ORIGINAL ARTICLE

Feasibility, safety and efficacy of two-stage hepatectomy for bilobar liver metastases of colorectal cancer: a LiverMetSurvey analysis

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Abstract

Background: The combination of liver resection and chemotherapy has become the standard of care for colorectal liver metastases (LM). The objective of the present study was to evaluate the impact of two-stage hepatectomy (TSH) on the long-term survival of patients with bilobar LM.

Methods: We included adult (over-18) patients from the LiverMetSurvey registry with confirmed multiple colorectal LM and having undergone either one-stage hepatectomy or TSH with curative intent. The "TSH (2/2)" group (n = 625) comprised patients having completed both stages of TSH; the "TSH (1/2)" group (n = 244) comprised patients having undergone only the first stage of TSH; the "hepatectomy" group. The primary outcome criterion was the overall survival (OS). The secondary outcomes were the morbidity and mortality rates.

Results: The 30- and 90-day mortality rates were respectively 3.8% and 9.3% in the TSH (2/2) group, 9.4% and 16.4% in the TSH (1/2) group, and 5.4% and 9.1% in the "hepatectomy" group. The three-year OS rate was 45% in the TSH (2/2) group, 30% in the TSH (1/2) group and 50.7% in the hepatectomy group.

Conclusion: The LiverMetSurvey registry's data indicate that TSH is associated with rather good long-term survival and acceptable morbidity and mortality rates.

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Introduction

The combination of liver resection and chemotherapy has become the standard of care for colorectal liver metastases (CRLM), and is currently the only potentially curative treatment for patients with bilobar LM.[1–3] However, only 20% of patients with CRLM are resectable at the time of diagnosis.[4,5] The resectability of CRLM is defined by two criteria: (i) adequate vascular inflow/outflow and biliary drainage, and (ii) a sufficient future liver remnant volume.[6] Advances in surgical strategies and cancer treatment have been developed in order to increase the proportion of resectable patients.[7–11]

In two-stage hepatectomy (TSH), two sequential liver resections are combined when it is impossible to resect all the patient's CRLM in a single procedure.[12] From an oncologic standpoint, TSH is associated with acceptable long-term outcomes;[7,10,13–18] however, data on fewer than 500 patients have been published to date.[14]

The objective of the present study was to evaluate the impact of TSH on the long-term survival of patients with CRLM.

Patients and methods

Population

Between January 2000 and December 2014, patients operated on for CRLM were included in an international registry (LiverMetSurvey, http://www.livermetsurvey.org) involving 359 investigating centers located in 60 countries.

We included adult (over-18) patients from the LiverMetSurvey registry with confirmed multiple colorectal LM and having undergone either one-stage hepatectomy or TSH with curative intent. Depending on the patient's clinical status, the LM could be resected immediately upon admission or after induction chemotherapy. Initial staging was performed at the attending physician's discretion and could include CT with contrast enhancement or MRI with liver-specific contrast enhancement. Patients with a single liver metastasis, patients with metastases in more than one extrahepatic site, patients not having undergone hepatectomy and patients operated on before 2000 were excluded from the study. The study flowchart is shown in Fig. 1.

The experimental group

The experimental group (n = 625) corresponded to the "TSH (2/2)" group, which comprised patients having completed the entire sequence (including either portal vein ligation or embolization). To be included in the TSH (2/2) group, a patient had to meet the following criteria: (i) a planned two-stage procedure; (ii) two separate dates for the confirmed performance of hepatectomy, and (iii) a time interval of less than 6 months between these two dates.

The control groups

The first control group (n = 244) corresponded to the "TSH (1/2)" group, which comprised patients having undergone only the

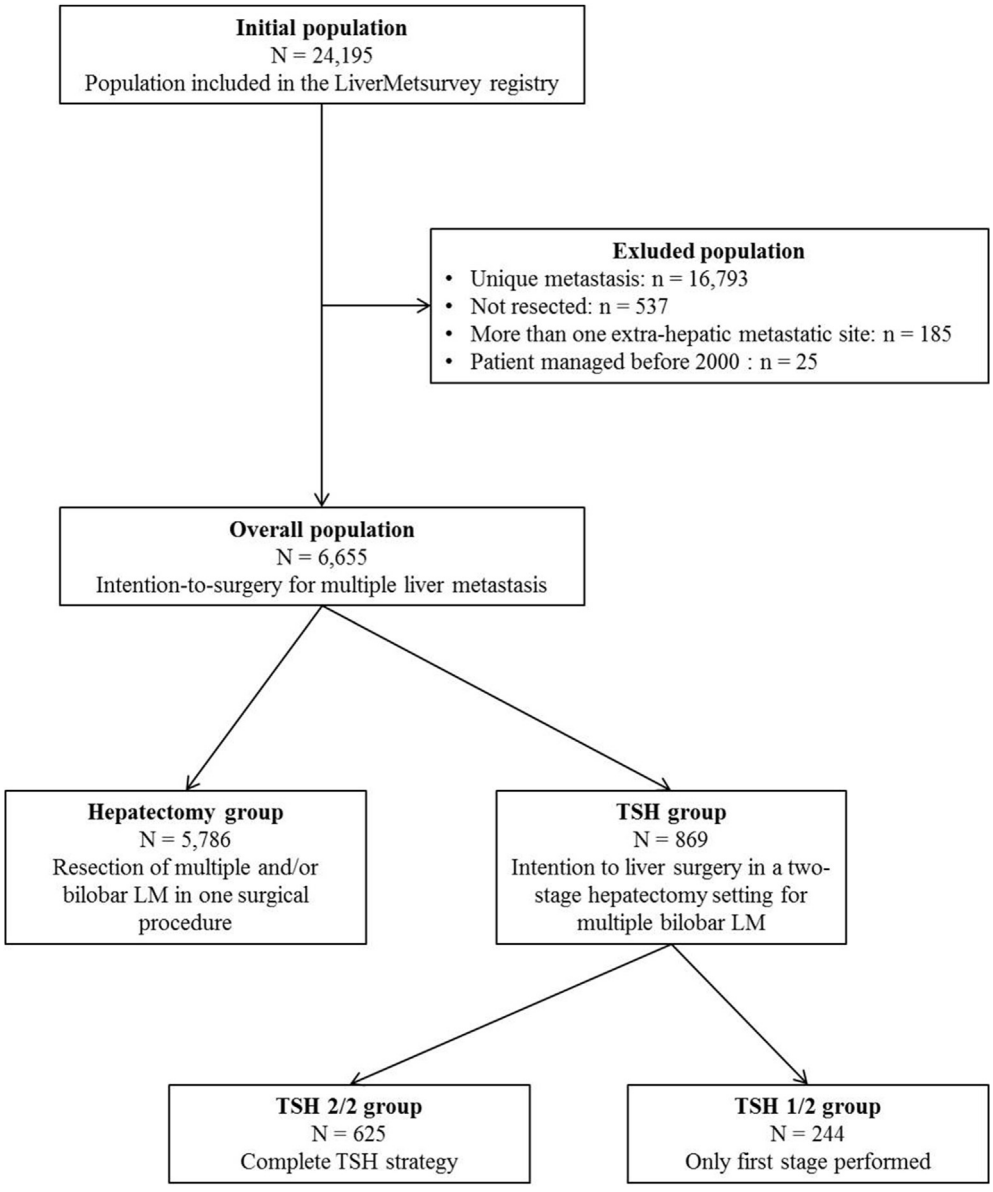


Figure 1 Study flowchart

first stage of TSH. To be included in the TSH (1/2) group, a patient had to meet the following criteria: (i) a planned two-stage procedure (as in the TSH (2/2) group) and (ii) a single date for the confirmed performance of hepatectomy. To ensure that the data were not missing, we always established whether a reason for non-completion of the entire sequence had been given in the patient's medical records.

The second control group (for short-and long-term comparisons with the TSH (2/2) group) corresponded to the "hepatectomy" group, which comprised patients (n = 5786) in whom all the LM could be resected in a single surgical procedure. To be included in the hepatectomy group, a patient had to meet the following criteria: (i) the presence of multiple liver metastases, and (ii) no planned two-stage procedure. The choice of type of hepatectomy (hepatectomy or TSH) was made by the surgeon after checking the number of metastases, their location (number of segments without tumor), the proximity with arterial and venous vessels, the patient's anatomy and the anticipated postoperative course (small for size syndrome, induced hepatocellular insufficiency).

Primary outcome

The primary outcome criterion was the overall survival (OS) time (the length of time between the first liver resection and last follow-up or death, as defined by the US National Cancer Institute). We also calculated the 3-year OS and 5-year OS rates.

Secondary outcomes

The secondary outcomes were variously related to:

1 non-completion of TSH (the TSH non-completion rate, risk factors for non-completion of TSH, and reasons for non-completion).
2 morbidity and mortality (the mortality rates at postoperative days 30, 60 and 90, defined as the number of deceased patients in each group at each time point; the morbidity rate (including hepatic events such as biliary fistulae and hepatocellular insufficiency) and remote events (pulmonary events, thromboembolic events, and wound-related events). In the TSH (2/2) group, incident events were noted after the second hepatectomy but included events occurring after the first or the second hepatectomy.
3 disease-free survival (DFS), defined as the length of time between completion of TSH and the last follow-up visit with no recurrence.
4 the prognostic value of TSH (defined as the non-inferiority of TSH vs. one-stage hepatectomy after patients had been matched via a propensity score (PS)); and long-term predictors of OS in the TSH (2/2) group.

Definitions

Non-completion rate: the proportion of patients who did not access the second hepatectomy stage.

Remote events: postoperative events that occurred far from the surgical site.

Data quality

The accuracy of the recorded data was not specifically assessed. Each center was responsible for completing its own data. Nevertheless, an independent data manager checked inconsistent data (e.g. a date of diagnosis that was later than the date of hepatectomy).

Statistical analysis

Quantitative variables were expressed as the mean ± standard deviation (SD) or the median (range). Qualitative variables were expressed as the number (percentage). Univariate analyses were based on a Mann–Whitney test (for quantitative variables) and Fisher's test (for qualitative variables) because of the distribution of data.

Survival data were presented as Kaplan–Meier curves showing the patients at risk. The Kaplan–Meier method was used to evaluate the probability of survival, and groups were compared in a log rank test. To identify predictors of long-term survival, a multivariate analysis with a Cox proportional hazards model and a backward conditional method was applied. The model including clinical characteristics (comorbidities), oncological characteristics, the surgical procedure performed during the first hepatectomy, the tumor characteristics recorded in the pathological assessment, the surgical procedure during the second stage and the management of extrahepatic metastases (e.g. lung metastases). The results were presented as a hazard ratio (HR) [95% confidence interval (CI)].

All clinical characteristics (comorbidities), oncological characteristics, the surgical procedure performed during the first hepatectomy and the tumor characteristics recorded in the pathological assessment were tested as potential risk factors for the non-completion of TSH. Variables with a p value ≤ 0.2 in a univariate analysis were included in a multivariate analysis. Only variables with a p value ≤ 0.1 were retained in the multivariate analysis. The results were presented as an HR [95% CI].

In view of certain differences in baseline demographic characteristics between the TSH (2/2) and hepatectomy groups, a PS-matched analysis was performed for OS, DFS and morbidity. The propensity score (PS) was defined as a patient's probability of allocation (comprised between 0% and 100%) to the TSH (2/2) group or the hepatectomy group when considering the presence of confounding factors. To calculate the PS, a univariate analysis was used to identify confounding factors (i.e. independent variables) that influenced the choice of the surgical procedure (TSH (2/2) vs. hepatectomy, i.e. the dependent variable). Factors with a p value ≤ 0.2 were included in the multivariate analysis. In the latter analysis, only factors with a p value ≤ 0.1 were retained. This matching enabled confounding factors to be distributed equally between the two groups. Both matched and non-matched analyses were performed: in matched analyses, a

Wilcoxon test was used for quantitative data and a Fisher test was used for qualitative data. For the assessment of interactions between quantitative variables, we used the variation of R^2; for the interactions between a quantitative variable and a qualitative variable on one side; between two qualitative variables on the other, we used the non-standardized odd ratio.

We performed multiple imputation with two hundred replications for patients not analyzed for the primary endpoint. Only age and sex were found to be predictive of missing data and were therefore included in the imputation model.

For all analyses, a p value ≤ 0.05 was considered to be statistically significant. Statistical analyses were performed with SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA) and PASW software (version 18, SPSS Inc., Chicago, IL, USA).

Results

Missing data

In this series, no missing data was reported for the follow up and the condition of the patient (alive yes/no). Less than 3% of patients had missing data for the T stade, the size of metastases, the use of radiological drainage and the cause of death. Between 7 and 9% of the patients had missing data for the presence of a postoperative outcome (7.9%); the reintervention (9.1%) and for the length of stay (7.3%) (eTable 1).

Population characteristics

The characteristics of the study population are summarized in Table 1. A total of 869 patients were included in the study (625 in the TSH (2/2) group and 244 in the TSH (1/2) group). In both the TSH (1/2) and (2/2) groups, over 60% of patients received chemotherapy before hepatectomy. Thirty-five percent of the patients had more than 6 cycles; 40% of these cycles were oxaliplatin-based and 20% were irinotecan-based. Fifty-one percent of the patients in the hepatectomy (control) group received chemotherapy before hepatectomy. Thirty percent of these cycles were oxaliplatin-based and 15% were irinotecan-based. During the first stage of the TSH procedure (i.e. TSH (1/2) and the first stage of TSH (2/2)), 799 patients (91.9%) underwent minor left hepatectomies, including left lobectomy and one or more wedge resections in the left lobe (p = 0.72).

Short-term mortality

The overall 30-day, 60-day and 90-day mortality rates were respectively 5.4%, 9.2% and 11.3% in the overall TSH population, 3.8%, 7.2% and 9.3% in the TSH (2/2) group, and 9.4%, 14.3% and 16.4% in the TSH (1/2) group. The intergroup differences in mortality were statistically significant at 30 days (p < 0.001), 60 days (p = 0.009) and 90 days (p = 0.013) (Table 2).

In the "hepatectomy" group, the 30-day, 60-day and 90-day mortality rates were respectively 5.4%, 7.2% and 9.1%. These rates did not differ significantly from those observed in the TSH groups at either 30 days (p = 0.84), 60 days (p = 0.31) or 90 days (p = 0.16).

Postoperative morbidity

The postoperative morbidity rates are reported in Table 2. There were no significance differences between the TSH (2/2) and TSH (1/2) groups in terms of the various types of postoperative adverse event (biliary fistulae, liver failure, thromboembolic events, and wound-related events). The incidence of postoperative radiological drainage was similar in the two groups (13.9% vs. 15.2% in the TSH (2/2) and TSH (1/2) groups, respectively; p = 0.54). This trend was the same for the repeat surgery rate (7.2% vs. 5.7% in the TSH (2/2) and TSH (1/2), respectively; p = 0.53). The incidence of pulmonary events was higher in the TSH (2/2) group than in the TSH (1/2) group (4.8% vs. 2.5%, respectively; p = 0.02).

There were no significance differences between the TSH groups and hepatectomy groups in terms of the various types of postoperative adverse events (biliary fistulae, hepatocellular insufficiency, thromboembolic events, and wound-related events). Likewise, there was no difference in the repeat surgery rate (6.8% in the pooled TSH group – i.e. TSH (2/2) plus TSH (1/2) – vs. 8.9% in the hepatectomy group, p = 0.40). The incidence of postoperative radiological drainage was three times greater in the pooled TSH group than in the hepatectomy group (14.3% vs. 4.1%, respectively; p = 0.007). The median length of stay was 2 days longer in the pooled TSH group than in the hepatectomy group (13 vs. 11 days, respectively; p = 0.03).

Non-completion of TSH

TSH was not completed in 28.1% of the study population; this was mainly due to tumor progression or disease recurrence after the first hepatectomy. Hence, the scheduled TSH plan was completed in 71.9% of the study population.

Risk factors for non-completion of TSH

The identified risk factors for non-completion of TSH were repeat hepatectomy for recurrence (HR [95% CI] = 26.66 [15.92–44.64]; p < 0.001), the presence of an extrahepatic metastatic site (HR [95% CI] = 1.87 [1.02–2.37]; p = 0.04), failure to achieve R0 resection in the first stage of TSH (HR [95% CI] = 2.31 [1.36–3.95]; p = 0.002), and the absence of chemotherapy before hepatectomy (HR [95% CI] = 1.86 [1.15–2.99]; p = 0.01).

Reasons for failure

Two hundred and forty-four patients did not access the second stage. Eighty-three patients (34%) experienced a postoperative outcome, including 11 cases of biliary fistulae; 17 (6.9%) reoperated, 88 (36.1%) presented another extrahepatic metastatic site, and 61 (25%) presented with R1 first-stage resection.

Overall survival

The maximum follow-up period for patients analyzed in this series was 10 years. For the TSH (2/2), TSH (1/2) and

Table 1 Characteristics of the study population

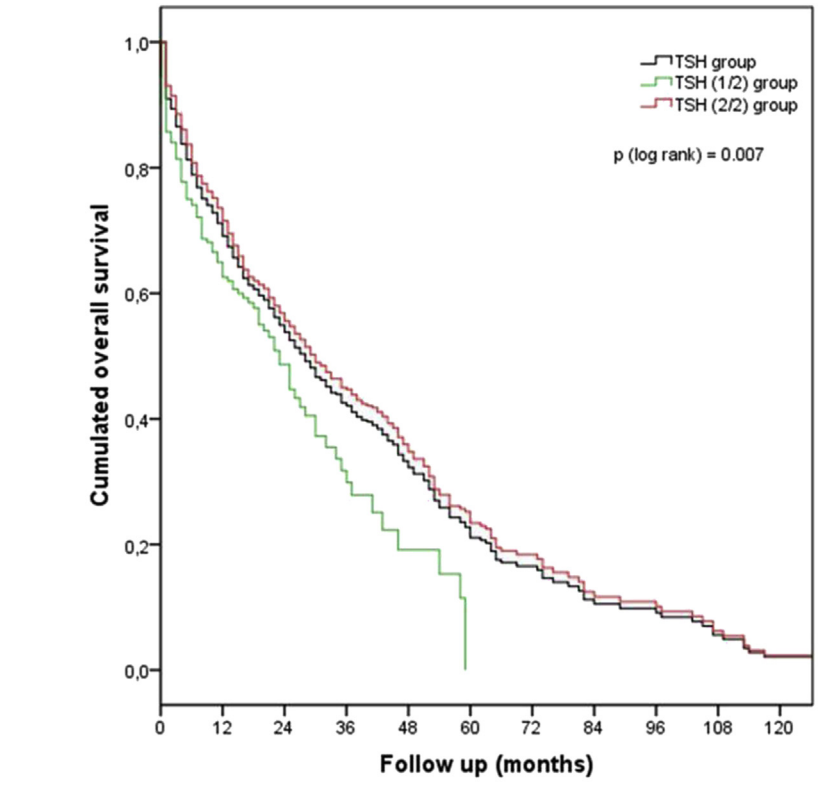
	TSH group n = 869	Hepatectomy group n = 5786	p Value
Age, median (range)	60 (23–96)	59 (29–94)	0.69
Male gender, n (%)	535 (62)	3529 (61)	0.84
T3–T4, n (%)	664 (76)	4513 (78)	0.31
N0, n (%)	218 (25)	1388 (24)	0.39
Synchronous LM, n (%)	709 (82)	4687 (81)	0.74
Tumor site, n (%):			0.12
Rectum	283 (33)	2083 (36)	
Left colon	418 (48)	2604 (45)	
Transverse	30 (4)	173 (3)	
Right colon	138 (16)	926 (16)	
Number of LM, median (range)	7 (2–41)	6 (2–37)	0.22
Size of LM, mean ± SD	45 ± 26	44 ± 27	0.41
Chemotherapy before hepatectomy, n (%)	554 (64)	3761 (65)	0.53
Number of chemotherapy cycles, median (range)	6 (1–66)	6 (1–42)	0.77
CEA level, median (range)	9 (0.4–10,271)	9 (0.3–2814)	0.84
Repeat hepatectomy, n (%)	499 (57)	1099 (19)	0.02
Laparoscopy, n (%)	45 (5)	174 (3)	0.04
Peroperative transfusion, n (%)	118 (14)	694 (12)	0.56
Anatomical resection, n (%)	340 (39)	2256 (39)	0.93
Pringle maneuver, n (%)	124 (14)	752 (13)	0.60
Pulmonary metastasis, n (%)	209 (24)	1157 (20)	0.04
Cancer-free margin, n (%)	505 (58)	3124 (54)	0.03
One or more positive lymph nodes, n (%)	35 (4)	231 (4)	0.74

Table 2 Postoperative morbidity and short-term mortality[a]

	TSH (2/2) n = 625	TSH (1/2) n = 244	p Value	TSH n = 869	Hepatectomy n = 5786	p Value
Postoperative adverse events, n (%)	157 (25.1)	71 (29.1)	0.10	228 (26.2)	1395 (24.1)	0.12
Biliary fistulae, n (%)	27 (4.3)	10 (4)	0.57	37 (4.3)	242 (4.2)	0.48
Hepatocellular insufficiency, n (%)	16 (2.6)	5 (2)	0.46	21 (2.4)	201 (3.5)	0.11
Pulmonary events, n (%)	31 (4.8)	6 (2.5)	0.02	37 (4.3)	272 (4.7)	0.36
Thromboembolic events, n (%)	6 (0.9)	0 (0)	0.09	6 (0.7)	48 (0.8)	0.61
Wound-related events, n (%)	23 (3.7)	8 (3.3)	0.78	31 (3.6)	118 (2.0)	0.39
Postoperative radiological drainage, n (%)	87 (13.9)	37 (15.2)	0.54	124 (14.3)	238 (4.1)	0.007
Repeat surgery, n (%)	45 (7.2)	14 (5.7)	0.53	59 (6.8)	513 (8.9)	0.40
30-day mortality, n (%)	24 (3.8)	23 (9.4)	<0.001	47 (5.4)	313 (5.4)	0.84
60-day mortality, n (%)	45 (7.2)	35 (14.3)	0.009	80 (9.2)	417 (7.2)	0.31
90-day mortality, n (%)	58 (9.3)	40 (16.4)	0.013	98 (11.3)	524 (9.1)	0.16
Length of stay, days, median (range)	13 (0–130)	13 (2–106)	0.31	13 (0–130)	11 (0–71)	0.03

[a] For all events, the data for the TSH (2/2) group were obtained after the second stage, and included events after both stages of hepatectomy.

hepatectomy groups, the mean follow-up periods were respectively 7, 4 and 9 years. The mean OS time in the whole study population (i.e. patients in whom TSH with curative intent was planned) was 38 ± 2 months (Fig. 2). In the TSH (2/2) and TSH (1/2) groups, the mean OS time was respectively 40 ± 2 months and 25 ± 2 months (p = 0.007). The 3-year OS rate after resection was 45% in the TSH (2/2) group and 30% in the TSH (1/2) group. The 5-year OS rate after



Patients at risk

TSH	869	507	288	178	97	55	28	16	14	8	3
TSH 2/2	625	399	250	161	93	55	28	16	14	8	3
TSH 1/2	244	108	38	17	4	0	0	0	0	0	0

Figure 2 Overall survival

resection was 23% in the TSH (2/2) group and 0% in the TSH (1/2) group.

Disease-free survival in the TSH (2/2) group

The data on DFS in the TSH (2/2) group are presented in eFig. 1. The mean DFS time was 41 ± 3 months. The TSH (2/2) group's 3-year and 5-year DFS rates were respectively 43% and 23%.

Prognostic value of TSH: comparison with hepatectomy

1 Calculation of the PS

The PS was calculated by taking account of confounding factors that influenced the choice of the surgical procedure (i.e. TSH vs. one-stage hepatectomy): the CEA level, the number of LM, the size of the LM, synchronous metastasis and R0 resection. In this model, no interaction between the retained variables was identified.

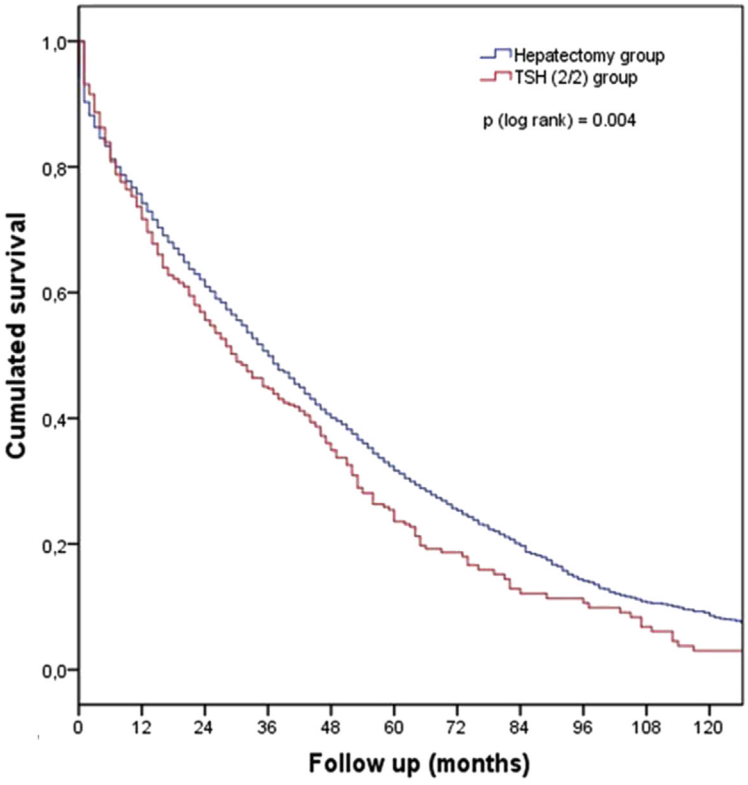
2 OS

Before PS matching, TSH was associated with a shorter OS (HR [95% CI] = 1.9 [1.7–2.1]; p = 0.03). After PS matching, TSH was still associated with a shorter OS (adjusted HR [95% CI] = 2.1 [1.5–2.7]; p = 0.003).

The OS data are presented in Fig. 3. The mean OS was 43 ± 2 months in the pooled TSH group and 49 ± 1 months in the one-stage hepatectomy group. The 3-year OS rates in the pooled TSH group and "hepatectomy" groups were respectively 43.7% and 50.7%, whereas the 5-year OS rates were 21.4% and 32.4% (p = 0.002).

3 DFS

Before PS matching, TSH status was associated with a shorter DFS (HR [95% CI = 1.4 [1.1–1.9]; p = 0.04). After PS matching, no difference was observed (adjusted HR [95% CI] = 1.2 [0.7–2.1]; p = 0.57).



Patients at risk											
Hepatectomy	5,786	3,847	2,495	1,590	973	621	407	275	182	126	96
TSH 2/2	625	401	260	162	94	56	29	17	15	9	3

Figure 3 Overall survival after PS matching

The DFS data are presented in eFig. 2. The mean DFS was 41 ± 3 months in the pooled TSH group and 45 ± 1 months in the hepatectomy group. The 3-year OS rate was 42.9% in the pooled TSH group and 46% in the hepatectomy group, whereas the 5-year OS rates were respectively 21.6% and 29.8% (p = 0.39).

Predictors of long-term survival in the TSH groups

Our data on predictors of long-term survival in the TSH groups are summarized in eTable 2. The absence of an extrahepatic metastatic site, curative lung resection, completed TSH, anatomic resection and healthy, non-cancerous liver parenchyma vs. other parenchyma (steatosis, blue liver, cirrhosis, fibrosis, etc.) were associated with longer survival, whereas use of the Pringle maneuver and the presence of one or more positive lymph nodes were associated with shorter survival.

Discussion

The present series is the largest reported to date for patients having undergone complete TSH after the year 2000. Our study was designed to determine the impact of TSH on the long-term prognosis of patients with CRLM. Our data showed that (i) TSH was completed in 72% of the patients, (ii) the morbidity and mortality rates in the TSH (2/2) group did not differ significantly from those observed after hepatectomy, and (iii) the TSH (2/2) group's OS rates at 3 and 5 years (45% and 23%, respectively) and DFS rates at 3 and 5 years (43% and 23%, respectively) were satisfactory (especially with regard to these patients' dismal prognosis in the absence of surgery).

This series provides new data on the morbidity and mortality associated with TSH. The morbidity rates were higher in the TSH (1/2) group than in the TSH (2/2) and hepatectomy groups, which reflects the greater frequency of adverse events after the first stage of the hepatectomy (even minor events); however, this difference was not statistically significant. This morbidity might have been due to the patients' frailty, more aggressive first-stage surgery and more advanced disease (i.e. possible reasons for the failure of TSH). Furthermore, the frequency of postoperative radiological drainage in the TSH (2/2) group was quite high (14%); however, it was lower than the values reported by Wicherts *et al.* (22%); Narita *et al.* (17%) and Passot *et al.*

(21%).[16,19,20] The 90-day mortality rate in the TSH (1/2) group was also high (16%), whereas that in the TSH (2/2) group it was similar to the value observed for one-stage hepatectomy (9%). Even though the mortality rate in the TSH (2/2) seems to be quite high, we suggest that other studies have underestimated the 30-day mortality rate. Our findings were not consistent with the literature data. In fact, Wicherts *et al.* (in 2008), Jaeck *et al.* (in 2004) and Narita *et al.* (in 2011) all reported that the occurrence of postoperative adverse events was higher after the second stage of TSH.[8,16,19] The overall morbidity rate in our TSH (2/2) group was around 25% – as previously reported by Tsai *et al.* and Brouquet *et al.* The significance of these outcomes (the morbidity rate and the 90-day mortality rate in the TSH (1/2) group, and the number of patients in whom postoperative radiological drainage of a postoperative collection was necessary in the TSH (2/2) group) should not be underestimated when considering the treatment strategy; the surgeon must discuss these issues with his/her patient.

We observed that TSH was not completed in 28% of the patients; this agrees with the literature data (with non-completion rates of between 20% and 28%, depending on the series).[14] This finding may be of value with regard to the completed sequence's impact on the patient's prognosis. In the present series, repeat hepatectomy, the presence of an extrahepatic metastatic site, failure to achieve R0 resection and the absence of chemotherapy before hepatectomy were found to be risk factors for the non-completion of TSH. These variables differ from the risk factors for non-completion reported by Turrini *et al.* (in 2011), Andreou *et al.* (in 2013), Faitot *et al.* (in 2015) and Passot *et al.* (in 2016);[20–23] none of the reported factors was patient-related, and most were tumor-, chemotherapy- or surgery-related. In fact, Turrini *et al.* found that only resection of the primary tumor during the first stage of TSH was predictive of non-completion.[20] The other three groups identified factors linked to chemotherapy (a high number of cycles, a pathological response or a switch to another chemotherapy regimen) or linked to the LM (number, size and location). Some series have combined risk factors in order to create a score for selecting the best candidates for various TSH strategies. Even though the application of this type of score is associated with lower morbidity and mortality rates after the first stage of hepatectomy, the scores have not been externally validated. Hence, it is still difficult for the surgeon to justify his/her refusal to consider a patient for the only potentially curative program (as reflected by the OS in the TSH (1/2) group).

Several aspects must be taken into account when ensuring that patients complete TSH and, above all, achieve R0 resection. This can be done by combining surgery with other treatment techniques (including local radiofrequency ablation). Nevertheless, R0 resection could be only achieved in 60% of patients and was found to be a prognostic factor (as also reported by Andreou *et al.*).[22]

Our results for OS confirm the oncologic effectiveness of TSH; the three-year OS rate of 45% is consistent with the data reported by Lam *et al.*[14] Moreover, the greater DFS rate emphasizes the long-term value of TSH in the management of LM. Nevertheless, the data we obtained in the TSH (1/2) group (i.e. a three-year OS rate of 30%) differ from those reported by Brouquet *et al.* (a three-year OS rate of 0%).[13] This could be due to the large sample size in our series and the selection criterion applied to the chemotherapy-only group in Brouquet *et al.*'s study (only patients having survived for a year after the first round of chemotherapy were included). Furthermore, the 3-year OS rate of 45% in our TSH (2/2) group is lower than the values of around 60% reported by Jaeck *et al.* (in 2004), Narita *et al.* (2011), Tsai *et al.* and Faitot *et al.*[8,18,19,23] Moreover, the DFS rate in our study is higher than that reported by Narita (17%), showing that TSH has a prognostic impact on OS and recurrence.[19] The relatively good OS observed in the TSH (1/2) group makes it hard for the surgeon to refuse to consider a patient for TSH – even when the strategy is incomplete and especially if the morbidity rate can be lowered further (e.g. by initiating an intensive pre-surgery program with prehabilitation and immunonutrition).

Our data confirmed that the OS is shorter for TSH than for hepatectomy. In our opinion, this difference means that (i) hepatectomy should always be considered first, and (ii) strategies that might facilitate hepatectomy should be implemented whenever possible. Furthermore, as shown by our DFS data, TSH has the same impact as hepatectomy on recurrence and progression rates; hence, TSH may not necessarily be associated with an increased risk of recurrence.

Our series had some limitations – most of which were inherent to its design. Given the long duration of the study, changes in practice may have influenced the results. In our series, we decided not to standardize the diagnosis and resection methods so that the clinical practice was as close as possible to "real life". Selection bias in this series could be due to the degree of center participation. Indeed, the participation of a center in this registry was not funded and was only based on the will of surgeon to fulfill the database. We agree that some centers especially the more recent participants may be more involved because they were more aware to this oncological condition. Besides, the attribution of patients to the study groups depends on the surgeon's choice. If the surgeon considered the patient would be managed in a two stage setting, the patient was attributed to the TSH group but if during the surgical procedure, only a single hepatectomy was performed, the patient was kept in the TSH group. This may be of importance in the analysis of the primary endpoint as patients from one group may have switched to the other with no information on this switch in the registry.

Given that the TSH non-completion rate in the present study was still high, alternatives (such as the "associating liver partition and portal vein ligation for staged hepatectomy" (ALPPS) procedure recently introduced by Schnitzbauer *et al.*[24]) should be considered. The ALPPS procedure induces rapid hypertrophy of the future liver remnant and shortens the time interval between

the two stages of surgery. The overall objective is to improve postoperative outcomes after major hepatectomy and limit the incidence of postoperative liver failure. Secondly, the short time interval between the two stages of surgery in the ALPPS procedure is likely to reduce the risk of development of *de novo* LM in the residual liver lobe – the major reason for failing to complete TSH (the frequency of which ranges from 21% to 38% in the literature).[13,19,25,26] The completion rate after ALPPS is nearly 100%. Nevertheless, the postoperative morbidity and mortality rates and oncologic outcomes associated with the ALPPS procedure are subject to debate in the literature. Indeed, the morbidity and mortality rates are high (essentially due to extrahepatic complications, such as kidney failure, pneumonia and pulmonary embolism). Our present results for conventional TSH should be of value in comparing the two strategies. To this end, Sun *et al.* performed a systematic review and comparative meta-analysis of the ALPPS and TSH procedures. The researchers concluded that the ALPPS procedure was associated with greater mortality and morbidity rates but less cancer progression between the two stages (relative to TSH). Based on this conclusion, appropriate target populations for each of these two techniques must now be defined.

Conclusion

The data collected in the present study indicate that TSH is associated with rather good long-term survival and acceptable morbidity and mortality rates.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.01.008.