preferred method for the treatment of advanced CRLM compared to other recent surgical developments such as two-stage hepatectomy or ALLPS procedure. While ALLPS procedure has been associated with significantly high major postoperative morbidity and mortality [38], oncologic outcomes of PVE and two-stage hepatectomy may be negatively affected by tumor progression during the interval for hypertrophy and due to the stimulus for liver regeneration [39]. Overall survival in our cohort was lower compared to other studies [1]. This may be explained by our current patient selection strategy. For patients referred to our tertiary center with extended and bilateral tumor burden, we tend to perform multi-step PSR combined with chemotherapy between resections and thus we may have been able to offer surgery to patients with advanced disease, who may have been otherwise deemed unresectable in other studies.

Minimal-invasive hepatectomy has been currently established as the standard of care in many specialized hepatobiliary centers [14]. Previous studies showed that laparoscopic hepatectomy is associated with less postoperative complications, shorter length of hospital stay [13,40], reduced need for transfusions, and improved R0 resection rates [40]. Laparoscopic liver resection was associated with lower median hospital stay in our study as well [4 (2–15) vs. 8 (3–50), $p < 0.001$] compared to open hepatectomy. Patients treated with minimal-invasive surgery, have fulfilled earlier our discharge criteria such as adequate nutrition, full mobilization, normal liver function, and lack of pain symptoms. Laparoscopic techniques have been increasingly performed in our center in the last 5 years as part of enhanced recovery after surgery concepts [40], thus significantly reducing the length of hospital stay for our patients.

A recent randomized controlled trial confirmed the surgery-related benefits of laparoscopic over open liver surgery among patients undergoing parenchymal-sparing hepatectomy defined as a resection of less than 3 consecutive liver segments [13]. Comparison of the same cohort has even found no difference in oncologic outcomes between minimal-invasive and open hepatectomy [41]. Another recent study underlined that laparoscopic PSR for multiple liver lesions provides surgical and oncologic outcomes comparable with those of single greater resections for multiple CRLM [42]. Our study compared the OS and RFS rates of patients undergoing laparoscopic PSR with those treated with open PSR and revealed equivalent outcomes between the two techniques. These findings support our current approach that laparoscopic PSR should be preferred for patients presenting with resectable CRLM.

Several limitations should be taken into consideration when

discussing our results. The findings of this retrospective study have been probably impacted by bias regarding the selection of the surgical approach. Thus, it is expected that patients with more advanced disease, and lesions closer to major vascular vessels may have been preferably treated with non-PSR and may have suffered more postoperative morbidity which influenced the long-term outcomes. Additionally, differences in regards to patient age and comorbidity status between the two groups, even though not statistically significant, may have influenced the results in favor of PSR. However, we have aimed to minimize the effect of tumor extent on our results by stratifying our patients according to the established TBS [24,43] creating comparable patient groups for low and high tumor burden. Additionally, we showed that the presence of superficially-located vs. deep-located CRLM was similar between PSR and non-PSR, independently of the tumor burden, which further reduces selection bias and strengthens the comparability of the two techniques in our study. Future randomized controlled trials comparing PSR with non-PSR may further eliminate this bias, however, randomization of treatment may be complicated in the current era of multimodal personalized precision medicine implementing multiple sessions of systemic therapy and repeat hepatectomy for initial and recurrent CRLM.

Furthermore, we are aware that our study included relatively small number of patients in each group making a statistical type II error possible. This is a result of excluding patients with extrahepatic metastases and patients undergoing concomitant ablation therapy for CRLM in an effort to create homogeneous cohorts for the meaningful comparison of oncologic outcomes between the two liver surgery approaches. The inclusion of simultaneous radiofrequency ablation [17,22] and patients with pulmonary metastases [22] in previous studies may have negatively influenced the resection margin rates and long-term survivals [44, 45].

Finally, our study is lacking data on somatic gene mutations to investigate the role of tumor biology on decision making regarding the appropriate surgical technique. A recent study advocated that PSR should be tailored according to tumor biology [30]. While no differences on long term survivals between PSR and non-PSR were found among patients with *KRAS* wild-type tumors, PSR was associated with worse RFS and worse intrahepatic RFS in patients with *KRAS*-mutated CRLM. Nevertheless, a more recent study including propensity score matching analysis indicated that similar oncologic outcomes can be achieved by PSR and non-PSR independently of the *RAS* mutational status [46]. This study explains this difference by the fact that although *RAS* mutation accounts for more aggressive disease, the risk for tumor progression is no

specific for intrahepatic recurrence and therefore cannot be prevented by non-PSR [47]. This hypothesis may be further supported by our recent study, reporting that PSR for CRLM may be justified, even if a R1 status is deemed very likely in the preoperative assessment, as R1 status is probably a surrogate factor for advanced disease and does not have a direct impact on the location of intrahepatic or extrahepatic tumor recurrence [18].

5. Conclusion

Our study indicated that PSR for CRLM can be performed with lower postoperative morbidity achieving equivalent oncologic outcomes compared to non-PSR. The benefits of PSR were confirmed regardless of the tumor burden. Our findings suggest that minimal-invasive PSR should be preferably performed for the treatment of curatively resectable CRLM, if allowed by tumor size and location.

Authors' contributions

All authors contributed substantially to 1) conception and design, acquisition of data, analysis and interpretation of data; 2) drafting the article and revising it critically for important intellectual content; and 3) provided final approval of the version to be published.

Funding/financial support

The study has not received any financial support.

Declaration of competing interest

A. Andreou, S. Gloor, J. Inglin, C. Di Pietro Martinelli, A. Lachenmayer, V. Banz, C Kim-Fuchs, D. Candinas, and G. Beldi have no conflicts of interest or financial interests to disclose concerning the findings of this study.

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