Ann Surg Oncol (2019) 26:4576–4586
https://doi.org/10.1245/s10434-019-07902-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Laparoscopic Parenchymal-Sparing Hepatectomy for Multiple Colorectal Liver Metastases Improves Outcomes and Salvageability: A Propensity Score-Matched Analysis

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ABSTRACT

Background. Parenchymal-sparing hepatectomy (PSH) is regarded as the standard of care for colorectal liver metastases (CRLMs) in open surgery. However, the surgical and oncological benefits of laparoscopic PSH compared with laparoscopic major hepatectomy (MH) have not been fully documented.

Methods. A total of 269 patients who underwent initial laparoscopic liver resections with curative intent for CRLMs between 2004 and 2017 were enrolled. Preoperative patient characteristics and tumor burden were adjusted with propensity score matching, and laparoscopic PSH was compared with laparoscopic MH after matching.

Results. PSH was performed in 148 patients, while MH was performed in 121 patients. After propensity score matching, 82 PSH and 82 MH patients showed similar preoperative characteristics. PSH was associated with lower rates of major postoperative complications compared with MH (6.1 vs. 15.9%; $p = 0.046$). Recurrence-free survival (RFS) and liver-specific RFS rates were comparable between both groups ($p = 0.595$ and 0.683). Repeat hepatectomy for liver recurrence was more frequently performed in the PSH group (63.9 vs. 36.4%; $p = 0.022$), and the PSH group also showed a trend toward a higher overall survival (OS) rate (5-year OS 79.4 vs. 64.3%; $p = 0.067$). Multivariate analyses revealed that initial MH was one of the risk factors to preclude repeat hepatectomy after liver recurrence (hazard ratio 2.39, $p = 0.047$).

Conclusions. Laparoscopic PSH provided surgical and oncological benefits for CRLMs, with less complications, similar recurrence rates, and increased salvageability through repeat hepatectomy, compared with laparoscopic MH. PSH should be the standard approach, even in laparoscopic procedures.

Liver resection offers the chance for long-term survival and is the only potentially curative therapy for patients with colorectal liver metastases (CRLMs).[1] The increasing number of liver resections, use of effective perioperative chemotherapy, and refinements in imaging modalities and patient selection have improved the outcomes of CRLMs.[2] Technical resectability depends on the ability to obtain negative margins while preserving an adequate functional liver remnant.[3] A better understanding of tumor biology, hepatic anatomy, and the use of intraoperative ultrasound have led to an increased application of parenchymal-sparing hepatectomy (PSH) in CRLM treatment.[4] Many now regard PSH as the standard of care for CRLMs in open surgery. Sparing liver parenchyma at an initial hepatectomy can provide more options for repeat hepatectomy when faced with iterative recurrences.[4,5] It has been established that repeat resection for recurrent CRLMs can offer prolonged survival and even possible cure.[6,7]

First Received: 23 May 2019;
Published Online: 11 October 2019

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The laparoscopic approach has managed to achieve comparable or improved short-term outcomes in liver surgery compared with the open approach, which has led to its increased implementation in the last 20 years;[8–12] however, the role of laparoscopic parenchymal-sparing strategy in the treatment of multiple CRLMs has not been fully documented. Laparoscopic PSH raises some concerns regarding technical feasibility and oncological outcome, mainly surgical margin status and liver recurrence rates.[8] No study to date has addressed whether laparoscopic PSH for multiple CRLMs leads to improved outcomes, better survival, or increased likelihood of repeat salvage hepatectomy compared with laparoscopic major hepatectomy (MH). Therefore, the aim of the present study was to evaluate the surgical and oncological benefits of laparoscopic PSH compared with laparoscopic MH in the treatment of multiple CRLMs.

METHODS

Patient Selection

The data of all consecutive patients who underwent an initial laparoscopic liver resection (LLR) with curative intent for CRLM from January 2004 to March 2017 at Institut Mutualiste Montsouris were retrieved from a prospectively maintained database. Patients with non-curative resection (R2) were excluded from the analysis. Patients were categorized according to the type of operation (laparoscopic PSH vs. laparoscopic MH). This study was approved by the Institutional Review Board of Institut Mutualiste Montsouris and was conducted in accordance with the Declaration of Helsinki.

Preoperative Chemotherapy

The overall surgical strategy consisted of complete tumor resection along with perioperative chemotherapy in order to achieve disease control. Preoperative chemotherapy consisted of FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, and irinotecan) based regimens. Molecular-targeting agents (bevacizumab or anti-epidermal growth factor receptor monoclonal antibodies) have been used since 2006, depending on tumor KRAS mutation status.[13] Chemotherapy administration was decided on a case-by-case basis after discussion at a multidisciplinary tumor board meeting. Neoadjuvant treatment consisted of four cycles of chemotherapy followed by tumor response evaluation through computed tomography (CT) scan and/or magnetic resonance imaging (MRI). Hepatectomy was then performed if tumor response was noted, or in the absence of tumor progression. Otherwise, four to six additional chemotherapy cycles were administered with subsequent similar response evaluation.

Surgical Procedures

MH was defined as the resection of three or more contiguous hepatic segments according to Couinaud,[14] whereas PSH included wedge and anatomical resections of fewer than three contiguous hepatic segments. Operative procedures, including the positioning of trocars, were as previously described.[15,16] Liver resectability was always confirmed by intraoperative ultrasonography.[17–20] When required, hepatectomy was associated with radiofrequency ablation for deeply located tumors. MH was performed instead of PSH whenever needed to achieve a 1 mm resection margin (through sacrificing of the corresponding portal or hepatic vein). This was the case if deeply located tumors could not be treated by radiofrequency ablation or PSH (due to size or proximity to major vessels). Ultrasonic laparoscopic coagulating shears and vessel-sealing devices were used for tissue dissection and hemostasis. Bipolar forceps provided retraction and rescue hemostasis.

Postoperative Outcomes

Postoperative complications were considered if they occurred within 90 days of surgery and were classified according to the Clavien–Dindo classification;[21] major complications were defined as those of grade III or higher. Overall burden of postoperative complications was analyzed through the Comprehensive Complication Index (CCI).[22] Liver failure was diagnosed according to the International Study Group of Liver Surgery (ISGLS) definition, clinically significant liver failure was defined as ISGLS grade B or higher,[23] and postoperative ascites was defined as abdominal drainage output of more than 10 mL/kg/day after the third postoperative day.[24] Biliary leakage was diagnosed according to the ISGLS definition; significant biliary leakage was defined as ISGLS grade B or higher.[25] Surgical margins were defined as either < 1 mm (R1) or > 1 mm (R0). Adjuvant chemotherapy was usually reintroduced with FOLFOX- or FOLFIRI-based regimens to complete a total of 12 perioperative cycles.

Study Design

Laparoscopic PSH was compared with laparoscopic MH before and after propensity score adjustment based on patient characteristics and tumor burden. Intra- and postoperative outcomes, recurrence-free survival (RFS), liver-specific RFS, and overall survival (OS) rates were compared between both groups. A subgroup analysis was

performed in order to compare laparoscopic PSH and MH in terms of liver recurrence. Liver recurrence pattern, treatment, and further subsequent liver recurrence were thus compared between both groups. Patients were stratified according to the treatment received for liver recurrence. Patients treated by repeat hepatectomy were compared with those with no possible surgical therapy in terms of OS. Multivariate analyses were performed to identify factors precluding repeat hepatectomy when confronted with liver recurrence.

Statistical Analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate, while continuous variables were compared using Student's *t* test or Mann–Whitney U test when appropriate. For propensity score matching analysis, the logistic regression model was based on the assessment of goodness-of-fit statistics.[26] In this setting, propensity score adjustment was performed on factors such as study period, baseline patient characteristics (age, sex, American Society of Anesthesiologists score, body mass index [BMI]), primary cancer characteristics (primary cancer site, lymph node metastasis), preoperative chemotherapy, liver tumor burden (maximal size, number of lesions), and intraoperative concomitant primary colorectal resection. Propensity score 1:1 matching was thus performed, with group comparability verification. Postoperative outcomes were compared between the matched groups. Regarding subgroup analysis, patients who presented with liver recurrence were compared after propensity score matching, taking into account number, size, and location of recurrences.

Cumulative RFS, liver-specific RFS, and OS rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. Any variables with a p value < 0.10 on univariate analysis using the above tests was considered a candidate for multivariate analysis using multiple logistic regression models. P values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP 11 (SAS Institute, Cary, NC, USA) and Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

Patient Characteristics

A total of 269 patients underwent initial LLR with curative intent for CRLM during the study period. One hundred and forty-eight (55%) patients underwent laparoscopic PSH and 121 (45%) patients underwent laparoscopic MH. Patient characteristics in the overall population and propensity score-matched (PSM) groups are detailed in Table 1. Overall, there were 167 men and 102 women, and median age was 65 years (range 26–89). After adjustment for preoperative and intraoperative characteristics, 82 PSH and 82 MH patients were matched. Matched PSH and MH groups were comparable in terms of preoperative and intraoperative variables (Table 1). Thirty-five (13%) patients had more than three lesions and 21 (8%) patients had more than five lesions.

Surgical Outcomes: Parenchymal-Sparing Hepatectomy (PSH) Versus Major Hepatectomy (MH)

Postoperative outcomes in the overall and PSM cohorts are detailed in Table 1. After propensity score matching, operative time in the PSH group was significantly shorter (196 vs. 250 min; $p < 0.001$) and intraoperative blood loss was significantly lower (120 vs. 300 ml; $p < 0.001$) compared with the MH group. Overall, RFA was performed in 32 (11.8%) patients (14.1% in the PSM group vs. 9.0% in the MH group; $p = 0.001$). R0 resection rates were similar between both groups (96.3 vs. 96.3%; $p = 1.000$). Overall, postoperative complications (11.0 vs. 37.8%; $p < 0.001$), major postoperative complications (6.1 vs. 15.9%; $p = 0.046$), major liver-specific complications (3.7 vs. 13.4%; $p = 0.025$), CCI (mean 2.5 vs. 9.8; $p < 0.001$), and grade B–C liver failure (0 vs. 6.1%; $p = 0.023$) remained significantly lower in the PSH group. Median postoperative hospital stay was significantly shorter in the PSH group (6 vs. 8 days; $p < 0.001$), but adjuvant chemotherapy administration was similar between both groups (51.2 vs. 51.2%; $p = 1.000$). The median time interval between liver resection and adjuvant chemotherapy was 42 $\pm$ 18 days; however, this time was significantly shorter in the PSH group (32 vs. 49 days; $p = 0.002$). Pathology results revealed that 151 (56.1%) patients had normal liver parenchyma, 69 (25.7%) had steatosis or steatohepatitis, 37 (13.7%) had moderate to severe sinusoidal injury, and 12 (4.5%) had liver fibrosis. These pathological findings were similar between groups ($p = 0.451$).

Oncological Outcomes: PSH Versus MH

Long-term RFS and OS rates in both groups are shown in Fig. 1. The median follow-up was 33.9 months, ranging from 6 to 120 months. Among these rates, intrahepatic recurrence alone developed in 72 (67.9%) patients, whereas the 34 remaining patients had combined intra/extrahepatic disease. After propensity score matching, RFS and liver-specific RFS in the PSH group were similar compared with the MH group (3-year RFS: 28.8 vs. 28.4%,

TABLE 1 Patient characteristics and outcomes following laparoscopic parenchymal-sparing hepatectomy and major hepatectomy: overall and propensity score-matched cohorts

Variables	Overall cohort [n = 269]			PSM cohort [n = 164]		
	PSH [n = 148]	MH [n = 121]	p Value	PSH [n = 82]	MH [n = 82]	p Value
Age, years [median (range)]	67 (33–89)	64 (26–85)	0.030	65 (33–83)	64 (43–85)	0.963
Sex, male/female [n]	92/56	75/46	0.976	50/32	51/31	0.873
BMI, kg/m^2 [median (range)]	24.6 (16.4–41.5)	25.4 (15.9–36.4)	0.462	24.8 (17.6–41.5)	25.1 (15.9–36.4)	0.938
ASA score $\geq$ 3	24 (16.2)	21 (17.4)	0.803	16 (19.5)	16 (19.5)	1.000
Diabetes	13 (8.8)	11 (9.1)	0.930	9 (11.0)	10 (12.2)	0.807
COPD	5 (3.4)	8 (6.6)	0.219	3 (3.7)	5 (6.1)	0.468
Rectal primary tumor	59 (39.9)	40 (33.1)	0.250	34 (41.6)	27 (32.9)	0.258
Primary lymph node metastasis	99 (66.9)	76 (62.8)	0.485	54 (65.9)	55 (67.1)	0.869
Synchronous/metachronous [n]	85/63	79/42	0.189	45/37	50/32	0.429
Preoperative chemotherapy	103 (69.6)	92 (76.0)	0.239	62 (75.6)	63 (76.8)	0.855
No. of tumors on baseline imaging [median (range)]	2 (1–7)	3 (1–25)	< 0.001	2 (1–7)	2 (1–8)	0.148
No. of resections [median (range)]	1 (1–6)	1 (1–4)	0.040	1 (1–6)	1 (1–3)	0.005
Maximal tumor size, mm [median (range)]	20 (5–150)	34 (5–200)	< 0.001	25 (5–150)	28 (5–130)	0.119
Primary colorectal resection	18 (12.2)	3 (2.5)	0.003	3 (3.7)	3 (3.7)	1.000
Operative time, min [median (range)]	180 (20–570)	270 (120–540)	< 0.001	196 (20–480)	250 (120–540)	< 0.001
Blood loss, mL [median (range)]	100 (0–2900)	300 (0–3000)	< 0.001	120 (0–2900)	300 (0–3000)	< 0.001
Intraoperative transfusion	4 (2.7)	18 (14.9)	< 0.001	2 (2.4)	14 (17.1)	0.002
Conversion	8 (5.4)	13 (10.7)	0.105	3 (3.7)	7 (8.5)	0.192
Intraoperative radiofrequency ablation	21 (14.1)	11 (9.0)	< 0.001	12 (14.6)	6 (7.3)	< 0.001
Negative surgical margin (R0)	143 (96.6)	118 (97.5)	0.666	79 (96.3)	79 (96.3)	1.000
Overall postoperative morbidity	25 (16.9)	51 (42.2)	< 0.001	9 (11.0)	31 (37.8)	< 0.001
Clavien–Dindo grade III–V complications	9 (6.1)	25 (20.7)	< 0.001	5 (6.1)	13 (15.9)	0.046
Liver-specific Clavien–Dindo grade III–V complications	6 (4.1)	21 (17.4)	< 0.001	3 (3.7)	11 (13.4)	0.025
CCI [mean (range)]	3.6 (0–33.7)	11.2 (0–100)	< 0.001	2.5 (0–33.7)	9.8 (0–100)	< 0.001
Hemorrhage	1 (0.7)	1 (0.8)	0.886	1 (1.2)	1 (1.2)	1.000
Liver failure [$\geq$ ISGLS grade B]	0 (0.0)	8 (6.6)	0.002	0 (0.0)	5 (6.1)	0.023
Ascites	1 (0.7)	8 (6.6)	0.007	1 (1.2)	6 (7.3)	0.053
Biliary leakage [$\geq$ ISGLS grade B]	4 (2.7)	15 (12.4)	0.002	2 (2.4)	7 (8.5)	0.087
Respiratory complication	1 (0.7)	11 (9.1)	< 0.001	1 (1.2)	7 (8.5)	0.030
Reoperation	3 (2.0)	4 (3.3)	0.512	2 (2.4)	1 (1.2)	0.560
Postoperative mortality	0 (0.0)	2 (1.7)	0.116	0 (0.0)	1 (1.2)	0.316
Hospital stay, days [median (range)]	6 (1–49)	9 (3–42)	< 0.001	6 (1–45)	8 (3–42)	< 0.001
Postoperative chemotherapy	85 (57.8)	63 (52.0)	0.346	42 (51.2)	42 (51.2)	1.000
Recurrence	78 (52.7)	70 (57.9)	0.399	49 (59.8)	49 (59.8)	1.000
Liver recurrence	57 (38.5)	49 (40.5)	0.741	33 (40.2)	36 (43.9)	0.635

Data are expressed as n (%) unless otherwise specified

ASA American Society of Anesthesiologists, *BMI* body mass index, *CCI* Comprehensive Complication Index, *COPD* chronic obstructive pulmonary disease, *ISGLS* International Study Group of Liver Surgery, *MH* major hepatectomy, *PSH* parenchymal-sparing hepatectomy, *PSM* propensity score-matched

5-year RFS: 21.1 vs. 21.6%, p = 0.529; 3-year liver-specific RFS: 48.5 vs. 51.0%, 5-year liver-specific RFS: 45.5 vs. 51.0%, p = 0.702) (Fig. 1a, b). The PSH group showed a trend toward a higher OS rate compared with the MH group (3-year OS: 85.1 vs. 76.9%, 5-year OS: 79.4 vs. 64.3%, p = 0.067) (Fig. 1c).

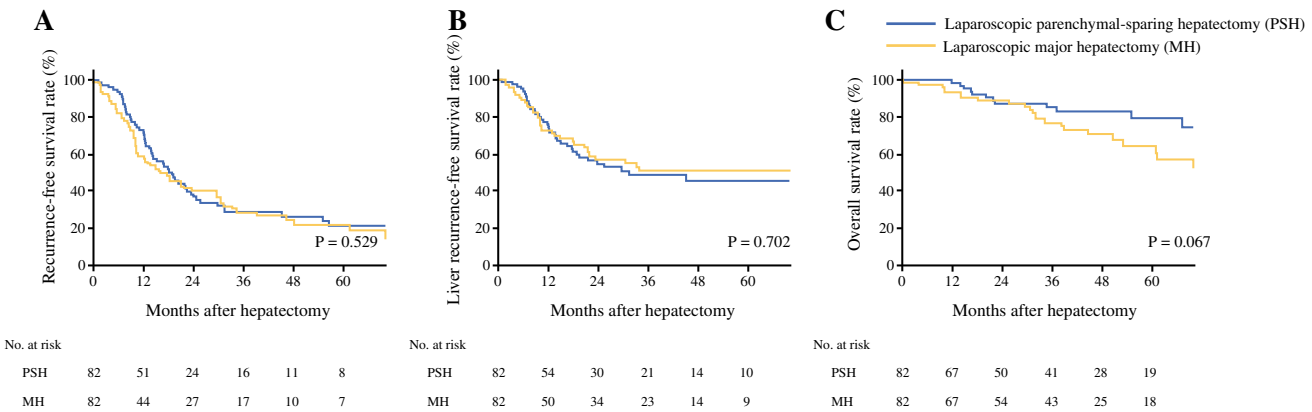

FIG. 1 Long-term survival in patients undergoing laparoscopic PSH (*solid blue line*) and laparoscopic MH (*dotted red line*) in the propensity score-matched cohort. **a** Recurrence-free survival; **b** liver-specific recurrence-free survival; and **c** overall survival. *PSH* parenchymal-sparing hepatectomy, *MH* major hepatectomy

Subgroup Analysis in Patients with Liver Recurrence

Baseline characteristics and type of treatment in patients who presented with liver recurrence are detailed in Table 2, and the management of liver recurrence in the PSM cohort is shown in Fig. 2. Overall, 36 patients in the PSH group and 33 in the MH group developed a first liver recurrence. No significant differences were observed in patient baseline characteristics, time interval to liver recurrence (median 12.1 vs. 10.3 months; $p = 0.438$), overall number of lesions (median 1 vs. 1; $p = 0.819$), and tumor size (median 26 vs. 23 mm; $p = 0.107$) between the PSH and MH groups; however, salvage repeat hepatectomy for liver recurrence was more frequently performed in the PSH group (63.9 vs. 36.4%; $p = 0.022$). On the other hand, RFA was more frequently performed in the MH group (0 vs. 15.2%; $p = 0.015$). In the PSH group, 17.4% of repeat hepatectomies consisted of MH, and 91.3% of repeat hepatectomies were performed by laparoscopy.

Following first liver recurrence treatment, 19 patients in the PSM cohort developed a second liver recurrence, with similar rates between both groups (43.5 vs. 52.9%; $p = 0.554$). A second repeat hepatectomy was more frequently performed in the PSH group (70.0 vs. 22.2%; $p = 0.037$). In the PSH group, a second repeat hepatectomy consisted of MH in 42.9% of patients, and all second repeat hepatectomies were performed laparoscopically.

Long-term survival rates of patients with liver recurrence after laparoscopic PSH and MH are shown in Fig. 3. In the PSM cohort, RFS rates were similar in both groups ($p = 0.591$) (Fig. 3a). The OS rate in the PSH group was slightly improved compared with the MH group, although the difference was not statistically significant (5-year OS: 74.0 vs. 58.4%; $p = 0.219$) (Fig. 3b). When analyzed according to liver recurrence treatment, the OS rate of patients undergoing repeat hepatectomy was improved compared with patients who were unable to undergo further curative treatment (5-year OS: 82.3 vs. 37.1%; $p = 0.003$). The OS rate of patients who underwent RFA was impaired compared with patients treated by repeat hepatectomy, although the difference was not statistically significant (5-year OS: 82.3 vs. 53.3%; $p = 0.396$) (Fig. 3c).

Multivariate analyses revealed that initial MH was the main risk factor to preclude repeat hepatectomy for liver recurrence (hazard ratio 2.39, 95% confidence interval 1.01–5.80; $p = 0.047$) (Table 3).

Time Trend of Surgical Procedures

The time trend of the surgical procedures in the 8 years from 2010 to 2017 is shown in Fig. 4. Consecutive initial LLRs with curative intent were performed in these 8 years. When these LLRs were divided into four groups in chronological order, the proportion of PSHs gradually increased over time from 39.0 to 65.9% ($p = 0.105$). In addition, the proportion of PSHs for tumors located at segments 4a/7/8 gradually increased over time from 19.5 to 46.3% ($p = 0.072$).

DISCUSSION

The present study revealed that laparoscopic PSH for the treatment of CRLMs could be performed safely, with favorable surgical and oncological outcomes. Laparoscopic PSH was associated with lower postoperative morbidity rates compared with laparoscopic MH. Although surgical margin status and recurrence rates were similar between both groups, PSH provided more frequent repeat salvage hepatectomy in case of liver recurrence. Although previous reports demonstrated the benefit of PSH in open hepatectomy series, the current study focused on the laparoscopic

TABLE 2 Baseline characteristics and treatment of patients with liver recurrence after parenchymal-sparing hepatectomy and major hepatectomy: overall and propensity score matched cohorts

Variables	Overall cohort [n = 106]			PSM cohort [n = 69]		
	PSH [n = 57]	MH [n = 49]	p Value	PSH [n = 36]	MH [n = 33]	p Value
Patient characteristics at initial LLR						
Age, years [median (range)]	67 (33–84)	64 (32–85)	0.318	68 (33–82)	66 (44–85)	0.601
Sex, male/female	38/19	32/17	0.883	25/11	26/7	0.377
BMI, kg/m^2 [median (range)]	24.7 (18.6–41.5)	24.8 (16.4–36.4)	0.433	26.0 (20.2–41.5)	25.9 (18.1–36.4)	0.788
ASA score $\geq$ 3	13 (22.8)	11 (22.5)	0.965	10 (27.8)	9 (27.3)	0.963
Primary cancer site: rectum	19 (33.3)	14 (28.6)	0.598	13 (36.1)	8 (24.2)	0.285
Primary lymph node metastasis	40 (70.2)	32 (65.3)	0.592	24 (66.7)	23 (69.7)	0.787
Synchronous/metachronous	35/22	38/11	0.073	15 (41.7)	10 (30.3)	0.327
Preoperative chemotherapy	45 (79.0)	39 (79.6)	0.935	31 (86.1)	25 (75.8)	0.272
Negative surgical margin	55 (96.5)	47 (95.9)	0.877	35 (97.2)	31 (93.9)	0.504
Postoperative chemotherapy	35 (61.4)	30 (61.2)	0.985	19 (52.8)	19 (57.6)	0.689
First liver recurrence after initial LLR						
Time to liver recurrence, months [median (range)]	12.3 (1.0–44.7)	10.3 (1.9–73.4)	0.165	12.1 (1.0–44.7)	10.3 (1.9–33.4)	0.438
Number of tumors [median (range)]	1 (1–15)	1 (1–20)	0.533	1 (1–12)	1 (1–20)	0.819
Maximal tumor size, mm [median (range)]	25 (11–80)	23 (5–90)	0.216	26 (15–80)	23 (5–65)	0.107
Treatment for first liver recurrence						
Local treatment	38 (66.7)	25 (51.0)	0.102	23 (63.9)	17 (51.5)	0.298
Repeat hepatectomy	36 (63.2)	19 (38.8)	0.012	23 (63.9)	12 (36.4)	0.022
Major resection	7 (19.4)	0 (0)	0.040	4 (17.4)	0 (0)	0.125
Laparoscopic resection	33 (91.7)	19 (100.0)	0.196	21 (91.3)	12 (100.0)	0.293
RFA	2 (3.5)	6 (12.2)	0.090	0 (0.0)	5 (15.2)	0.015
Second liver recurrence after local treatment						
Second liver recurrence	14 (36.8)	13 (52.0)	0.234	10 (43.5)	9 (52.9)	0.554
Treatment for second liver recurrence						
Local treatment	9 (64.3)	5 (38.5)	0.180	8 (80.0)	5 (55.6)	0.252
Repeat hepatectomy	8 (57.1)	2 (15.4)	0.025	7 (70.0)	2 (22.2)	0.037
Major resection	3 (37.5)	0 (0)	0.201	3 (42.9)	0 (0)	0.257
Laparoscopic resection	8 (100.0)	2 (100.0)	–	7 (100.0)	2 (100.0)	–
RFA	1 (7.1)	3 (23.1)	0.244	1 (10.0)	3 (33.3)	0.213

Data are expressed as n (%) unless otherwise specified

ASA American Society of Anesthesiologists, *BMI* body mass index, *LLR* laparoscopic liver resection, *MH* major hepatectomy, *PSH* parenchymal-sparing hepatectomy, *PSM* propensity score-matched, *RFA* radiofrequency ablation

approach and revealed surgical and oncological benefits of the laparoscopic parenchymal-sparing strategy in the treatment of CRLMs through PSM analysis.

PSH has been developed in open surgery to maximize functional liver remnant while ensuring sufficient surgical margins. A growing number of series have demonstrated the technical feasibility and oncological benefits of PSH in comparison with MH.[4,27–29] While superficial wedge resections are frequently performed laparoscopically, formal anatomical segmentectomies and resection of deeply located tumors have not gained widespread adoption because they are technically demanding due to the limitation of manipulation.[8,30] In the laparoscopic approach, PSH for deeply located tumors in difficult-to-access areas sometimes requires intricate curved transection planes, which are technically more challenging in comparison with MH consisting of a single and straight transection plane.[31,32] Furthermore, controlling potential bleeding may prove to be difficult due to reduced visualization and access. For all the aforementioned reasons, MH (mainly

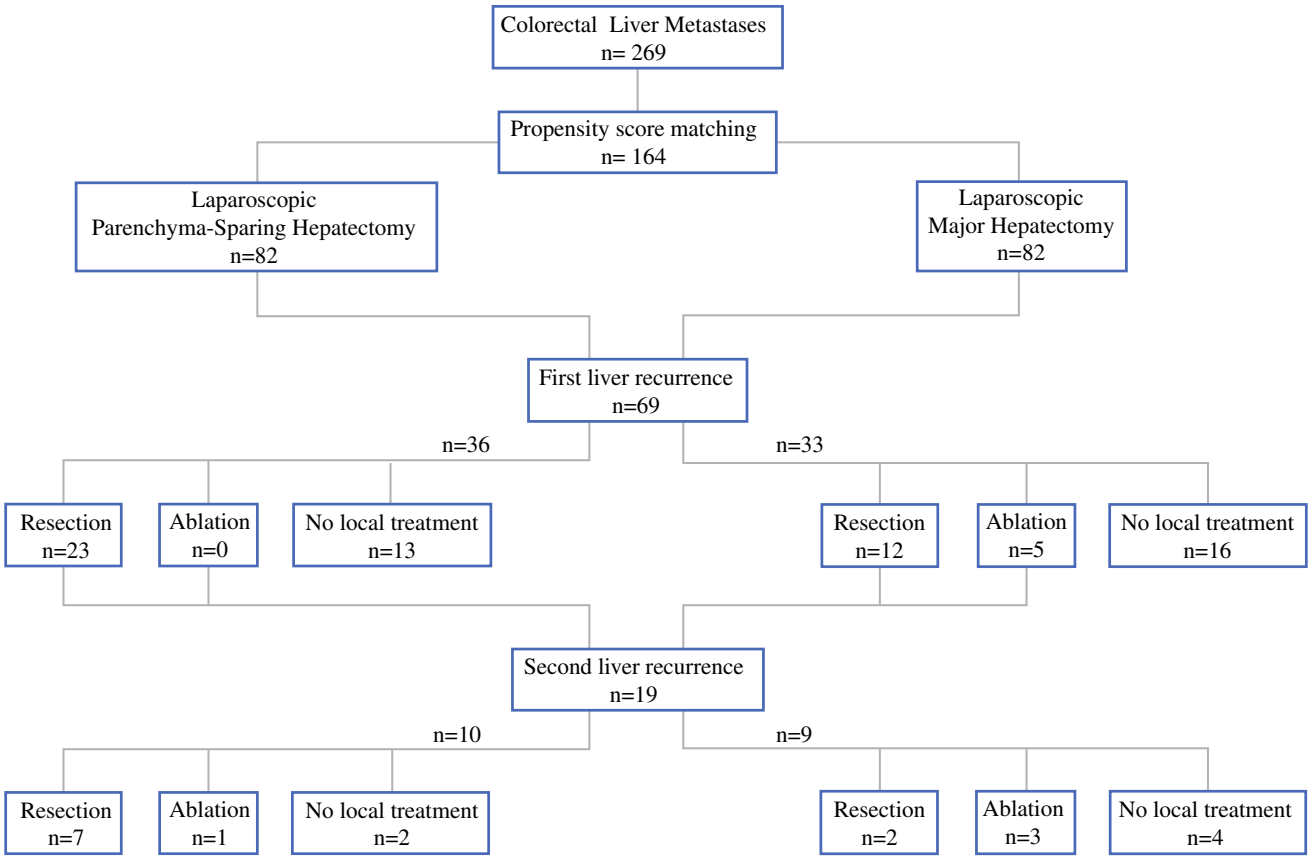

FIG. 2 Treatment of liver recurrence following laparoscopic liver resection in the propensity score-matched cohort

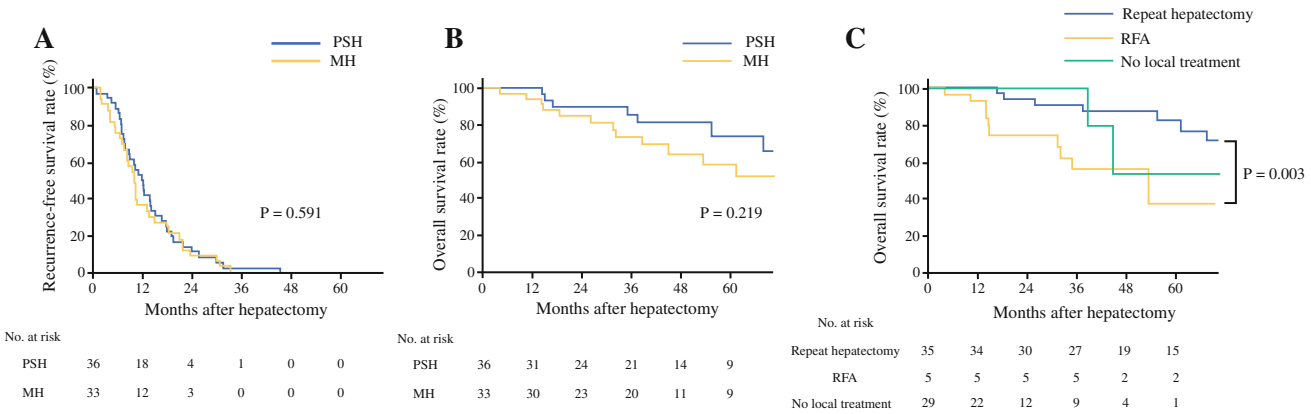

FIG. 3 **a**, **b** Long-term survival in patients with liver recurrence after laparoscopic PSH (*solid blue line*) and laparoscopic MH (*dotted red line*) in the propensity score-matched cohort (**a** recurrence-free survival; **b** overall survival). (**c**) Overall survival rates in patients with liver recurrence treated by repeat hepatectomy (*solid blue line*), RFA (*small dotted green line*), and with no possible surgical treatment (*large dotted red line*) in the propensity score-matched cohort. *PSH* parenchymal-sparing hepatectomy, *MH* major hepatectomy, *RFA* radiofrequency ablation

right or left hepatectomy), which extensively sacrifices non-tumorous parenchyma beyond what is required to achieve tumor clearance, is often preferred when a laparoscopic approach is chosen. Recent technical advancements and better understanding of hepatic anatomy have enabled us to perform laparoscopic PSH even in difficult-to-access lesions,[18] such as upper central[33] or postero-superior segments,[15,16] with a subsequent decrease in the MH rate, as shown in Fig. 4. Furthermore, improved energy devices, flexible cameras, and high-definition three-dimensional optics have played a role in developing easier

TABLE 3 Factors associated with repeat hepatectomy for liver recurrence

Variables	Univariate analysis			Multivariate analysis		
	Repeat hepatectomy, $N = 55$ [n (%)]	Non-repeat hepatectomy, $N = 51$ [n (%)]	p Value	HR	95% CI	p Value
Baseline characteristics						
Age > 70 years	18 (32.7)	18 (35.3)	0.780			
Male sex	38 (69.1)	32 (62.8)	0.491			
ASA score ≥ 3	12 (21.8)	12 (23.5)	0.833			
Primary lesion						
Rectal cancer	17 (30.9)	16 (31.4)	0.959			
Lymph node metastasis positive	38 (69.1)	34 (66.7)	0.789			
Initial liver metastasis						
Synchronous metastasis	35 (63.6)	38 (74.5)	0.227			
Disease-free interval[a] < 1 year	38 (60.1)	40 (80.0)	0.202			
Preoperative chemotherapy	45 (81.8)	39 (76.5)	0.498			
Multiple lesions	29 (52.7)	33 (64.7)	0.211			
Maximal size > 25 mm	27 (49.1)	33 (64.7)	0.105			
Major hepatectomy	19 (34.6)	30 (58.8)	0.012	2.39	1.01–5.80	0.047
Operative time > 180 min	33 (60.0)	36 (70.6)	0.253			
Blood loss > 500 mL	12 (21.8)	10 (19.6)	0.779			
Intraoperative transfusion	4 (7.3)	7 (13.7)	0.276			
Postoperative major complication	8 (14.6)	5 (9.8)	0.457			
Positive surgical margin	2 (3.6)	1 (2.0)	0.603			
Postoperative chemotherapy	32 (58.2)	33 (64.7)	0.490			
Liver recurrence after liver resection						
Disease-free interval[b] < 1 year	21 (38.2)	38 (74.5)	< 0.001	4.33	1.83–10.78	< 0.001
Multiple tumors	24 (43.6)	36 (70.5)	0.005	3.18	1.34–7.92	0.008
Maximal size > 25 mm	31 (56.4)	33 (64.7)	0.380			

[a]From primary resection to first liver recurrence

[b]From initial liver resection to second liver recurrence

ASA American Society of Anesthesiologists, *CI* confidence interval, *HR* hazard ratio

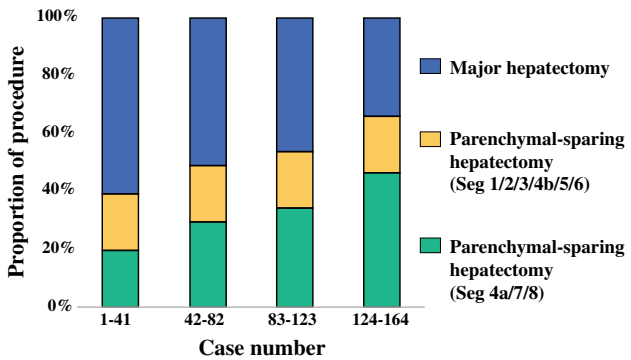

FIG. 4 Trend evolution in surgical procedures over the past 8 years (2010–2017)

and safer procedures. Therefore, the role of a parenchymal-sparing strategy should be re-evaluated in the modern laparoscopic era.

Historically, a minimum of 1 cm was required to consider resection at a safe surgical margin in CRLMs, which is why MH was often preferred.[34,35] However, recent studies demonstrated that surgical margin width does not affect oncological outcomes as long as the margin itself is histologically negative.[36,37] A 1 mm cancer-free resection margin is therefore now considered the standard of care.[38] However, there still exists some concern about a potential increase in positive margins during laparoscopic PSH due to the technical difficulty.[8] Regarding PSH, some authors have reported increased recurrence rates due to remnant

liver ischemia (supposedly more common in PSH), although these results have yet to be confirmed by other cohorts.[39] Nonetheless, in the present study, R0 resection rates were not significantly different between PSH and MH, and were in accordance with results reported in open surgery series.[40] Unfortunately, information about R1 location (parenchyma or vessels) was unavailable in a significant proportion of patients. Because the impact of R1 varies according to location (parenchymal, vascular)[41] and tumor biology (KRAS mutational status),[42] the inclusion of this subset of patients was relevant because it allowed removal of inherent bias in the interpretation of results.

Strategies to ensure an adequate margin in PSH include the use of intraoperative ultrasound to accurately map out neighboring vascular structures and define the limits of resection, early dissection and control of peritumoral vessels, and maintaining a clear visual field. In addition, the use of multimodal treatment with combined RFA could increase the possibility of achieving CRLM clearance while maintaining PSH strategy.

Striving to preserve remnant liver as much as possible in CRLM resection reduces the risk of post-hepatectomy liver failure (PHLF), which remains the main cause of postoperative mortality.[43] Indeed, chemotherapy-induced liver injury exposes CRLM patients to the risk of PHLF.[44,45] In this PSM cohort, preoperative chemotherapy was used in 76.2% of patients without significant difference between the PSH and MH groups. However, not surprisingly, the rate of PHLF in the PSH group was significantly lower than that observed in the MH group. Postoperative complications following CRLM resection are associated with impaired long-term outcome.[18] Indeed, an intense postoperative inflammatory response could be responsible for an increased local recurrence rate.[19,20] Enabling early adjuvant chemotherapy could partly explain why the PSH group showed a trend toward an improved OS rate. Another important benefit of preserving remnant liver parenchyma is to provide the possibility of repeat hepatectomy in case of recurrence. Repeat salvage hepatectomy for recurrence after liver resection is associated with long-term survival and possible cure.[6,7] Previous studies demonstrated that PSH was associated with increased salvageability with repeat hepatectomies.[4,5] Our data are in accordance with these reports. Repeat hepatectomy and second repeat hepatectomy rates in the PSH group were significantly higher compared with the MH group. As shown in Table 2, patients initially treated by PSH could be salvaged by repeat MH when required, but those initially treated by MH could not undergo repeat MH. Patients treated by repeat hepatectomy had significantly better OS rates compared with those without possible curative treatment. Laparoscopic PSH provided more salvageability through repeat resections, which may be associated with better OS compared with MH. Indeed, the difference was not significant, probably due to the small number of matched patients. In this setting, RFA represents an important therapeutic option, enabling PSH strategy in patients with multiple and small CRLMs.[46]

There are several limitations to this study, mainly its retrospective nature, spanning over a relatively long study period. Therapeutic management modifications during the study period, including patient selection, chemotherapy regimens (mainly targeted therapy), and also surgical procedures might have influenced strategy over time. Indeed, similar to open versus laparoscopic surgery for CRLMs,[47] there is a potential bias due to the shift over the years in therapeutic management (increasing PSH and decreasing MH). Propensity score analysis did not take into account the effect of time and this point should be taken into consideration when interpreting the current results. Moreover, the relatively small number of events, especially after propensity score matching, might have led to insufficient statistical power, with the possibility of a type II error in the comparison of outcomes between the groups. Furthermore, although preoperative patient characteristics and tumor burden, including tumor size and total number of lesions, were adjusted for in the PSM cohort, all tumors cannot represent a good indication for PSH. Indeed, a certain percentage of tumors close to the major hepatic vessels entail mandatory MH, even though the proportion of PSH has steadily increased in these recent years.

Nonetheless, the laparoscopic parenchymal-sparing strategy yielded encouraging results and should be attempted whenever technically feasible. Comparison of the laparoscopic parenchymal-sparing approach with the open procedure was not performed due to the limited number of open procedures in our institute. However, the comparability of laparoscopic PSH with open PSH has already been demonstrated in a randomized controlled study,[12] and the outcomes of LLR in the present study were in accordance with those reported in previous studies reporting the results of open liver resection.[48]

CONCLUSIONS

The present study suggests that laparoscopic PSH for multiple CRLMs had both surgical and oncological benefits compared with laparoscopic MH. Laparoscopic PSH was associated with decreased postoperative complications, similar recurrence rates, and increased salvageability through repeat hepatectomy for recurrence compared with laparoscopic MH. The parenchymal-sparing strategy should be the standard of care, even when using the laparoscopic approach.

FUNDING No financial support was received from any sources for this study.

DISCLOSURES Shinya Okumura, Nicolas Tabchouri, Universe Leung, Pascale Tinguely, Christophe Louvet, Marc Beaussier, Brice Gayet, and David Fuks have no conflicts of interest to declare in relation to this study.

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