Transplant International

ORIGINAL ARTICLE

Liver transplantation versus liver resection for colorectal liver metastasis: a survival benefit analysis in patients stratified according to tumor burden score

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SUMMARY

Liver transplantation (LT) for colorectal liver metastasis (CRLM) may provide excellent survival rates in patients with unresectable disease. High tumor load is a risk factor for recurrence and low overall survival (OS) after liver resection (LR). We tested the hypothesis that LT could offer better survival than LR in patients with high tumor load. LR performed at Padua University Hospital for CRLM was compared with LT for unresectable CRLM performed both at Oslo and Padua. High tumor load was defined as tumor burden score (TBS) ≥ 9, and inclusion criteria were as in the SECA-I transplant study. 184 patients were eligible: 128 LRs and 56 LTs. 5-year OS after LR and LT was 40.5% and 54.7% ($P = 0.102$). In the high TBS cohort, 5-year OS after LR and LT was 22.7% and 52.2% ($P = 0.055$). In patients with Oslo score ≤ 2 and TBS ≥ 9 (13 LR; 24 LT) the 5-year OS after LR and LT was 14.6% and 69.1% ($P = 0.002$). The corresponding disease-free survival (DFS) was 0% and 22.9% ($P = 0.005$). Selected CRLM patients with low Oslo score and high TBS could benefit from LT with survival outcomes that are far better than what is achieved by LR.

Transplant International 2021; 34: 1722–1732

Key words
colorectal liver metastasis, liver resection, liver transplantation, overall survival, tumor burden

Received: 8 July 2021; Revision requested: 13 July 2021; Accepted: 14 July 2021

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide with high prevalence in the developed countries [1]. Almost half of patients will develop metastasis, and the liver is the most often involved organ. Liver resection (LR) is standard of care for colorectal liver metastasis (CRLM) and may yield a 5-year survival rate between 50% and 60% [2]. Nevertheless, only 20–25% of patients with CRLM are suitable for resection during the course of the disease [3]. Hence, the available treatment option for most patients remains palliative chemotherapy, with predicted 5-year overall survival (OS) rates of about 10% [4].

After early disappointing experience [5], liver transplantation (LT) for unresectable CRLM has been

doi:10.1111/tri.13981

investigated in the SECA trials and demonstrated a 5-year overall survival (OS) rate of up to 83% [6]. Concomitantly, robust clinical risk factors that can be utilized in patient selection for poor outcome have been identified (so called Oslo criteria) [6,7]. Even though LT for unresectable CRLM is burdened by low disease-free survival (DFS), the impact of recurrence on patient survival is modest [6,8–11], since the majority of relapses are pulmonary metastases that grow slowly and can be resected with curative intent.

Worldwide, LT for CRLM is being investigated in several prospective trials [12] limited to unresectable disease. However, the concept of resectability of liver tumors has changed considerably during the last twenty years. Patients with initially unresectable disease are nowadays evaluated for different treatments such as downstaging with neoadjuvant biological agents, interventional radiology, two-stage hepatectomy (TSH) with or without portal vein embolization (PVE), associated liver partition and portal vein ligation for staged hepatectomy (ALPPS), and, in some cases, even ex-vivo procedures to obtain an R0 resection. Since it is easier to obtain a free resection margin in patients with fewer and smaller tumors than in patients with several or larger ones, some authors have questioned whether margin status is an independent variable for oncological outcome. The concept of tumor burden score (TBS) was introduced by Sasaki *et al.* [13] Based on this concept, Oshi *et al.* [14] demonstrated that the more the TBS increases, the less significant the margin status is for DSF and OS, while biological factors, such as KRAS status, CEA level, and response to preoperative chemotherapy, gain significance accordingly. Recently, it has been showed that patients with unresectable CRLM and extensive liver tumor load have long OS after LT, exceeding the survival outcome of patients with similar tumor load but treated with PVE and LR [15]. Thus, although resectability is clearly related to better outcomes than palliative chemotherapy [16–22], resectability is first and foremost a technical and anatomical founded parameter rather than an objective biological predictor in patients with high hepatic tumor burden. Hence, there may be a threshold of tumor load for which LR yields acceptable survival so one might hypothesize whether LT could provide survival benefit over LR in a subset of patients with high tumor load.

The purpose of this study is to test the hypothesis that LT could offer better survival than LR for technically resectable patients, when hepatic tumor load is above a certain threshold (in terms of total number of lesions and size of the largest metastasis). To our knowledge, no data are available on this topic so far.

Patients and methods

Data on liver resections (LR) performed at the Hepatobiliary Surgery and Liver Transplantation Unit, Padua University Hospital (Italy), in metastatic colorectal cancer patients, between 2010 and 30 June 2019, were compared with LT for unresectable CRLM performed both by the Department of Transplantation Medicine, Oslo University Hospital (Norway), and by the Hepatobiliary Surgery and Liver Transplantation Unit, Padua University Hospital (Italy), between 2006 and 30 Jun 2019.

The present study has been conducted in compliance with regional ethics committees and national laws of the participating institutions: No patient approval was needed for retrospective studies. Patients gave written consent for every procedure performed in the hospitals, including use of data for medical purposes. Patients underwent LT for unresectable CRLM as part of approved prospective studies. All patients provided written informed consent before inclusion, which was obtained in a manner that was consistent with the Declaration of Helsinki, and all procedures were performed in accordance with the Declaration of Istanbul. No one received compensation or was offered any incentive for participating in this study. All protocols were approved by the regional ethics committees and institutional review boards of Oslo and Padua University Hospitals.

Inclusion criteria for the study were the same as for the SECA-I study [7] in order to minimize the selection bias and to include only potentially transplantable patients from the resection cohort, as part of an intention-to-treat study. Hence, the exclusion criteria were as follows: age over 71 years (increased from 60 years of the original trial, for consistency with subsequent trials), liver first approach or resection of the primary performed at the same time of LR, extrahepatic metastases, less than 6 weeks of neoadjuvant chemotherapy, standard contraindications to LT (namely active drug or alcohol abuse, acute alcoholic hepatitis, invasive fungal infection, and less than 5-year interval from curative cancer treatment of another malignancy) [23], concurrent other malignancy, weight loss of more than 10%, Eastern Cooperative Oncology Group (ECOG) Performance Status more than 1, and, finally, follow-up less than 6 months. Unlike the SECA-I, BMI was excluded from the selection criteria as these data were missing for 64 (34.8%) patients.

Parameters included in the current analysis were as follows: demographics (age, sex, BMI, American Society of Anesthesiologists (ASA) grade); primary tumor-related factors (location, treatment before colon resection,

KRAS/BRAF status, time from primary diagnosis to LR or LT, American Joint Committee on Cancer (AJCC) T and N stage); liver metastasis variables (synchronous metastasis, response evaluation criteria in solid tumors (RECIST) [24], number of lesions and size of the largest at last available radiology, last CEA level); postoperative variables (number of lesions and size of the largest in the final histopathological report, intensive care unit (ICU) stay, length of hospital stay (LOS), 30 days postoperative complication according to Clavien-Dindo classification and adjuvant chemotherapy); and follow-up parameters (recurrence site and treatment, patient status).

Oslo score [7] was calculated both in resection and LT cohorts. For the purpose of this study, we considered Oslo score ≥ 3 as high-risk score.

For each patient, the TBS was calculated by combining tumor size and the total number of lesions as described previously [13] using measures from both last available radiology and final histopathological report. Patients were then divided into 3 groups according to the TBS model (zone 1: TBS <3; zone 2: TBS ≥ 3 to < 9; and zone 3: TBS ≥ 9). For the purpose of this study, we considered TBS ≥ 9 (zone 3) as high tumor load.

Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. Disease recurrence was censored at its first appearance at CT scan during follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence, and survival after recurrence (SAR) was calculated from the date of recurrence to the date of death or date of last follow-up.

Statistical analysis

Continuous variables are expressed as medians (interquartile ranges) and were analyzed by the independent t-test. Categorical-nominal variables are presented as a number (percent) and were analyzed by the chi-square or Fisher's exact tests, as appropriate. Survival data were estimated using the Kaplan–Meier method. Log-rank tests were used to compare outcomes between subgroups. For all tests, a 2-sided $p < 0.05$ was considered statistically significant. Analyses were performed with PRJCTS by Ledidi™.

Results

Overall, 418 metastatic colorectal cancer patients were treated in both units between January 2006 and June 30, 2019. Three hundred sixty-two patients were resected, and 56 underwent LT for unresectable CRLM.

In the resection cohort, eighty-six patients were more than 71 years old; 49 patients had the primary tumor not resected (liver first approach) or resected at the same time of the liver; 19 had extrahepatic localization; 38 had less than 6 weeks of neoadjuvant chemotherapy before procedure; and 42 patients had less than 6 months of follow-up. All patients had ECOG Performance Status of 0 or 1; no patients had weight loss more than 10%, concomitant other malignancies, or standard contraindications for LT.

After applying the exclusion criteria, 184 patients were eligible for the study: 128 LRs, and 56 LTs. Figure 1 shows a flowchart of the selection process.

Median follow-up was 30.7 (16.8–57.5) months. Notably, LR cohort had a median follow-up of 27.1 (15.2–45) months, while after LT, median follow-up was 43.3 (25.8–76.4) months ($P < 0.001$).

The characteristics of the two groups are shown in Table 1. The distribution of sex, age, and BMI was similar between the groups. ASA grade was significantly higher in the LT group (2 vs. 3, $P < 0.001$). The two groups were similar in terms of primary tumor characteristics except for KRAS status that was mutated in 30 (43.5%) patients in the resection cohort versus 14 (25.5%) in LT cohort ($P = 0.040$). Eighty-one (63.3%) patients had synchronous CRLM in resection group versus 50 (89.3%) in the LT group ($P < 0.001$).

Tumor characteristics at last radiology were significantly different between resection and LT, both per number of lesions (3 vs. 10 respectively, $P < 0.001$) and per size of the major lesion (3 cm vs. 3.8 cm, respectively, $P = 0.003$). Median radiological TBS was 5.3 (3.7–8) in the resection group and 11.9 (8.2–16.4) in the LT group ($P < 0.001$). The pathological TBS, calculated using the final histopathological report, is significantly correlated to radiological TBS (Spearman's rank correlation coefficient $r = 0.696$; $P < 0.001$); on this basis, it is been decided to use only the radiological TBS to stratify the patients in order to reinforce the concept that TBS could be a tool to select the patient in the preclinical, ambulatorial, setting. Among resection group, 15 (11.9%) patients were classified TBS Zone 1, 86 (68.3%) TBS Zone 2, and 25 (19.8%) TBS Zone 3; among LT group, 1 (1.8%) patient was classified TBS Zone 1, 18 (32.7%) TBS Zone 2, and 36 (65.5%) TBS Zone 3 ($P < 0.001$).

There were no differences in the distribution of patients according to Oslo score between the groups.

ICU stay and LOS were longer in the LT group. Even if 30 days postoperative complications rate was similar, major postoperative (Clavien-Dindo ≥ 3) was more

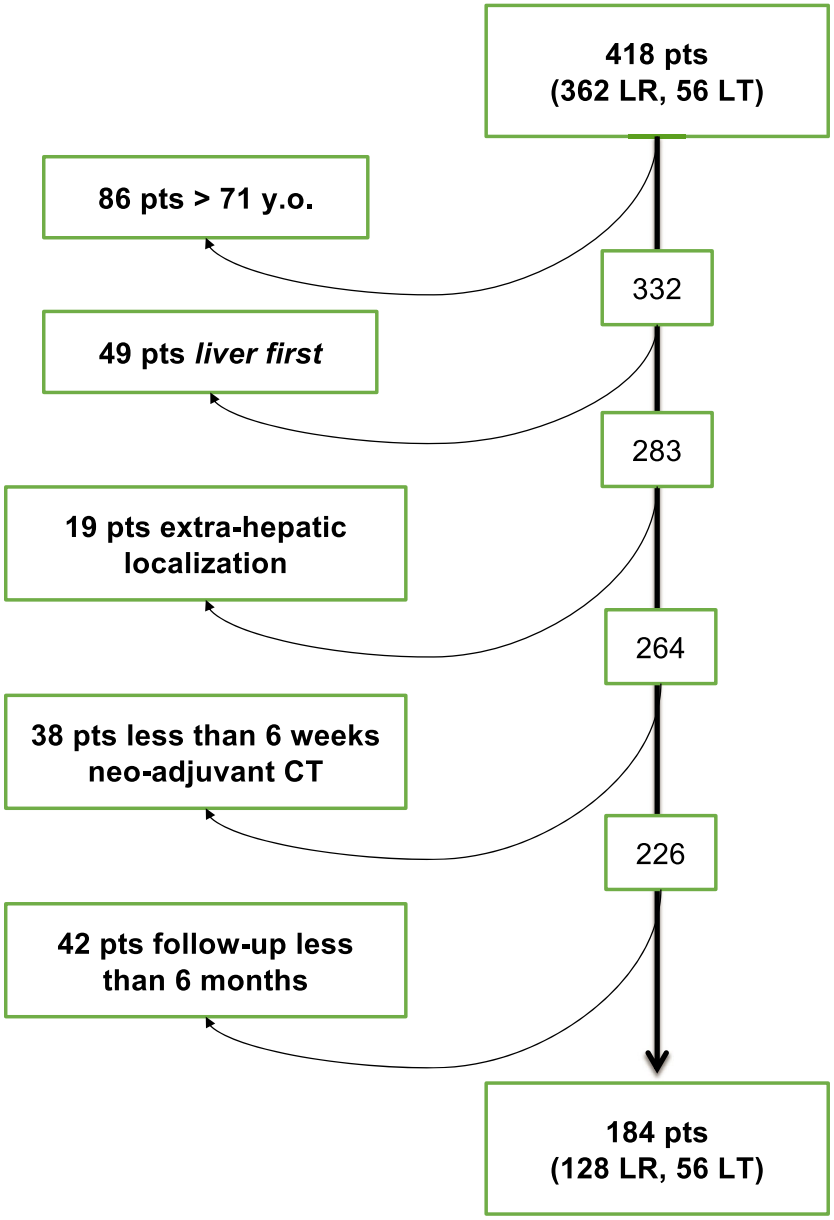

Figure 1 Patient flow diagram. Abbreviations: pts, patients; LR, liver resection; LT, liver transplantation; y.o., years old; CT, chemotherapy.

frequent in LT cohort compared to the resection group (respectively, 16 vs. 7, $P < 0.001$).

There were no differences in recurrence rate after resection and LT. The pattern of recurrence was, however, different. Liver was the main recurrence site after resection while lung metastasis was most frequent recurrence pattern after LT ($P < 0.001$).

Survival analysis

Overall survival (OS) after LR at 1, 3, 5, and 7 years was 91.9%, 63.9%, 40.5%, and 31.9%, respectively; 1-, 3-, 5-, and 7-year OS after LT was 92.9%, 71.2%, 54.7%, and 42.3%, respectively ($P = 0.102$; Fig. 2a). Disease-free survival (DFS) after LR was 37.6%, 10.3%, 7.8%, and 7.8% at 1, 3, 5, and 7 years, respectively; 1-, 3-, 5-, and 7-year DFS after LT was, respectively, 41.8%, 20.6%, 14.1%, and 14.1% ($P = 0.077$; Fig. 2b).

Categorizing patients according to Oslo score, 119 had low score (77 LR and 42 LT), and 25 patients had high Oslo score (12 LR and 13 LT). In the low Oslo category, OS after LR at 1, 3, 5, and 7 years was, respectively, 94.6%, 66.6%, 42.2%, and 35.1%; 1-, 3-, 5-, and 7-year OS after LT was 95.1%, 87.6%, 65.3%, and 58.5%, respectively ($P = 0.009$; Fig. 3a). In the high Oslo score category, OS after LR at 1, 3, 5,

Table 1. Comparison between patients underwent liver resection and liver transplantation.

Variables	LR *N* = 128	LT *N* = 56	*P*
Demographic			
Age	59.2 (52.3–64.1)	56.3 (49.8–60.6)	0.057
Gender (Male)	77 (60.2%)	31 (55.4%)	0.626
BMI	24.4 (22.4–28.4) *56	26.9 (23.5–28.9) *8	0.361
ASA grade	2 (2–2) *40	3 (3–3) *7	**<0.001**
Primary tumor			
Location			
Right	29 (22.7%)	10 (17.9%)	0.650
Transversum	6 (4.7%)	1 (1.8%)	
Left	60 (46.9%)	27 (48.2%)	
Right & Left	1 (0.8%)	0 (0%)	
Rectum	32 (25%)	18 (32.1%)	
Treatment before resection of primary			
No treatment	108 (4.4%)	42 (75%)	0.228
Chemotherapy	14 (10.9%)	8(14.3%)	
Chemoradiation	6 (4.7%)	6 (10.7%)	
KRAS mutated	30 (43.5%) *59	14 (25.5%) *1	**0.040**
BRAF mutated	3 (6%) *78	2 (3.7%) *2	0.670
Time from diagnosis (mo)	20.8 (11.8–34.1)	18.8 (13.3–30.4) *3	0.702
pT-stage	*23	*22	0.139
pT0	0 (0%)	0 (0%)	
ypT0	0 (0%)	1 (2.9%)	
ypTis	1 (0.9%)	0 (0%)	
pT1	1 (0.9%)	1 (2.9%)	
ypT1	0 (0%)	0 (0%)	
pT2	11 (10.5%)	0 (2.9%)	
ypT2	4 (3.8%)	3 (8.8%)	
pT3	57 (54.3%)	13 (38.2%)	
ypT3	9 (8.6%)	7 (20.6%)	
pT4	19 (18.1%)	6 (17.6%)	
ypT4	3 (2.9%)	2 (5.9%)	
pN-stage	*23		0.713
pN0	29 (27.6%)	13 (23.2%)	
ypN0	5 (4.7%)	6 (10.7%)	
pN1	31 (29.5%)	15 (26.8%)	
ypN1	9 (8.6%)	5 (8.9%)	
pN2	28 (26.7%)	14 (25%)	
ypN2	3 (2.9%)	3 (5.4%)	
Colorectal liver metastasis			
Synchronous (yes)	81 (63.3%)	50 (89.3%)	**<0.001**
RECIST		*1	
CR	0 (0%)	1 (1.8%)	**<0.001**
SD	45 (35.2%)	4 (7.3%)	
PR	39 (30.5%)	35 (63.6%)	
PD	44 (34.4%)	15 (27.3%)	
Number of lesions	3 (1–6) *1	10 (6.5–16) *1	**<0.001**
Size major lesion (cm)	3 (2–4.4) *2	3.8 (2.8–6.8) *1	**0.003**
CEA (μg/l)	8.7 (2.3–30.7) *38	5.2 (2–26) *1	0.381
Scores			
TBS	5.3 (3.7–8) *2	11.9 (8.2–16.4) *1	**<0.001**
TBS Zones	*2	*1	
Zone 1 (<3)	15 (11.9%)	1 (1.8%)	**<0.001**
Zone 2 (≥3; <9)	86 (68.3%)	18 (32.7%)	
Zone 3 (≥ 9)	25 (19.8%)	36 (65.5%)	

Table 1. Continued.

Variables	LR *N* = 128	LT *N* = 56	*P*
pTBS	4.7 (3.4–6.7) *2	10.4 (6.8–14.2) *16	**<0.001**
Oslo score	*39	*1	
Low (0 – 2)	77 (86.5%)	42 (76.4%)	0.173
High (3 – 4)	12 (13.5%)	13 (23.6%)	
Postoperative variables			
ICU stay (days)	0 (0–1)	1 (1–2) *1	**<0.001**
LOS (days)	6.5 (5–8.5)	14 (9.5–17) *1	**<0.001**
30 days postoperative complications (yes)	63 (49.2%)	32 (58.2%) *1	0.333
Clavien-Dindo ≥ 3	7 (5.5%)	16 (29.1%) *1	**<0.001**
Adjuvant chemotherapy (yes)	65 (65.7) *29	1 (1.8%)	**<0.001**
Follow-up			
Recurrence (yes)	108 (84.4%)	46 (82.1%)	0.829
Recurrence site			
Colon	1 (0.9%)	0 (0%)	**<0.001**
Liver	35 (32.4%)	4 (8.7%)	
Lung	7 (6.5%)	20 (43.5%)	
Liver & Lung	25 (23.1%)	8 (17.4%)	
Multisite	40 (37%)	14 (30.4%)	
Last patient status			
NED	24 (18.8%)	20 (35.7%)	**<0.001**
AWD	49 (38.3%)	7 (12.5%)	
DEAD	55 (43%)	29 (51.8%)	

ASA, American Society of Anesthesiologists; AWD, alive with diseaseBMI, body mass index; CR, complete response; ICU, intensive care unit; LOS, length of hospital stay; LR, liver resection; LT, liver transplantation; mo, months; MWA, microwave ablation; NED, nonevidence of disease; PD, progressive disease; PR, partial response; pTBS, pathological TBS; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TBS, tumor burden score.

*Missing data.

and 7 years was 72.9%, 48.6%, 32.4%, and 0%, respectively, whereas LT yielded 1-, 3-, 5-, and 7-year OS rates of 84.6%, 36.9%, 12.3%, and 0% ($P = 0.808$; Fig. 3b).

To test our hypothesis, we compared survivals stratifying patients according to TBS. One hundred and twenty patients had low TBS (<9), 101 underwent LR and 19 LT; 61 patients (25 LR and 36 LT) had high TBS (≥ 9). In the high TBS cohort, OS after LR at 1, 3, 5, and 7 years was 72.6%, 45.3%, 22.7%, and 0%; 1-, 3-, 5-, and 7-year OS after LT was 91.7%, 60.1%, 52.2%, and 34.8% ($P = 0.055$; Fig. 4).

Moreover, restricting the analysis only to the patients with both low Oslo score and high TBS (13 LR and 24 LT), survivals were as follows: 1-, 3-, 5- and 7-year OS in resection cohort was 75%, 43.8%, 14.6%, and 0% whereas the OS after LT was 91.7%, 76%, 69.1%, and 69.1% at 1, 3, 5, and 7 years ($P = 0.002$; Fig. 5a). DFS after LR was 11.5% and 0% at 1 and 3 years, respectively; 1-, 3-, and 5-year DFS after LT was, respectively, 54.2%, 22.9%, and 22.9% ($P = 0.005$; Fig. 5b). In this super-selected group of patient, the ones who recurred after LT (18 patients) showed a longer SAR, although not significant, compared to 12 patients who recurred after LR (LR-SAR at 1-, 3-, 5-, and 7-year was 62.3%, 16.6%, 16.6%, and 0%; LT-SAR at 1-, 3-, 5-, and 7-year was 81.9%, 66.2%, 57.9%, and 57.9%; $P = 0.060$; Fig. 5c). Given the discrepancy observed in TBS between LR and LT groups, one may speculate that the survival of LT cohort with far higher TBS than in the resected patients may underestimate the survival difference. Hence, a subset analysis was conducted including only LT patients with a TBS up to the highest value observed in the LR cohort (i.e., 16.2). OS after LT (15 patients) at 1, 3, 5, and 7 years was 86.7%, 78%, 68.2%, and 68.2% respectively, compared to OS in resection cohort ($P = 0.014$; Fig. 5d). In this subset analysis, DFS observed in LT cohort was 53.3%, 32%, and 32% at 1, 3, and 5 years ($P = 0.003$; Fig. 5e). For the 10 patients who recurred after LT, SAR changed to 80%, 68.6%, 57.1%, and 57.1% at 1, 3, 5, and 7 years, respectively ($P = 0.184$; Fig. 5f).

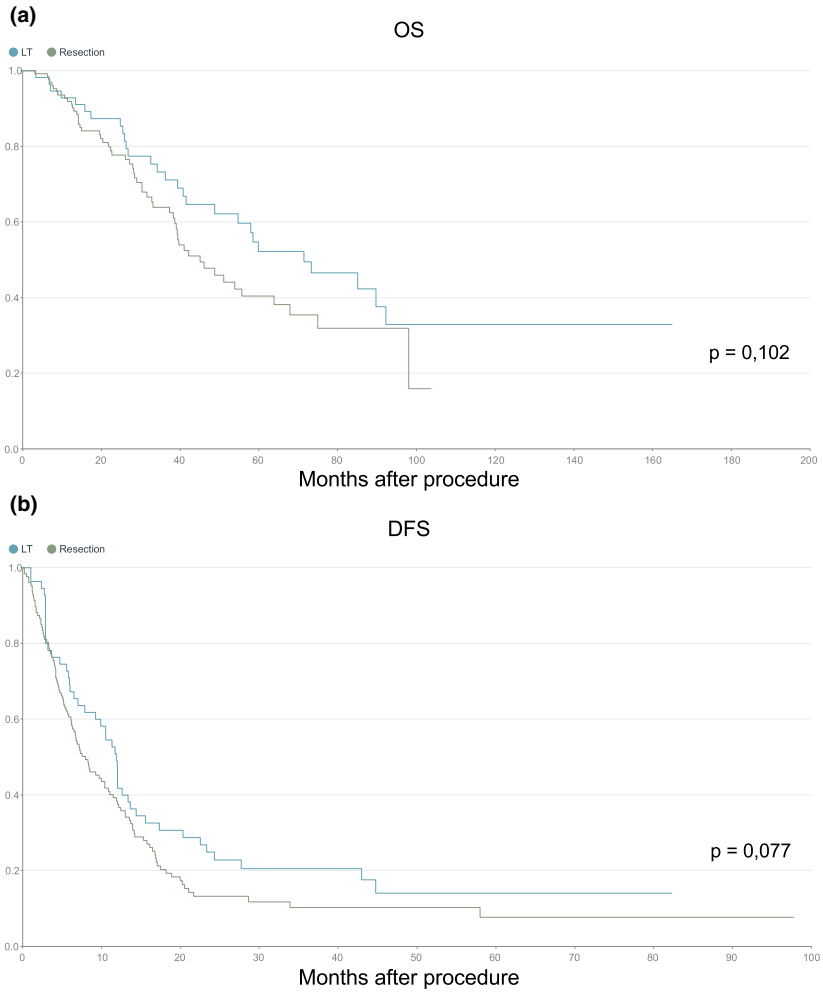

Figure 2 Kaplan–Meier curves describing the comparison of OS (panel a) and DFS (panel b) between LR and LT patients. Abbreviations: OS, overall survival; DFS, disease-free survival; LR, liver resection; LT, liver transplantation.

Discussion

To the best of our knowledge, this is the first study that compare the outcome of LR and LT on a selected cohort of patients with secondary liver tumor from colorectal cancer. The demographic characteristics of the two populations were similar, and they differed only for KRAS mutation.

The major difference between the two treatment groups was the hepatic tumor load, which is a major risk factor for low survival following liver resection [25]. The transplanted patients had on average, larger, and more numerous metastases. This is to be expected since the transplant patient population were, by protocol, deemed as unresectable.

As expected, there is no clear statistical difference in postprocedural OS between the whole resection group compared with the transplant population, and the same finding is valid concerning DFS. However, in patients with low Oslo score, the survival of transplanted patients is significantly higher.

The clinically most significant and controversial finding of this study was that in patients with high tumor burden score, the 5-year OS after transplantation was 52.2% compared to only 22.7% after liver resection (Fig. 4).

Since there is a published ILTS consensus paper stating that liver transplantation for CRLM should be limited to low-risk patients (Oslo score 0-2) [12], it was logical to perform a subanalysis where high TBS and low Oslo score were combined. In this setting, the 5-year survival rate after LT was as high as 69.1% compared to only 14.6% after LR (Fig. 5a), suggesting that there may be a subgroup of patients with technically resectable high tumor volume disease that may achieve a substantial treatment benefit by transplantation compared to standard of care liver resection. These findings

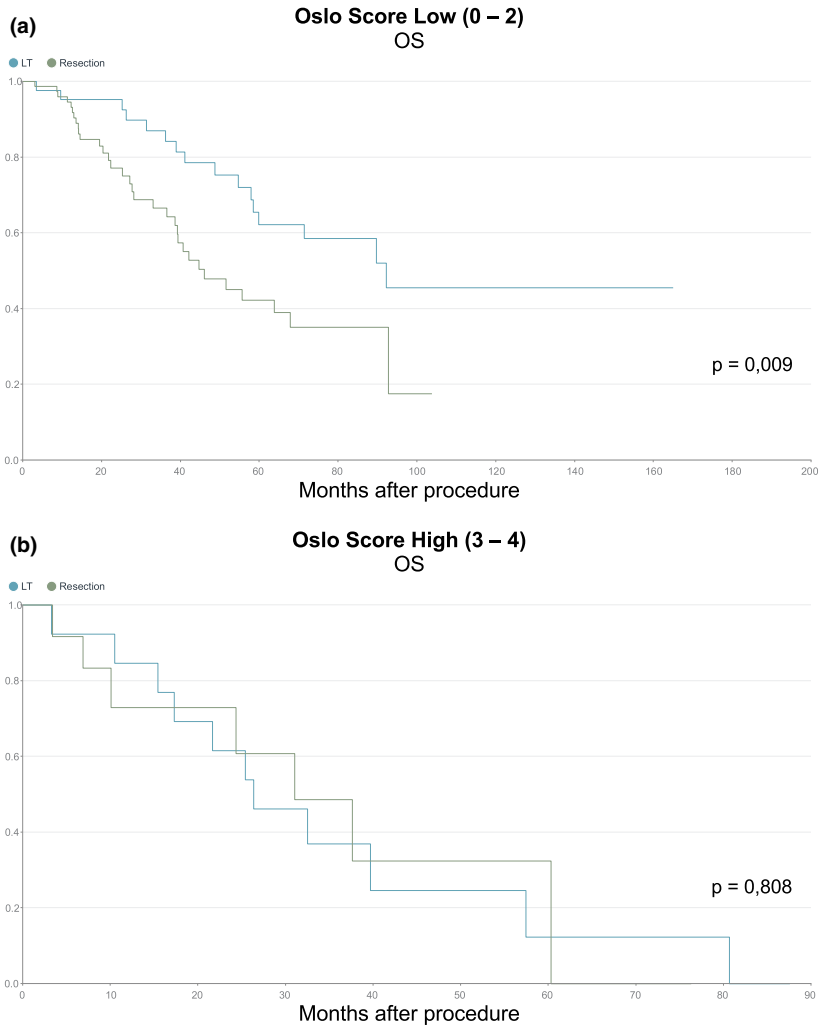

Figure 3 Kaplan–Meier curves describing the comparison of OS between LR and LT patients stratified according to Oslo score low (0 – 2) (panel a) and high (3 – 5) (panel b). Abbreviations: OS, overall survival; LR, liver resection; LT, liver transplantation.

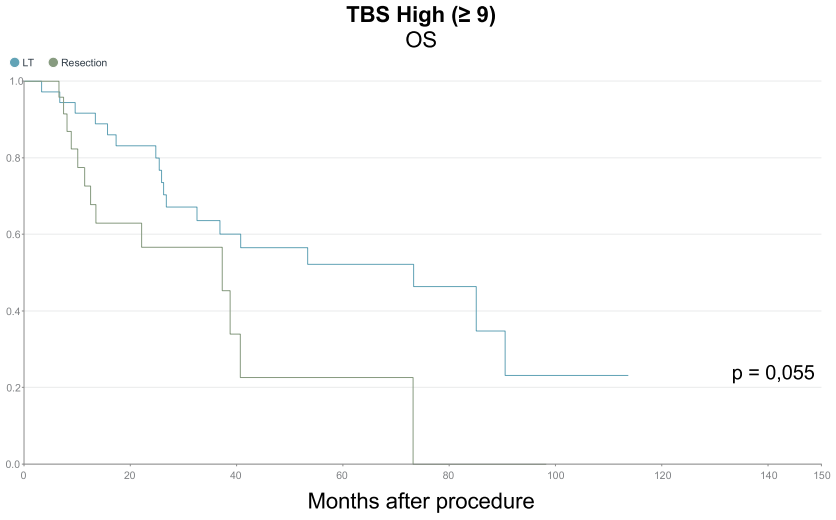

Figure 4 Kaplan–Meier curves describing the comparison of OS between LR and LT patients with high TBS (≥ 9). Abbreviations: OS, overall survival; LR, liver resection; LT, liver transplantation; TBS, tumor burden score.

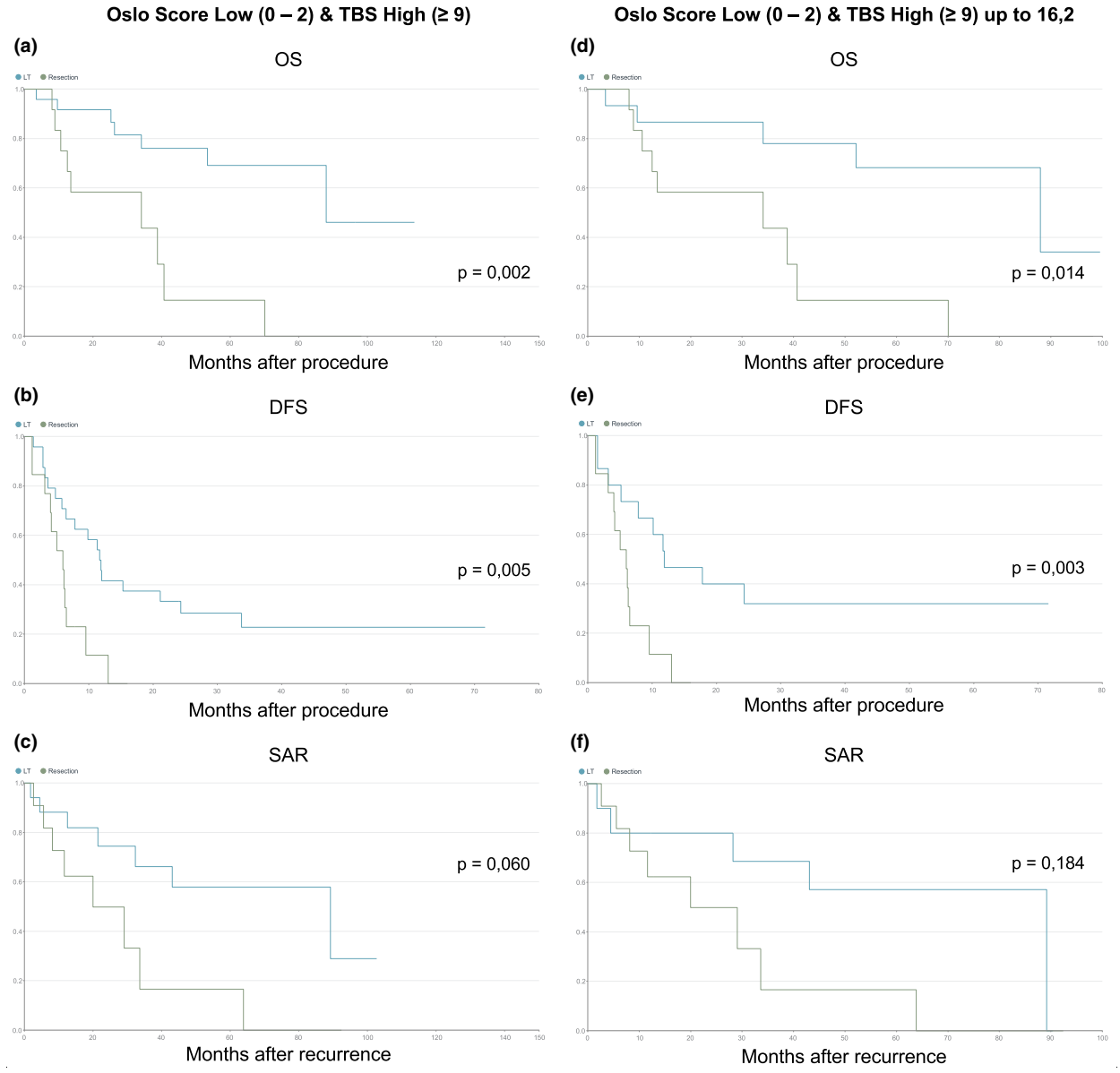

Figure 5 Kaplan–Meier curves describing the comparison of OS (panel a), DFS (panel b), and SAR (panel c) between LR and LT in the cohort of patients with both high TBS (≥ 9) and low Oslo score (0 – 2). Panels d, e, and f show, respectively, the Kaplan–Meier curve comparison of OS, DFS, and SAR after TBS cut-off value (TBS ≤ 16.2) was applied. Abbreviations: OS, overall survival; DFS, disease-free survival; SAR, survival after recurrence; LR, liver resection; LT, liver transplantation; TBS, tumor burden score.

were reinforced excluding LT patients with TBS exceeding the highest value observed in LR cohort (Fig. 5d).

The impact of recurrence on survival after both resection and transplantation has been extensively investigated previously [8–10,26–29]. Our study confirms previous findings that there is a different pattern of recurrence between resection and transplantation. Lung is the predominant site of relapse after LT while tumor recurrence after resection is more often multicentric or in the liver. Although it has already been studied that disease recurrence, as long as it is pulmonary and resectable, has a modest impact on survival after transplantation, there were no data so far, comparing the impact of recurrence after LT versus LR. Our study shows that in a super-selected cohort of patients with low Oslo and high TBS, if the disease recurs, the survival rate after recurrence shows a better trend for transplant patients although this did not reach statistical significance, most likely for lack of statistical power due to low number of subjects (Fig. 5c,f).

The fact that after 5 years from LT, 20% to 30% of patients are disease-free could imply that

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transplantation has a curative potential for some patients (Fig. 5b,e), and this is supported by recent literature [30]. All these findings may result in better long-term survival beyond 5 years increasing the overall transplant benefit over systemic therapy alone [31].

As long as systemic chemotherapy was the only approved treatment in patients with unresectable CRLM [4], all the efforts by the surgical community have been focused on ways to transform an unresectable metastatic disease into a resectable one. Two-stage hepatectomies gained acceptance because of the benefit over chemotherapy, even if they are hampered by high morbidity, high mortality, and low long-term survival [18–21,32–34]. Moreover, the very definition of resectable disease is related to experience of the individual surgeons and the resources of the Center. Finally, LT set a new standard of care for unresectable CRLM as long as patients fit in the Oslo criteria [6,7]. The experience made over these years clearly indicates that the prognosis after LT for CRLM is linked to morphological and biological characteristics of the tumor, such as tumor burden, metabolic tumor volume, genetic phenotype, and response to chemotherapy [30,35–37]. Therefore, if the findings from this study can be confirmed, transplantation may be the therapy of choice for a highly selected, small group of technically resectable patients with high tumor burden.

We do not know the impact this may have on the waiting list, on the mortality on the list and on the dropout rate, but considering the original 362 patients who underwent liver resection over 10 years, only 13 (3.6%) would have been transplantable according to the selection criteria outlined here (Oslo score ≤ 2 and TBS ≥ 9), which would correspond to just over one transplant per year. Since patients with CRLMs have normal liver function, they can tolerate a lower quality graft than a patient with end-stage liver failure. Hence, it is our opinion that the few resources needed to expand the transplant program are readily available through the expansion of the donor pool, increased utilization of extended criteria donor (ECD) grafts, split livers, and the RAPID technique [38].

This study has several limitations: The retrospective data collection in the resection cohort limited to one center may cause selection bias even though this was minimized by applying the inclusion criteria as in the prospective SECA-I study for both groups. The small sample size limits the statistical power and precludes propensity score matching. Therefore, a larger multicenter study is strongly needed to test the validity of the current findings.

Conclusion

Selected patients with CRLM with low Oslo score and high tumor load seem to obtain better survival outcomes after liver transplantation than after liver resection. Stringent selection criteria are important to avoid futile use of grafts. To further improve the outcomes based upon shared best practices, multicenter randomized controlled trials are needed to establish high level evidence for such an approach.

Authorship

Jacopo Lanari performed study, collected data, analyzed data, and wrote the paper. Morten Hagness collected data and critically revised the work. Alessandra Sartori and Eugenia Rosso collected data. Enrico Gringeri, Svein Dueland and Umberto Cillo: critically revised the work. Pål-Dag Line designed the study and critically revised the work.

Funding

The authors have declared no funding.

Conflicts of interest

The authors declare that they have no conflict of interest.

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