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Laparoscopic versus open two-stage hepatectomy for bilobar colorectal liver metastases: a bi-institutional, propensity scorematched study.

Brief title: Laparoscopic two-stage hepatectomy for CRLM.

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Key words:

Laparoscopic liver resection; two-stage hepatectomy; colorectal liver metastases; bilobar metastases

Abbreviations

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Comprehensive Complication Index; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; CT, computed tomography; FOLFIRI, Folinic acid Fluorouracil Irinotecan; FOLFOX, Folinic acid Fluorouracil Oxaliplatin; FRL, future remnant liver; ISGLS, International Study Group of Liver Surgery; OS, overall survival; PSM, propensity score matching; PVE, portal vein embolization; PVO, portal vein occlusion; RFA, radiofrequency ablation; RFS, recurrence-free survival; TSH, two-stage hepatectomy.

ABSTRACT

Background. The safety and feasibility of laparoscopic, two-stage hepatectomy (TSH) for bilobar colorectal liver metastases (CRLM) is poorly evaluated.

Methods. We reviewed retrospectively 86 consecutive patients who underwent complete TSH (left lobe clearance as the first stage and standard/extended right hepatectomy as the second stage) for bilobar CRLM between 2007 and 2017 in two tertiary centers were. Short and long-term outcomes were compared between laparoscopic and open TSH before and after propensity score matching.

Results. Laparoscopic TSH was performed in 38 patients, and open TSH in 48. After propensity score matching, 25 laparoscopic and 25 open patients showed similar preoperative characteristics. For the first stage, a laparoscopic approach was associated with lesser hospital stays (4 vs. 7.5 days; $P < 0.001$). For the second stage, a laparoscopic approach was associated with less blood loss (250 vs. 500 ml; $P = 0.040$), less postoperative complications (32% vs. 60%; $P = 0.047$), shorter hospital stays (9 vs. 16 days; $P = 0.013$), and earlier of chemotherapy (1.6 vs. 2.0 months; $P = 0.039$). Overall survival (OS), recurrence-free survival (RFS), and liver-RFS were comparable between the groups (3-year OS: 80% vs. 54%; $P = 0.154$; 2-year RFS: 20% vs. 18%; $P = 0.200$; 2-year liver-RFS: 39% vs. 33%; $P = 0.269$). Although both groups had comparable recurrence patterns, repeat hepatectomies for recurrence were performed more frequently in the laparoscopic TSH group (56% vs. 0; $P = 0.006$).

Conclusion. Laparoscopic TSH for bilobar CRLM is safe and feasible with favorable surgical and oncologic outcomes compared to open TSH.

INTRODUCTION

Hepatic resection is the only potentially curative therapy for patients with colorectal liver metastases (CRLM)¹. The increasing number of liver resections and the use of effective perioperative chemotherapy along with better imaging technology and patient selection have improved the prognosis of patients with CRLM². Nevertheless, extensive bilobar CRLM still remain a therapeutic and operative challenge.

Two-stage hepatectomy (TSH) has been advocated for patients with bilobar CRLM which cannot be resected in a single procedure³⁻⁸. Although a variety of staged procedures have been described^{3 4 8 9}, the usual sequence of TSH relies on clearance of the left lobe in the first stage associated with right portal vein occlusion (PVO), followed by a standard/extended right hepatectomy in the second stage. In selected patients with sufficient response to chemotherapy, TSH has been associated with favorable oncologic outcomes^{5-7, 10}. But the procedure may still be technically demanding, especially during the second stage. The formation of heavy adhesions due to the first stage operation along with the inflammation and hypertrophic changes due to PVO and chemotherapy may lead to increased intraoperative blood loss and transfusion¹¹. Moreover, this procedure may be associated with relatively high rates of postoperative morbidity and mortality^{10, 12}.

In liver surgery, the laparoscopic approach has been associated with comparable or better short-term outcomes compared to open approach, which led to its increased use in the last decades^{13 14, 15 16, 17}. Because a laparoscopic approach is associated with less postoperative formation of adhesions and intraoperative bleeding by minimizing operative trauma and the pneumoperitoneum¹⁸, these advantages may be particularly useful in the TSH procedure.

Some concerns, however, still exist regarding the technical feasibility and oncologic

outcomes of a laparoscopic approach, especially in the setting of the complex TSH procedure¹³. The role of a laparoscopic approach in TSH has not been fully determined^{19 20}. To our knowledge, no study to date has addressed whether laparoscopic TSH for CRLM provides equivalent or better short and long-term outcomes compared to open TSH. Therefore, the aim of the present study was to evaluate the safety, feasibility, and long-term outcomes of a laparoscopic TSH compared to an open TSH in the treatment of bilobar CRLM.

METHODS

Patient Selection

Data of all consecutive patients who underwent TSH for bilobar CRLM were retrieved from prospective databases at the following centers: 1) Hôpital Pitie Salpêtrière (2014-2017), 2) Hôpital Saint-Antoine (2009-2014) [1) and 2) were performed by the same surgical team], and 3) Institut Mutualiste Montsouris (2007-2017). Only the patients who completed the first stage (left lobe clearance with partial hepatectomies) and the second stage (standard/extended right hepatectomy) were included to allow appropriate comparison of operative characteristics. According to the type of operative approach, patients were categorized into two groups; laparoscopic TSH (both stages were performed by laparoscopic approaches) and open TSH (both stages were performed by open approaches). Patients who underwent differing approaches between the first and second stage were excluded from the analysis. We compared preoperative patient characteristics, intra- and postoperative outcomes, the interval period from TSH to adjuvant chemotherapy, rates of both overall survival (OS) and

recurrence-free survival (RFS), recurrence patterns, and treatments for intrahepatic recurrences between the groups. This study was approved by the institutional review board of each center and conducted in accordance with the Declaration of Helsinki.

Preoperative evaluation and treatment

Patients with bilobar CRLM routinely underwent preoperative chemotherapy, except in the case of symptomatic primary tumors needing emergent operative intervention. Preoperative chemotherapy consisted of a FOLFOX- or FOLFIRI-based regimen. Molecular-targeting agents (bevacizumab or anti-epidermal growth factor receptor antibodies) were also administered according to the KRAS mutational status²¹. The response to chemotherapy was assessed by computed tomography (CT) using the Response Evaluation Criteria in Solid Tumors, and only patients who exhibited adequate downstaging or stable disease were considered eligible for TSH.

Two-stage hepatectomy

During the first stage hepatectomy, partial liver resections were performed in the left-side future remnant liver (FRL). In selected patients with synchronous CRLM, concomitant resections of the primary colorectal lesions were performed during the first stage.

Before the second stage hepatectomy, Portal vein occlusion (PVO) was performed if the estimated FRL volume would be less than 30% of the total liver volume²². The PVO procedure included either right portal vein ligation during the first stage or percutaneous portal vein embolization (PVE) (right portal vein±branches of segment IV) after the first stage. Interval chemotherapy between the first and second stage to control tumor progression while awaiting liver regeneration was performed in selected patients on a case-by-case basis.

The timing of the second stage hepatectomy was determined by the adequacy of liver regeneration and tumor response to chemotherapy.

During the second stage hepatectomy, a standard/extended right hepatectomy was performed. Patients who had multiple *de novo* metastases in the FRL were not eligible for the second stage hepatectomy; however, for patients with limited *de novo* lesions, associated wedge resections or local ablations in the FRL were performed during the second stage.

After the second stage hepatectomy, adjuvant chemotherapy was usually reintroduced with FOLFOX- or FOLFIRI-based regimens to complete a total of 12 cycles including both preoperative and postoperative period. In patients already treated with prolonged preoperative chemotherapy, administration of adjuvant chemotherapy was determined on an individual basis after discussion at a multidisciplinary tumor board meeting. Patients were screened for recurrence with biologic tumor markers and CT or magnetic resonance imaging every three months during the first two years and every six months thereafter until five years after the second stage hepatectomy.

Operative procedures

In the laparoscopic TSH group, liver resection was performed under a 12mm Hg pneumoperitoneum using 4 to 6 abdominal trocars. Intraoperative ultrasonography was used routinely to guide resection and confirm resectability²³. Transection of the liver parenchyma was performed with ultrasonic laparoscopic coagulating shears or an ultrasonic dissector according to surgeon preference. In the second stage, an anterior approach without earlier mobilization of the right lobe was applied in most patients^{24, 25}..**ELSEVIER NO VIDEO**

In the open TSH group, the procedures were performed through a J-shaped or bilateral subcostal incision. Liver transection was performed using an ultrasonic dissector or ye

crush-clamping method according to surgeon preference. In the second stage, liver resection was performed using the hanging maneuver without earlier mobilization of the right lobe in most patients²⁶.

Postoperative outcomes

Postoperative complications were stratified according to the Clavien-Dindo classification²⁷. To summarize the whole burden of postoperative complications, the Comprehensive Complication Index (CCI) was calculated for each patient²⁸. Clinically relevant liver failure was defined as International Study group of Liver Surgery (ISGLS) grade \geq B²⁹. Ascites was defined as abdominal drainage output of more than 10ml per kg per day after the third postoperative day³⁰. Clinically relevant biliary leakage was defined as ISGLS grade \geq B³¹. Liver-specific complications were determined as liver failure, liver abscess, biliary leakage, biliary stricture, ascites, and abscess formation around the remnant liver. Complications and operative mortality included those that occurred within 90 days after the second stage hepatectomy. Surgical margins were defined as either R0 (microscopically more than 1 mm) or R1 (microscopically less than 1 mm).

Statistical analysis

Data are presented as medians with ranges for continuous variables. Continuous variables were analyzed with a non-parametric approach using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. For propensity score matching (PSM), the logistic regression model was based on the assessment of goodness-of-fit statistics³². In this setting, propensity score adjustment was performed on the factors including baseline patient characteristics [age, sex, American Society of

Anesthesiologists physical status score (ASA score)], primary cancer locations (colon/rectum), preoperative chemotherapy, maximal size and number of lesions, concomitant colorectal resection, and PVO. Using these propensity scores, patients treated with laparoscopic TSH and those treated with open TSH were matched randomly 1:1 with a caliper width of 0.20 of the standard deviation of the score. After assuring the comparability of the groups, postoperative outcomes were compared between the groups. Rates of OS, RFS, and liver-RFS were calculated from the date of the second stage hepatectomy. Cumulative OS, RFS, and liver-RFS rates were calculated using the Kaplan-Meier method with differences between the curves evaluated using the log-rank test. $P < .05$ values were considered statistically significant. All statistical analyses were performed using JMP 11 (SAS Institute, Cary, NC) and Prism 6 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Patient characteristics

A total of 90 patients underwent complete TSH for bilobar CRLM during the study period. Among these, the four patients were treated by a laparoscopic first stage followed by an open second stage hepatectomy were excluded from the analysis. Therefore, 86 patients were reviewed in this study. These patients were separated into two groups: laparoscopic TSH (n = 38) and open TSH (n = 48). After the adjustment of preoperative variables by propensity scoring, 25 patients from each of the laparoscopic and open TSH groups were matched (**Figure 1**).

Patient characteristics in the overall and PSM cohort are detailed in **Table 1**. In the PSM

cohort, there were no differences between the two groups regarding age, sex, BMI, ASA score, primary cancer locations, and lymph node metastases. Similar number and size of liver metastases were observed. Preoperative chemotherapy was performed in all patients, and the median cycles of chemotherapy were comparable between the groups.

First stage hepatectomy

Patient surgical outcomes during the first stage hepatectomy are detailed in **Table 2**. There were no differences between the two groups regarding concomitant colorectal resections, intraoperative blood loss, and postoperative complications. Postoperative hospital stay was much less in the laparoscopic TSH group (4 (0-14) vs. 7.5 (4-15) days; $P < 0.001$).

Second stage hepatectomy

Patient perioperative outcomes during the second stage hepatectomy are detailed in **Table 3**. In the PSM cohort, PVO was performed in all patients in both groups. The interval period between the first and the second stage was comparable between the groups. Interval chemotherapy was performed without differences between the groups.

During the second stage hepatectomy, operative time was comparable between the groups [319 (180-480) vs. 313 (210-490) minutes; $P = 0.508$]. A laparoscopic approach was associated with less intraoperative blood loss [250 (50-1300) vs. 500 (100-2200) ml; $P = 0.040$], less postoperative overall complications (32% vs. 60%; $P = 0.047$), a lesser CCI [0 (0-100) vs. 2e (0-100); $P = 0.045$] and a lesser postoperative hospital stay [9 (4-49) vs. 16 (6-46) days; $P = 0.013$].

Adjuvant chemotherapy was performed without differences between the groups. The interval period between the second stage and adjuvant chemotherapy in the laparoscopic TSH

group was two weeks less than that in the open TSH group [1.6 (1.0-1.8) vs. 2.0 (1.6-3.3) months; $P = 0.039$].

Survival rates after TSH

The rates of OS, RFS, and liver-RFS in the overall and PSM cohort are shown in **Figure 2**. In the PSM cohort, the rates of OS (3-year OS: 80% vs. 54%; $P = 0.154$), RFS (2-year RFS: 20% vs. 18%; $P = 0.200$) and liver-RFS (2-year liver-RFS: 39% vs. 33%; $P = 0.269$) were comparable between the groups (**Figure 2D-F**).

Recurrence patterns and treatments for recurrence after TSH

Patient recurrence patterns and treatments for intrahepatic recurrences after TSH are detailed in **Table 4**. No differences were observed in the recurrence patterns between the groups; however and notably, repeat hepatectomies for intrahepatic recurrences were more performed frequently in the laparoscopic TSH group (56% vs. 0; $P = 0.006$).

DISCUSSION

The present study shows that laparoscopic TSH in the treatment of bilobar CRLM is safe and feasible with favorable postoperative outcomes for selected patients in expert centers. Laparoscopic TSH was associated with less intraoperative blood loss during the second stage, less postoperative complications after the second stage, and a much lesser postoperative hospital stay in both stages, which allowed patients in the laparoscopic TSH group to receive adjuvant chemotherapy two weeks earlier. While both the laparoscopic and open TSH groups

had comparable recurrence rates and recurrence patterns, repeat hepatectomies for intrahepatic recurrences were performed more frequently in the laparoscopic TSH group.

TSH strategy for patients with initially unresectable bilobar CRLM was first introduced in 2000³. This strategy was further developed in association with chemotherapy and PVO, allowing 5-year survival rates of 30 to 50%^{4, 6, 7, 33}. Several types of staged hepatectomies have been reported^{3 9, 20}, which is representative of the heterogeneity of the patients eligible for this strategy. To overcome this heterogeneity and focus on the impact of one operative procedure, we evaluated only patients treated with preoperative chemotherapy, left lobe clearance as the first stage, PVO before the second stage, and a standard/extended right hepatectomy as the second stage after PSM, which made the patient characteristics highly comparable between the laparoscopic and open TSH groups.

For bilobar CRLM, the first choice in our policy is a one stage, multiple parenchyma-sparing hepatectomies. But not all the patients with bilobar CRLM can be resected with these procedures, and major hepatectomies are sometimes inevitable due to tumor sizes or locations. Even if major hepatectomy is necessary, a one stage major hepatectomy with concomitant wedge resections on the other lobe is also performed if the estimated remnant liver volume is enough. The indication for this type of TSH (first stage: left lobe clearance; second stage: major right/extended right hepatectomy) would involve patients with tumors that will require a right-sided major hepatectomy due to tumor sizes and locations close to major vessels but with insufficient estimated remnant liver volume after one stage multiple resections. In this study, only the patients with these indications were reviewed, which minimized the heterogeneity of the patients with bilobar CRLM.

From a technical point of view, the technical difficulty in the TSH lies mainly within the second stage. Although open TSH is widely accepted in specialized centers, the second stage

major hepatectomy is still technically demanding. The plane of liver transection often needs modification between the anatomic lines to achieve margin-negative resections for multiple tumors while preserving sufficient FRL volume. The liver is usually injured by long-term preoperative chemotherapy, which may be responsible for the sinusoidal obstruction syndrome and chemotherapy-associated steatohepatitis, and can be associated with intraoperative bleeding and postoperative morbidity^{34, 35}. Adhesions and inflammation after the first stage and PVO make the dissection of hepatic vessels difficult. To overcome these difficulties, several technical refinements have been proposed, including the use of bioresorbable membranes to avoid adhesions³⁶ or taping the major vascular structures and performing a hanging maneuver during the first stage to make the second stage dissection easier³⁷.; however, these technical tips have not contributed to a fundamental solution.

The laparoscopic approach has multiple theoretic benefits in the technical aspects of TSH. Laparoscopy provides less adhesion formation after the first stage, less intraoperative bleeding because of the the pneumoperitoneum¹⁸, and good visibility of the operative field due to the magnifying effect^{18, 24}, which could be a fundamental solution to overcome the above-mentioned difficulties. For such reasons, our group has gradually switched from the open to the laparoscopic TSH after the step-by-step learning curve of laparoscopic minor and major hepatectomies. Moreover, to facilitate the laparoscopic vascular control during the second stage, we systematically ask the interventional radiologist during PVE procedure to leave at least one-centimeter of the right portal vein and keep the segment I tributary free to avoid heavy inflammation and keep the vessels soft. Furthermore, preserving the gall bladder intact during the first stage may facilitate dissection of the right pedicle during the second stage. The results of the present study suggest that laparoscopic TSH would be technically acceptable for selected patients in expert centers.

Another advantage of a laparoscopic TSH would be less incisions, which contributes not only to decrease the operative trauma, postoperative pain, and adhesions but also to decrease the time of laparotomy and wound closure. In this study, the operative time in the first stage was somewhat less in the laparoscopic group. In the first stage, the time of liver transection and liver mobilization is relatively less than that of the second stage, and the time of laparotomy and abdominal closure is important to determine the overall operative time. Although there could exist potential selection bias, the results of this study showed this benefit of laparoscopic approach in the first stage.

From an oncologic point of view, the key issues are to complete the two-staged sequence without interruption and continue appropriate postoperative treatments after the completion of TSH. The main determinant of prognosis is the completion of resection³⁸; the inability to complete the TSH is reported to be 15-30% related primarily to tumor progression during the interval period^{7, 39}. In this context, it is important to perform the first stage with a quick recovery and less complications to allow completion of the second stage or to restart chemotherapy as soon as possible. In the present study, laparoscopic first stage hepatectomy allowed patients to be discharged earlier, which is reflective of less operative stress and quick recovery and would facilitate the following sequence of the treatment. Even though there was no difference in complication rates and other intraoperative outcomes which showed that both approaches were safe for the first stage, a laparoscopic, first stage hepatectomy had advantages for quicker recovery compared to the open approach. Contrary to our expectations, however, the interval periods between the stages were not different between the groups. One reason would be that the interval period is determined mainly determined by the adequacy of liver regeneration even if the patient has recovered quickly.

The role of adjuvant chemotherapy in improving RFS in patients presenting with

resectable CRLM as demonstrated previously^{40 41}. Although the role of adjuvant chemotherapy after TSH has not been fully documented, several previous studies revealed its association with greater OS after TSH^{7, 39}. Moreover, a recent study revealed that a shortm chemotherapy-free interval was associated with improved oncologic outcomes in patients undergoing TSH⁴². Our group also demonstrated the benefits of laparoscopy to shorten the interval from operation to adjuvant chemotherapy within 8 weeks in a larger CRLM cohort⁴³. In the present study, the laparoscopic second stage hepatectomy provided quick patient recovery, which allowed the start of adjuvant chemotherapy two weeks earlier. These results suggest that one of the potentially important oncologic benefits of laparoscopic TSH would be a faster initiation of adjuvant chemotherapy.

Regarding long-term recurrence after TSH, no differences (or improvements) were observed between the groups in the RFS and liver-RFS rates in the PSM cohort. Notably, however, repeat hepatectomies for intrahepatic recurrences were performed more frequently performed in the laparoscopic TSH group. The impact of repeat hepatectomy on long-term survival for CRLM recurrence after TSH was reported previously⁴⁴. Because the reported recurrence rate is quite high after TSH, repeat operations for recurrence would be crucial for ensuring long-term survival in these patients⁴⁴. Laparoscopic TSH would be a favorable approach to facilitate a third or more repeat hepatectomies thanks to the decreased invasiveness and adhesion formation.

There are several limitations in this study. First, this is a retrospective study over a relatively long study period. The relatively small number of events might have led to insufficient statistical power with the possibility of a type II error in the comparison of outcomes between groups. Although patient characteristics were well-matched in the PSM cohort, this study was not a prospective randomized trial. We believe that the inclusion of

data from multiple centers that were experienced in two-stage procedures reinforce the observed results. It should be noted that ven though the number and size of the tumors were matched, the tumor locations were not matched, however, only the patients with the indication of TSH including right-sided major hepatectomy were included in this analysis , which minimized the differences of the operative outcomes. Second, the follow-up period was relatively short to make conclusions regarding long-term, oncologic outcomes in patients with CRLM, although it might be acceptable to evaluate RFS, because since 70% of recurrences develop within two years after hepatectomy in patients with CRLM⁴⁵ and the tumor characteristics of bilobar CRLM are more aggressive. Third, due to the multi-institutional design, the operative techniques, especially that of laparoscopic TSH, may differ between the centers despite the fact that the laparoscopic procedures were performed by expert surgeons well-experienced in both laparoscopic and liver surgeries, which minimizes the difference of surgical quality among the institutions.

CONCLUSION

The present study demonstrated the safety and feasibility of laparoscopic TSH for bilobar CRLM. Laparoscopic TSH was associated with less postoperative complications and a lesser hospital stay, which led to earlier administration of adjuvant chemotherapy compared to open TSH. While both groups had comparable rates of postoperative complications and recurrence and recurrence patterns, repeat hepatectomies for intrahepatic recurrences were performed more frequently performed in the laparoscopic TSH group. Laparoscopic TSH would be technically feasible and would have both surgical and oncologic benefits for

selected patients.

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FIGURE LEGENDS

Figure 1.

Flow diagram of the process of patient selection and propensity score matching.

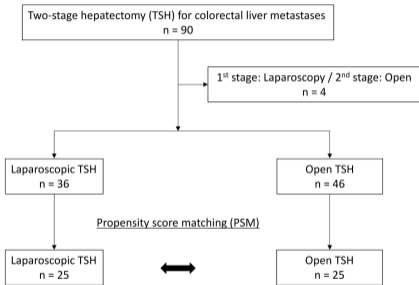
Figure 2.

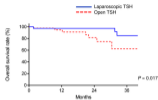
A)-C) Survival rates in patients undergoing laparoscopic two-stage hepatectomy (TSH) (blue, solid) and open TSH (red, dotted) in the overall cohort.

(A: Overall survival rate, B: Recurrence-free survival rate, C: Liver-recurrence-free survival rate)

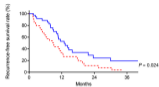
D)-F) Survival rates in patients undergoing laparoscopic two-stage hepatectomy (TSH) (blue, solid) and open TSH (red, dotted) in the propensity score matching cohort.

(D: Overall survival rate, E: Recurrence-free survival rate, F: Liver-recurrence-free survival rate)

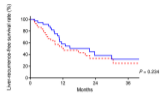


A

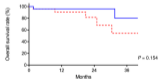
No. at risk	0	12	24	36
Laparoscopic TSH	38	33	20	12
Open TSH	48	27	15	3

B

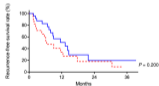
No. at risk	0	12	24	36
Laparoscopic TSH	38	15	5	3
Open TSH	48	18	3	0

C

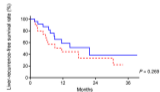
No. at risk	0	12	24	36
Laparoscopic TSH	38	16	6	4
Open TSH	48	18	5	3

D

No. at risk	0	12	24	36
Laparoscopic TSH	38	21	9	3
Open TSH	25	15	7	2

E

No. at risk	0	12	24	36
Laparoscopic TSH	25	8	2	1
Open TSH	26	8	2	0

F

No. at risk	0	12	24	36
Laparoscopic TSH	25	9	3	1
Open TSH	26	7	3	0

Table 1. Patient characteristics of laparoscopic two-stage hepatectomy (TSH) and open TSH: the overall cohort and propensity score matching (PSM) cohort.

Variables	Overall cohort (n = 86)			PSM cohort (n = 50)		
	Laparoscopy (n = 38)	Open (n = 48)	P	Laparoscopy (n = 25)	Open (n = 25)	P
Age, y	62 (32-85)	61 (35-76)	0.589	62 (36-82)	62 (48-76)	0.484
Sex, Male / Female	26 / 12	27 / 21	0.249	16 / 9	18 / 7	0.544
BMI, kg/m ²	23.4 (16.4-32.4)	24.7 (17.2-37.9)	0.287	23.0 (18.0-31.1)	25.1 (18.4-35.4)	0.309
ASA score \geq 3	6 (16)	10 (20.4)	0.551	3 (12)	6 (24)	0.270
Primary cancer location: Rectum	11 (29)	11 (23)	0.524	7 (28)	6 (24)	0.747
Lymph node metastasis	27 (71)	30 (63)	0.405	20 (80)	15 (60)	0.123
Preoperative chemotherapy	38 (100)	46 (96)	0.203	25 (100)	25 (100)	-
Number of cycles	7.5 (4-16)	7 (0-14)	0.935	9 (4-16)	8 (4-14)	0.721
Molecular-targeting agents	21 (55)	23 (48)	0.499	14 (56)	13 (52)	0.776
Bevacizumab	16 (42)	14 (29)	0.211	9 (36)	8 (32)	0.765
Cetuximab or Panitumumab	5 (13)	9 (19)	0.485	5 (20)	5 (20)	1.000
Synchronous metastases	35 (92)	44 (92)	0.941	24 (96)	22 (88)	0.297
Preoperative CEA (First stage)	7.3 (1.7-270.0)	7.1 (1.3-95.0)	0.586	7.0 (1.7-53.7)	7.7 (2.0-29.2)	0.848
Duration from primary resection to first stage hepatectomy, months	4.6 (0-82.7)	5.2 (0-58.9)	0.557	6.5 (0-82.7)	5.8 (0-58.9)	0.807
Concomitant extrahepatic disease	3 (8)	5 (10.4)	0.689	2 (8.0)	4 (16)	0.384
Number of lesions (First stage)	2 (1-6)	2 (1-6)	0.831	2 (1-5)	2 (1-6)	0.621
Number of lesions (Second stage)	3.5 (1-11)	4 (1-20)	0.817	4 (1-11)	4 (1-20)	0.695
Number of lesions (Total)	6 (2-13)	5 (2-23)	0.758	7 (2-13)	8 (2-23)	0.725
Maximal size of lesions (First stage), mm	16.5 (3-50)	15 (4-40)	0.764	16 (3-40)	15 (7-40)	0.801
Maximal size of lesions (Second stage), mm	27.5 (10-160)	40 (10-130)	0.418	35 (10-160)	40 (14-130)	0.398
Maximal size of lesions (Total), mm	35 (15-160)	40 (10-130)	0.628	35 (15-160)	40 (17-130)	0.367

Data are expressed as median (range) or n (%) unless otherwise indicated.

ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen.

Table 2. Perioperative outcomes of laparoscopic and open first stage hepatectomy: the overall cohort and propensity score matching (PSM) cohort.

Variables	Overall cohort (n = 86)			PSM cohort (n = 50)		
	Laparoscopy (n = 38)	Open (n = 48)	P	Laparoscopy (n = 25)	Open (n = 25)	P
Concomitant colorectal resection	14 (36.7)	15 (31)	0.586	4 (16)	4 (16)	1.000
Inflow clamping	9 (24)	17 (35)	0.239	9 (36)	8 (32)	0.765
Duration of inflow clamping, min	0 (0-30)	0 (0-65)	0.313	0 (0-30)	0 (0-65)	0.924
Operative time, min	159 (70-415)	210 (125-420)	0.001	137 (70-383)	210 (125-360)	<0.001
Blood loss, ml	50 (0-350)	50 (0-500)	0.469	50 (0-350)	50 (0-400)	0.254
Intraoperative transfusion	0	0	-	0	0	-
Conversion to open surgery	1	-	-	0	-	-
Resection margin status (R0)	37 (97)	44 (92)	0.262	24 (96)	22 (88.0)	0.297
Postoperative complications	6 (16)	12 (25)	0.297	3 (12)	6 (24)	0.270
Clavien-Dindo I-II complications	3 (8)	8 (17)	0.226	1	4 (16)	0.157
Clavien-Dindo III-V complications	3 (8)	4 (8)	0.941	2	2	1.000
Liver-specific complications	0	4 (8)	0.068	0	2	0.149
Liver-specific Clavien-Dindo I-II complications	0	2	0.203	0	1	0.312
Liver-specific Clavien-Dindo III-V complications	0 (0.0)	2 (4.4)	0.203	0 (0.0)	1	0.312
CCI	0 (0-33.7)	0 (0-47.3)	0.284	0 (0-33.7)	0 (0-47.3)	0.297
Hemorrhage	0	0	-	0	0	-
Liver failure (≥ISGLS grade B)	0	0	-	0	0	-
Biliary leakage (≥ISGLS grade B)	0	3 (6)	0.117	0	2	0.149
Respiratory complication	0	4 (8)	0.068	0	3 (12)	0.074
Leakage of colorectal anastomosis	1	1	0.867	1	0	0.312
Reoperation	2	3 (6)	0.846	1	1	1.000
Postoperative mortality	0	0	-	0	0	-
Hospital stay, day	6 (0-34)	7 (4-29)	0.012	4 (0-14)	7.5 (4-15)	<0.001

Data are expressed as median (range) or n (%).

CCI, Comprehensive Complication Index; ISGLS, International Study Group of Liver Surgery; PSM, propensity score matching.

Table 3. Perioperative outcomes of laparoscopic and open second stage hepatectomy: the overall cohort and propensity score matching (PSM) cohort.

Variables	Overall cohort (n = 86)			PSM cohort (n = 50)		
	Laparoscopy (n = 38)	Open (n = 48)	P	Laparoscopy (n = 25)	Open (n = 25)	P
Interval period between the first and second stage hepatectomy, months	2.8 (0.7-11.5)	2.5 (1.3-11.0)	0.225	2.3 (0.7-9.9)	2.5 (1.4-11.0)	0.838
Portal vein occlusion	25 (66)	48 (100)	< 0.001	25 (100)	25 (10)	-
Interval chemotherapy	18 (47)	16 (33)	0.186	7 (28.)	9 (36)	0.544
Extended right hepatectomy	10 (26)	16 (33)	0.482	10 (40)	9 (36)	0.771
Associated wedge resection	3 (8)	4 (8)	0.941	1	2	0.552
<u>Number of wedge resection</u>	<u>0 (0-2)</u>	<u>0 (0-2)</u>	<u>0.949</u>	<u>0 (0-1)</u>	<u>0 (0-2)</u>	<u>0.540</u>
Associated radiofrequency ablation	2	1	0.425	2	0	0.149
<u>Number of radiofrequency ablation</u>	<u>0 (0-1)</u>	<u>0 (0-1)</u>	<u>0.428</u>	<u>0 (0-1)</u>	<u>0</u>	<u>0.153</u>
Operative time, min	305 (150-480)	300 (210-490)	0.765	319 (180-480)	313 (210-490)	0.508
Blood loss, ml	225 (50-1300)	450 (50-2200)	0.026	250 (50-1300)	500 (100-2200)	0.040
Inflow clamping	15 (40)	24 (50)	0.330	14 (56)	10 (40)	0.258
Duration of inflow clamping, min	0 (0-120)	0 (0-75)	0.835	15 (0-120)	0 (0-75)	0.164
Intraoperative transfusion	5 (13.)	14 (29)	0.076	2	9 (36)	0.017
Conversion to open surgery	4 (11)	-	-	2	-	-
<u>Resection margin status (R0)</u>	<u>36 (95)</u>	<u>44 (92)</u>	<u>0.579</u>	<u>23 (92)</u>	<u>22 (88)</u>	<u>0.637</u>
Postoperative complications	10 (26)	24 (50)	0.026	8 (32)	15 (60)	0.047
Clavien-Dindo I-II complications	3 (8)	9 (19)	0.149	2 (8)	3 (12)	0.637
Clavien-Dindo III-V complications	7 (18)	15 (31)	0.176	6 (24)	12 (48)	0.077
Liver-specific complications	9 (24)	21 (44)	0.053	7 (28.0)	15 (60)	0.023
Liver-specific Clavien-Dindo I-II complications	2	7 (15)	0.161	1	3 (12)	0.297
Liver-specific Clavien-Dindo III-V complications	7 (18.4)	14 (29)	0.249	6 (24)	12 (48)	0.077
CCI	0 (0-100)	4.4 (0-100)	0.032	0 (0-100)	22.6 (0-100)	0.045
Hemorrhage	0	1	0.371	0	1	0.312
Liver failure (≥ISGLS grade B)	2	2	0.811	2	1	0.552
Biliary leakage (≥ISGLS grade B)	4 (11)	9 (19)	0.290	3 (12)	8 (32)	0.088
Ascites	2	4 ()	0.579	2	2	1.000
Respiratory complication	1	6 (12.5)	0.097	1	3 (12)	0.297
Reoperation	0	1	0.371	0	1	0.312
Postoperative mortality	1	1	0.867	1	1	1.000
Hospital stay, day	9 (4-49)	14 (6-46)	<0.001	9 (4-49)	16 (6-46)	0.013
Postoperative adjuvant chemotherapy	22 (57.9)	23 (48)	0.358	13 (52)	11 (44)	0.571
Interval period between the second stage hepatectomy and adjuvant chemotherapy, months	1.4 (0.9-3.5)	2.0 (1.6-3.3)	0.007	1.6 (1.0-1.8)	2.0 (1.6-3.3)	0.039

Data are expressed as median (range) or n (%) unless otherwise indicated.

CCI, Comprehensive Complication Index; ISGLS, International Study Group of Liver Surgery; PSM, propensity score matching.

Table 4. Recurrence patterns and treatments for recurrence after two-stage hepatectomy: the overall cohort and propensity score matching (PSM) cohort.

Variables	Overall cohort (n = 86)			PSM cohort (n = 50)		
	Laparoscopy (n = 38)	Open (n = 48)	<i>P</i>	Laparoscopy (n = 25)	Open (n = 25)	<i>P</i>
Recurrence pattern						
Intrahepatic recurrence	17 (45)	17 (35)	0.380	9 (3)	10 (40)	0.771
Extrahepatic recurrence	13 (34)	22 (46)	0.276	8 (32)	9 (36)	0.765
Combined intra/extrahepatic recurrence	8 (21)	10 (21)	0.980	4 (1)	5 (20)	0.713
Lung recurrence	9 (24)	14 (29)	0.568	6 (24)	7 (28)	0.747
Peritoneal recurrence	6 (16)	6 (13)	0.662	3 (12)	1	0.297
Lymph node recurrence	1	3 (6)	0.429	1	1	1.000
Primary colorectal recurrence	2	1	0.425	1	0	0.312
Brain recurrence	0	2	0.203	0	1	0.312
Treatment for intrahepatic recurrence; n (% of intrahepatic recurrence)						
Repeat hepatectomy	10 (59)	2 (12)	0.004	5 (56)	0	0.006
Radiofrequency ablation	2 (12)	1	0.545	1 (11)	1 (10)	0.937
Radiotherapy	0	1	0.310	0	1 (10)	0.330
Chemotherapy only	5 (2)	13 (77)	0.006	3 (33)	8 (80)	0.040

Data are expressed as median (range) or n (%) unless otherwise indicated.

PSM, propensity score matching.