# Case-controlled study comparing peri-operative and cancer-related outcomes after major hepatectomy and parenchymal sparing

http://dx.doi.org/10.1016/j.hpb.2017.04.007 HPB

ORIGINAL ARTICLE

# Case-controlled study comparing peri-operative and cancer-related outcomes after major hepatectomy and parenchymal sparing hepatectomy for metastatic colorectal cancer

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## Abstract

**Introduction:** Liver resection is potentially curative in selected patients with colorectal liver metastases (CLM). There has been a trend towards parenchyma sparing hepatectomy (PSH) rather than major hepatectomy (MH) due to lower perioperative morbidity. Although data from retrospective series suggest that long-term survival after PSM are similar to MH, these reports may be subject to selection bias. The aim of this study was to compare outcomes of PSH and MH in a case-controlled study.

**Patients and methods:** 917 consecutive patients who underwent liver resection for CLM during 2000–2010 were identified from a prospective database. 238 patients who underwent PSH were case-matched with 238 patients who had MH, for age, gender, tumour number, maximum tumour diameter, primary Dukes' stage, synchronicity and chemotherapy status using a propensity scoring system. Peri-operative outcomes, recurrence and long-term survival were compared.

**Results:** Fewer PSH patients received peri-operative blood transfusions ($p < 0.0001$). MH patients had greater incidence of complications ($p = 0.04$), grade III/IV complications ($p = 0.01$) and 90-day mortality ($p = 0.03$). Hospital stay was greater in the MH group ($p = 0.04$). There was no difference in overall/disease-free survival.

**Conclusion:** Patients with resectable CLM should be offered PSH if technically feasible. PSH is safer than MH without compromising long-term survival.

Received 4 December 2016; accepted 6 April 2017

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## Introduction

Colorectal cancer is the second commonest cause of cancer-related death in the western world, and more than half of patients will develop metastatic disease, frequently limited to the liver.[1,2] Without treatment, the prognosis of patients with colorectal cancer liver metastases (CLM) is dismal. For selected patients with CLM, long-term survival and even cure has become feasible due to advances in liver surgical techniques and availability of effective chemotherapeutic agents.[1–3] In recent years, there has been a trend in favour of parenchymal-sparing hepatectomy (PSH) over major hepatectomy (MH) for patients with resectable liver-only disease.[4,5] Early reports indicated that PSH was associated with higher positive margin rates and worse long-term survival compared to MH.[6–8] These differences were not observed in several recent series,[1,9] including a meta-analysis of 1662 patients.[5] Due to the retrospective, uncontrolled nature of these studies, it is feasible that any differences in oncological results between PSH and MH may have been concealed by selection bias.[10] Risk factors for disease recurrence after resection of CLM, such as tumour size and number, use of perioperative chemotherapy, perioperative blood transfusion and post-operative complications,[1,2,5,11] must be taken into account when evaluating the relative merits of PSH and MH. Our aim was to perform a case-controlled analysis of the outcomes of patients undergoing parenchymal-sparing or major hepatectomy for colorectal liver metastases in a single high volume institution.





Please cite this article in press as: Lordan JT, et al., Case-controlled study comparing peri-operative and cancer-related outcomes after major hepatectomy and parenchymal sparing hepatectomy for metastatic colorectal cancer, HPB (2017), http://dx.doi.org/10.1016/j.hpb.2017.04.007

## Patients and methods

This was a case controlled comparison analysis of prospectively collected data over an eleven year period (January 2000 to December 2010). All consecutive patients who underwent liver resection for CLM during the study period were identified (n = 917, Table 1). Data were anonymous according to the ethical standards of the *Medical Research Council Good Clinical Practice in Clinical Trials*.[12]

Patients were grouped according to type of liver resection; those who had major hepatectomies (MH, n = 634) and those who had parenchymal sparing hepatectomy (PSH, n = 283). At the time of surgery, patients were selected for MH or PSH according to the surgeon's preference. MH were defined as liver resections removing ≥3 segments, and PSH had fewer than 3 segments removed. Patients receiving PSH were 1:1 matched to MH on a case by case basis using a propensity scoring system,[13] which was guided by a statistician (JH).

Patients were included if they potentially could have undergone either MH or PSH on review of the preoperative imaging. Exclusion criteria included patients with small isolated peripheral lesions, left lateral segmentectomies, portal vein embolisations, and patients who underwent radiofrequency ablation.

**Table 1** All available cases prior to matching

| | Major hepatectomy (n = 634) | Parenchymal sparing hepatectomy (n = 283) |
|---|---|---|
| Gender ratio M:F | 1.7:1 | 1.8:1 |
| Mean age/years (range, SD) | 67 (21–86, 2.02) | 67 (31–87, 1.90) |
| Chemotherapy | | |
| Yes (%) | 401 (63.3) | 170 (60.1) |
| No (%) | 233 (36.8) | 113 (39.9) |
| Number of CLM/n (%) | | |
| Single metastasis | 382 (60.3) | 190 (67.1) |
| 2 metastases | 124 (19.6) | 57 (20.1) |
| 3 metastases | 78 (12.3) | 16 (5.7) |
| 4 metastases | 34 (5.4) | 12 (4.2) |
| >4 metastases | 16 (2.5) | 8 (2.8) |
| Mean maximum tumour diameter/mm (range, SD) | 4.7 (0.1–20, 3.46) | 3.2 (0.5–14, 1.90) |
| Primary tumour Dukes' Stage (%) | | |
| A | 14 (2.2) | 13 (4.6) |
| B | 147 (23.2) | 65 (23.0) |
| C | 398 (62.8) | 193 (68.2) |
| D | 2 (0.3) | 1 (0.4) |
| Synchronous metastases/n (%) | 41 (6.5) | 18 (6.4) |

SD = Standard deviation.

Furthermore, patients with large lesions that could not have undergone PSH safely were also excluded. Therefore, 238 PSH patients were included in the study.

The factors used in the matching were age, gender, tumour number, maximum tumour diameter, primary Dukes' stage, cancer involved resection margins, synchronous metastases and chemotherapy status (238 patients in each group). Age matches were within ±2 years, whist the dichotomous variables (e.g. gender) were matched exactly. Where a PSH patient could potentially be paired with multiple MH patients, the match whose date of surgery was closest chronologically was used.

The pre-operative imaging of patients who underwent MH were reviewed and those who were potentially eligible for parenchymal-sparing resection were included in the matching process. Standardised differences were calculated for each matched variable, to determine the quality of matching.[14] A standardised difference of <0.1 was deemed to be indicative of a closely matched variable.[14]

Parenchymal sparing resections were undertaken in a non-anatomical fashion, with the objective of achieving negative margins. Nine of the PSH patients had a laparoscopic resection.

Data included patients' demographics, peri-operative blood transfusions, peri-operative complications, 30-day, 90-day and hospital mortality, lengths of critical care (intensive care or high dependency) and hospital stays, resection margin status, hepatic insufficiency (defined by the International Study Group of Liver Surgery),[15] neo-adjuvant chemotherapy, disease free survival (DFS) and overall survival (OS). Cancer involved resection margins (R1) were defined as <1 mm. Peri-operative complications were graded according to the Clavien classification.[16] Post-operative mortality was defined as death in hospital or within 90 days of surgery. DFS and OS were defined from the date of index liver resection to the date of first recurrence, death or latest follow up appointment. Patients were followed up six monthly for the first 3 years, and once a year thereafter. Patients underwent redo liver resections if the disease was technically resectable and the patient was deemed fit and willing for further surgery.

Statistical analyses were performed using SPSS (version 21). Continuous data was reported as means and SD with $p$ values from Paired T tests, and categorical data reported as percentages and $p$ values from McNemar or Fishers exact tests. Survival curves were constructed using the Kaplan–Meier technique with log-rank tests used to compare between groups. Recurrence and death were considered time-to-event end points in the Kaplan–Meier analysis. Odds ratios (OR) and 95% confidence intervals (CI) were estimated and $p < 0.05$ was considered to be statistically significant throughout.

All clinically relevant variables were included in a multivariable cox regression model, alongside the type of surgery, in order to account for potentially confounding factors for the entire cohort prior to matching. All statistical analyses were guided by our specialist statistician (Mr James Hodson).




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## Results

During the study period, the number of liver resections performed for CLM in our unit increased progressively from year 1 to year 11 (Fig. 1). The proportion of patients who underwent PSH each year also increased. The decision to undergo MH or PSH was decided preoperatively at a specialist hepatobiliary multidisciplinary meeting, guided by tumour characteristics and the predicted size of the future liver remnant. In individual cases, the procedure may have been modified by the operating surgeon depending on intra-operative findings.

There was no difference in patients who received neo-adjuvant chemotherapy between the groups (8.4% v 7.1% respectively, $p = 0.25$, Table 3). In the PSH group, the type of neo-adjuvant chemotherapy given included oxaliplatin and 5-flurourocil (5-FU) (n = 16) and 5-FU alone (n = 1). Of these patients, 5 received greater than 4 cycles of neo-adjuvant chemotherapy. In the MH group, the type of neo-adjuvant chemotherapy given included oxaliplatin and 5-FU (n = 17), 5-FU alone (n = 2) and Capecitabine/Irinotecan (n = 1). Of these patients, 3 received greater than 4 cycles of neo-adjuvant chemotherapy.

Standardised differences of matched variables were reported in Table 2. There was no significant difference in matched variables

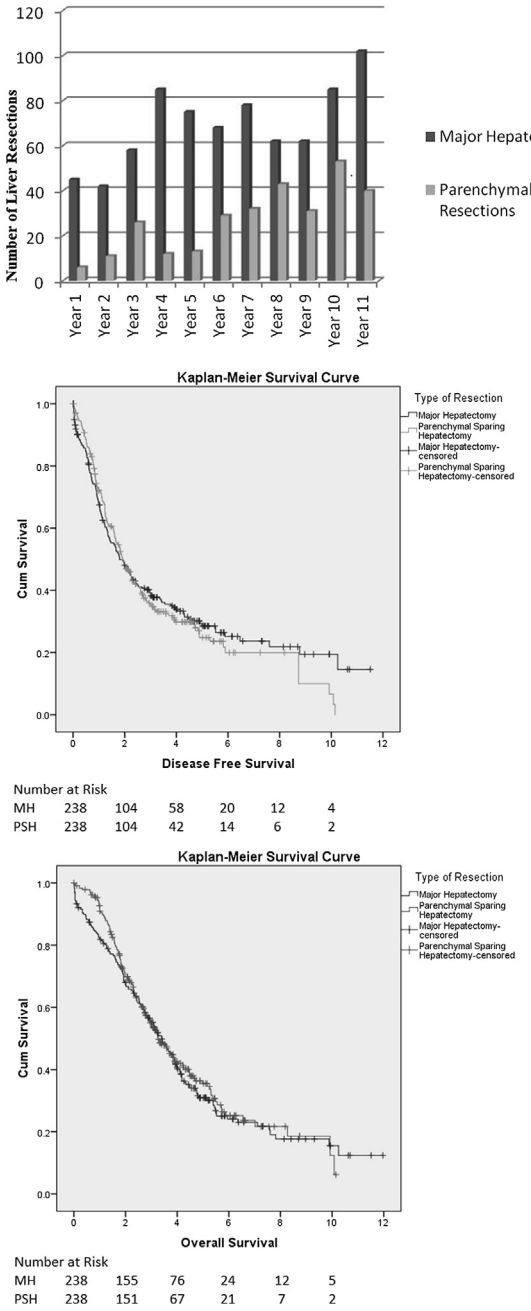


**Figure 1** All consecutive liver resections performed between Jan 2000 and Dec 2010 (n = 917), demonstrating proportion of parenchymal sparing hepatectomy and major hepatectomy each year; Kaplan–Meier curve demonstrating disease free survival of case-matched patients following MH and PSH for CLM (Log rank test $p = 0.62$); Kaplan–Meier curve demonstrating overall survival of case-matched patients following MH and PSH for CLM (Log rank test $p = 0.56$)

**Table 2** Standardised differences of matched variables between MH and PSH groups

| | Major hepatectomy (n = 238) | Parenchymal sparing hepatectomy (n = 238) | Standardised difference[14] |
|---|---|---|---|
| Gender ratio M:F | 1.2:1 | 1.3:1 | 0.01 |
| Mean age/years (range, SD) | 64.8 (24–86, 9.68) | 65.7 (31–87, 9.99) | 0.09 |
| Chemotherapy | | | |
| Yes (%) | 135 (56.7) | 139 (58.4) | <0.01 |
| No (%) | 103 (43.3) | 99 (41.6) | |
| Number of CLM/n (%) | | | |
| Single metastasis | 161 (67.7) | 153 (64.3) | <0.01 |
| 2 metastases | 44 (18.5) | 51 (21.4) | <0.01 |
| 3 metastases | 14 (5.9) | 15 (6.3) | 0.01 |
| 4 metastases | 9 (3.8) | 12 (5.0) | 0.01 |
| >4 metastases | 9 (3.8) | 7 (2.9) | 0.02 |
| Mean maximum tumour diameter/mm (range, SD) | 3.2 (0.4–20, 1.8) | 3.1 (0.5–14, 1.8) | 0.06 |
| Primary tumour Dukes' Stage (%) | | | |
| A | 6 (2.5) | 9 (3.8) | 0.06 |
| B | 62 (26.1) | 49 (20.6) | 0.1 |
| C | 145 (60.9) | 132 (55.5) | 0.09 |
| D | 0 | 1 (0.4) | <0.01 |
| Synchronous metastases/n (%) | 14 (5.9) | 15 (6.3) | 0.02 |

SD = Standard deviation.
Standardised difference of <0.1 suggests a closely matched variable.[11]




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**Table 3** Peri-operative outcomes of case-matched patients who underwent major hepatectomy and parenchymal sparing hepatectomy during Jan. 2000 and Dec. 2010

| | Major hepatectomy (n = 238) | Parenchymal sparing hepatectomy (n = 238) | *p* value |
|---|---|---|---|
| Incidence of peri-operative blood transfusions (%) | 66 (27.7) | 24 (10.1) | <0.0001 |
| Neo-adjuvant chemotherapy (%) | 20 (8.4) | 17 (7.1) | 0.25 |
| Mean days in ITU/ Days (range, SD) | 1.49 (0–75, 6.25) | 0.68 (0–18, 2.73) | 0.02 |
| Median hospital stay/days (range, SD) | 7.0 (4–91, 7.27) | 6.0 (3–68, 5.73) | 0.4 |
| Complications (%) | 88 (37.0) | 69 (29.0) | 0.04 |
| Complications[16] | | | |
| Grade III & IV (%) | 22 (9.2) | 9 (3.8) | 0.01 |
| Grade I & II (%) | 66 (27.7) | 60 (25.2) | |
| Peri-operative mortality/n (%) | 9 (3.8) | 2 (0.8) | 0.03 |
| Hepatic insufficiency/n (%) | 13 (5.5) | 0 | <0.0001 |
| Involved resection margins/R1/2 (%) | 18 (7.6) | 27 (11.3) | 0.14 |

SD = Standard deviation.
Continuous data reported as means and SD with *p* values from Paired T tests, and categorical data reported as percentages and *p* values from Fishers exact test.[11]

except Dukes' stage B between patients who underwent PSH compared to MH. The median time difference between dates of surgery for the matched cases was 17 months (range, 7–22 months).

MH patients were more likely to receive a perioperative blood transfusion than PSH patients (66 (27.7%) v 24 (10.1%), $p < 0.0001$). Median length of intensive care stay and hospital stay were significantly higher in MH patients (1.49 vs. 0.68 days; $p = 0.02$ and 7 vs 6 days $p = 0.04$ respectively, Table 3).

There was a significantly greater incidence of peri-operative complications (37.0% vs. 29.0%; $p = 0.04$), Clavien grade III/IV complications (9.2% vs. 3.8%; $p = 0.01$) and 90-day mortality (3.8% vs. 0.8%; $p = 0.03$) in the MH group (Table 3).[16] Hepatic insufficiency was the only liver related complication which had a significantly different incidence between the two groups (MH 13 (5.5%), PSH 0, $p < 0.0001$, Table 3).

A greater number of patients who had PSH underwent repeat hepatectomy due to disease recurrence (redo liver resections), but this was not statistically significant (MH 23 (9.7%), PSH 35 (14.7%), $p = 0.09$).

The median long-term follow up for the cohort was 3 years (range, 0.01–12 years). The 1, 3 and 5 year OS in the MH group were 82.3%, 55.6% and 34.9% respectively (Fig. 1). The 1, 3 and 5 year OS in the PSH group were 92.3%, 54.0% and 35.5% respectively ($p = 0.56$).

The 1, 3 and 5 year DFS in the MH group were 67.9%, 39.2% and 28.5% respectively (Fig. 1). The 1, 3 and 5 year DFS in the PSH group were 72.2%, 34.8% and 24.8% respectively ($p = 0.62$).

The pattern of liver only recurrence, systemic recurrence, or both liver and systemic recurrence were recorded in Table 4. There was a significantly higher incidence of both liver and systemic recurrence in the PSH group (10.5% vs. 5.0%; $p = 0.03$). However, there was no difference in liver only recurrence or systemic only recurrence. Furthermore, there was no significant difference in recurrence at the resection margin.

The multivariable cox regression model of the entire cohort prior to matching (Table 5), found that the main predictors of mortality were involved resection margins ($p < 0.001$) and increasing numbers of tumours ($p = 0.003$). In addition to these, increasing age at surgery ($p = 0.047$) and the use of peri-operative FFP ($p = 0.04$) were also associated with higher mortality rates. After accounting for all of the factors in the model, the difference between the types of surgery was non-significant ($p = 0.343$), with a hazard ratio of 0.89 (95% CI = 0.70–1.13) for PSH, relative to MH.

## Discussion

To the authors' knowledge, there have been no previous randomised or case-matched analyses regarding the peri-operative and long term outcomes of parenchymal sparing versus major hepatectomy for CLM. Furthermore, this was the largest comparative analysis in the literature to date.

Peri-operative blood transfusions and morbidity, especially complications requiring intervention, have been shown to independently adversely affect long-term survival in patients

**Table 4** Pattern of recurrence of disease following major hepatectomy and parenchymal sparing hepatectomy for CLM

| | Major hepatectomy (n = 238) | Parenchymal sparing hepatectomy (n = 238) | *p* Value |
|---|---|---|---|
| Total recurrence/n (%) | 161 (67.7) | 167 (70.2) | 0.51 |
| Liver recurrence/n (%) | 125 (52.5) | 112 (47.1) | 0.25 |
| Liver recurrence at resection margin/n (%) | 5 (2.1) | 7 (2.9) | 0.42 |
| Systemic recurrence/n (%) | 25 (10.5) | 30 (12.6) | 0.46 |
| Liver and systemic recurrence/n (%) | 12 (5.0) | 25 (10.5) | 0.03 |

Categorical data reported as percentages and *p* values from Fishers exact test.[11]




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**Table 5** Univariable and multivariable analyses of patient survival of the entire cohort before matching

| Factor | Univariable | | Multivariable | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | *p*-Value | Hazard ratio (95% CI) | *p*-Value |
| Surgery type (PSH) | 0.86 (0.96–1.08) | 0.192 | 0.89 (0.70–1.13) | 0.343 |
| Age | | 0.085 | | **0.047** |
| <60 | – | – | – | – |
| 60–70 | 1.12 (0.88–1.42) | 0.365 | 1.10 (0.86–1.41) | 0.431 |
| >70 | 1.31 (1.03–1.67) | 0.028 | 1.36 (1.06–1.76) | **0.017** |
| Gender (Female) | 0.90 (0.74–1.10) | 0.289 | 0.92 (0.75–1.14) | 0.452 |
| Year | | 0.574 | | 0.624 |
| 2000–2002 | – | – | – | – |
| 2003–2005 | 1.14 (0.89–1.46) | 0.307 | 1.19 (0.91–1.55) | 0.199 |
| 2006–2008 | 1.20 (0.91–1.57) | 0.191 | 1.14 (0.86–1.52) | 0.356 |
| 2009–2011 | 1.24 (0.78–1.97) | 0.374 | 1.19 (0.74–1.92) | 0.479 |
| Periop blood transfusion | 1.10 (0.89–1.37) | 0.375 | 0.94 (0.72–1.22) | 0.651 |
| Periop FFP | 1.46 (1.05–2.04) | **0.024** | 1.56 (1.02–2.38) | **0.040** |
| Periop platelets | 1.25 (0.52–3.02) | 0.621 | 0.70 (0.27–1.85) | 0.476 |
| Days on ITU | | **0.019** | | 0.312 |
| 0 | – | – | – | – |
| 1–5 | 1.11 (0.78–1.59) | 0.562 | 0.98 (0.67–1.43) | 0.898 |
| >5 | 1.88 (1.21–2.93) | **0.005** | 1.47 (0.88–2.43) | 0.140 |
| Involved resection margins | 1.78 (1.34–2.31) | **<0.001** | 1.61 (1.23–2.10) | **<0.001** |
| Max tumour size | | 0.092 | | 0.078 |
| <5 | – | – | – | – |
| 5–10 | 1.06 (0.85–1.31) | 0.632 | 1.04 (0.83–1.30) | 0.726 |
| >10 | 1.62 (1.05–2.50) | 0.029 | 1.67 (1.07–2.62) | 0.024 |
| Tumour number (>3) | 1.61 (1.20–2.16) | **0.001** | 1.61 (1.18–2.19) | **0.003** |
| Any complications | 1.38 (1.12–1.70) | **0.003** | 1.22 (0.97–1.54) | 0.096 |

Results from Cox regression models, with death as the outcome.
Bold *p*-values are significant at $p < 0.05$.
PSH = parenchymal sparing hepatectomy.

following liver resection for CLM.[1,2,5,17–19] The significantly fewer complications and blood transfusions in patients who underwent PSH may have reflected technical difficulties in the MH group.[5] This may also explain the significantly lower 90-day mortality seen in the PSH group.

The incidence of PSH increased throughout the study period. It is possible, therefore, that the improved peri-operative outcome in this group may have reflected the overall increase in the experience of the liver unit over time. Yet, the patients who underwent MH, who were matched, were selected throughout the same study period, which would suggest that experience in the unit would benefit these patients to a similar degree. However, the patients were not necessarily matched according to each year, which may have introduced bias into the study.

Studies have shown that cancer involved resection margins independently predicts poor outcome following liver resection for CLM.[18,20] While early studies recommended MH,[6] pre- and peri-operative imaging have advanced over the years to allow more accurate parenchymal transection.[21] This may explain why there was no difference in involved resection margins between the groups in this study, and suggests that there may be no oncological difference between MH and PSH. However, it was not possible to determine if the recurrence within the liver was a new liver metastasis, or a recurrence at the resection margin due to cancer involved margins.

The groups were matched on a case-by-case basis in an attempt to achieve highly accurate marching, using a propensity score.[13] However, data were not available to study certain previously described risk factors, including ASA, primary tumour lymph node status, underlying liver parenchyma histopathological status and CEA levels.[13,17] Further potential bias may has been introduced due to the less than perfect matching according to age and Dukes' stage C, despite matching all the variables as closely as possible between groups. In the assessment of all




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proposed clinical risk scores the Fong score was shown to be particularly unhelpful in stratifying DFS and DSS amongst patients undergoing CRLM resection with an actual follow up of 10 years minimum.[22] Thus comparing patients by clinical risk score is probably of limited benefit.

The literature has reported evidence that neo-adjuvant chemotherapy followed by liver resection may confer significant long term benefit for patients with CLM.[1,3,23] However, the hepato-toxic effects of chemotherapeutic drugs have been shown to be cumulative.[24] As hepatopancreatobiliary (HPB) units increasingly treat patients with neo-adjuvant chemotherapy, the reported associated increased peri-operative morbidity and 90-day mortality,[24] and in particular hepatic insufficiency,[25] may put further pressure on HPB surgeons to perform PSH. The data from this study suggest that while this may be appropriate from a peri-operative perspective, HPB surgeons and patients must be aware of the potentially increased risk of liver recurrence following PSH compared with MH.

Although these data suggest that PSH is safer during the peri-operative period than MH, it is important to note that this study was conducted over a 10 year period whereby there was a shift in tendency towards performing PSH. As a result of the non-contemporaneous data, bias may has been introduced. This may account for the greater requirement of peri-operative transfusion in the MH group from the earlier period of the study.

Furthermore, as liver surgery becomes safer in the peri-operative period, redo liver resections are becoming more feasible. Indeed, this study did not show a difference in patients undergoing redo resections in both groups. Redo liver resections for CLM have been shown to be safe and to confer long term benefit.[26] Also, the similar long term survival rates seen in the current study may have reflected the advances in adjuvant chemotherapy, in particular oxaliplatin, irinotecan and monoclonal antibody based regimens.[27–30]

For PSH, it would be advisable to have a low threshold for consideration of redo surgery for liver recurrence. As such, with a more aggressive policy to perform redo liver resections, further studies may show a significantly greater long term OS in patients who undergo PSH versus MH for CLM.

In conclusion, for patients with CLM, oncologic clearance can be achieved by parenchymal-sparing/minor hepatectomy in selected patients with colorectal liver metastases with significantly lower peri-operative morbidity and 90-day mortality compared to major hepatectomy. We believe parenchymal-sparing/minor resection should be considered if technically feasible, even for patients with multifocal disease, regardless of treatment with or without chemotherapy.

## Conflicts of interest

None to declare.

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