Current Transplantation Reports (2020) 7:311–316
https://doi.org/10.1007/s40472-020-00298-8

MACHINE PRESERVATION OF THE LIVER (C MILLER AND C QUINTINI, SECTION EDITORS)

Liver Transplantation for Colorectal Liver Metastasis

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Accepted: 7 October 2020 / Published online: 14 October 2020

Abstract

Purpose of Review Accumulating evidence suggest that selected patients with nonresectable liver only metastases from colorectal cancer can be offered liver transplantation with acceptable outcome. This review provides an update on the scientific literature.

Recent Findings The SECA-I study showed an estimated 5-year survival of 60% in a heterogenous patient population and guided the development of the first clinical selection criteria. In the sequel SECA-II trial, an estimated 5-year survival of 83% was obtained. A recent study shows that an Oslo score of 0–2, a metabolic tumor volume below 70 cm^3 on PET-CT or Fong score of 0–2 at time of listing, can stratify patients with superior survival. Recurrence is common, but about 70% are slow-growing lung metastases, whereof the majority are resectable.

Summary Liver transplantation for colorectal liver metastasis is an option in highly selected patients. Futile use of grafts can be avoided by applying stringent selection criteria.

Keywords Colorectal cancer · Disease-free survival · Liver transplantation · Overall survival

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide with a particular high prevalence in the developed countries [1]. For the last decennials, there has been an increase in cases in the younger age groups [2, 3].

Almost 50% of CRC patients will develop metastasis, and the liver is the most often involved organ. The only treatment option providing potential long-term survival for colorectal liver metastasis (CRLM) is hepatic resection. The outcomes in terms of overall survival rates (OS) following liver resection are variable, ranging from about 30 to 60% at 5 years. Prognostic factors influencing OS are metastatic tumor load in terms of number of liver metastases and maximal size of the largest lesion, plasma CEA levels, mutational status of the RAS oncogenes, node status of the primary, presence of extrahepatic metastases, and sideness (right sided versus left sided) of the primary tumor [4–8]. Well-selected patients may obtain a 5-year survival rate between 50 and 60% [9].

Criteria for resectability have changed over time by the introduction of efficient chemotherapy for downstaging and techniques like two-stage hepatectomy (TSH) [8, 10]. Furthermore, the size of the future liver remnant (FLR) may be augmented by portal vein embolization (PVE) or associating liver partition and staged hepatectomy (ALPPS) to increase resectability [11]. Nevertheless, only 20–25% of patients with CRLM are suitable for resection during the course of the disease [12]. Hence, the standard treatment option for most patients remains palliative chemotherapy and the 5-year overall survival rates are about 10% [13].

The idea of LT to treat hepatic malignances is as old as transplant itself [14], but the early enthusiasm was curbed by dismal results. In 1991 the Vienna Group reported an OS at 5 years of 12% and recurrence rate over 60% for LT in patients with unresectable CRLM [15]. In the same era, according to European Liver Transplant Registry data, 45 patients

This article is part of the Topical Collection on *Machine Preservation of the Liver*

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underwent LT because of CRLM and 3- and 5-year OS rates were only 32% and 19%, respectively [16, 17]. Based on these experiences, CRLM were considered a contraindication for LT and for many years the Vienna study remained an isolated experience.

Study Outcomes

The first proof of concept trial, the SEcondary CAncer (SECA) I study, was started in Oslo in 2006 [18] The outcomes reported in 21 patients were beyond expectations for unresectable CRLM with estimated OS of 95%, 68%, and 60% at 1, 3, and 5 years, respectively. The recurrence rate was, however, high, with disease-free survival (DFS) as low as 35% at 1 year. Most recurring patients developed slow-growing lung metastases, and a large proportion of these were resectable. Due to aggressive policy of resection of all possible recurrences, a favorable overall survival was obtained despite the short DFS. Based on the SECA-1 trial, the following risk factors for poor outcome were identified [18]: maximal tumor diameter > 5.5 cm, time from primary cancer surgery < 2 years, CEA levels > 80 μg/L, and progression disease after chemotherapy at the time of LT. Assigning 1 point to each adverse factor led to the development of the so-called Oslo Score for risk stratification.

In the sequel trial (SECA-II), the Oslo score was not applied prospectively, but the more stringent inclusion criteria resulted in selection of a cohort with an Oslo score of 0–2 [19••]. As anticipated, with stricter patient selection, survival improved accordingly. The estimated 1-, 3-, and 5-year OS was 100%, 83%, and 83%, respectively. Median DFS was 13.7 months with 1-, 2-, and 3-year DFS of 53%, 44%, and 35%. Nevertheless, survival after relapse at 1, 2, and 4 years was 100%, 73%, and 73%, respectively. Again, about 70% of the recurrences observed were lung metastases and the majority were resected.

A comparison between patients transplanted for CRLM- and HCC shows that patients with nonresectable CRLM with a pre-transplant Oslo score of 0–2 had a 5-year survival rate better than or similar to patients with HCC [20]. Even though HCC patients have much better DFS, HCC recurrence after transplant is associated with a dismal prognosis for almost all patients since there is a lack of effective salvage treatment, while the 2-year OS rate after relapse is 86% in well-selected CRLM patients.

The Controversy of Resectability of CRLM

The whole experience with LT for CRLM has been based on patients with unresectable disease. The concept of resectability of liver tumors has however changed considerably during the last 20 years.

A systematic review of the literature on TSH [21] reports a median 5-year OS of 42% while 5-year DFS was reported only in three studies of the aforementioned meta-analyses at values of 13%, 14%, and 20%, respectively. Furthermore, only 77% of the patients completed the two stages. More recently, Regimbeau [22] analyzed the data from the international LiverMetSurvey registry. The scheduled TSH plan was completed in 71.9% of the study population. The 5-year OS rate after resection was 23%. No patient that failed to complete the two stages survived for 5 years according to this study.

The overall perioperative safety seems to be better following TSH compared to ALPPS, but oncological outcomes including recurrence-free and overall survival are comparable [23]. The first randomized controlled trial, comparing traditional TSH with the ALPPS procedure, shows that the resectability rate was significantly higher with ALPPS than with TSH, with similar rates of severe complications, mortality, and negative surgical margins in the liver [11]. Even if resectability rate can be greatly improved by extended techniques like TSH and ALPPS, the outcomes are mostly inferior compared to upfront resectable patients.

The concept of *tumor burden* score was introduced by Sasaki et al. [24]. Based on this concept, Oshi et al. [25] demonstrate that the more the TBS increases, the less significant the margin status is for DSF and OS, while biological factors, like KRAS status, CEA level and response to preoperative chemotherapy, gain significance accordingly. Thus, there may be a threshold of tumor load for which liver resection can yield acceptable outcomes, independent of technique. One might hypothesize whether LT could provide far better outcomes than liver resection in a subset of patients with borderline resectable disease. In fact, some of the best outcomes after LT for CRLM have been in patients previously resected but finally becoming unresectable due to recurrence in the liver. The concept of including a small subset of resectable patients is however highly controversial and still merely an untested hypothesis. To our knowledge, no data are available on this topic but this might be a possible extension when LT for CRLM gains broader acceptance.

The Impact of Recurrence

An Achilles heel of LT for CRLM may be the high recurrence rate and relatively short DFS. Toso et al. reported a DFS of 56% ± 14%, 38% ± 15%, and 38% ± 15% at 1, 3, and 5 years respectively [26•]. The OSLO experience, from the SECA II trial is very similar [19••]. The median time to recurrence was 6 months, and the lung was the first single site of recurrence in majority of cases [27]. It is noteworthy that the pattern of recurrence is vastly different between liver transplantation

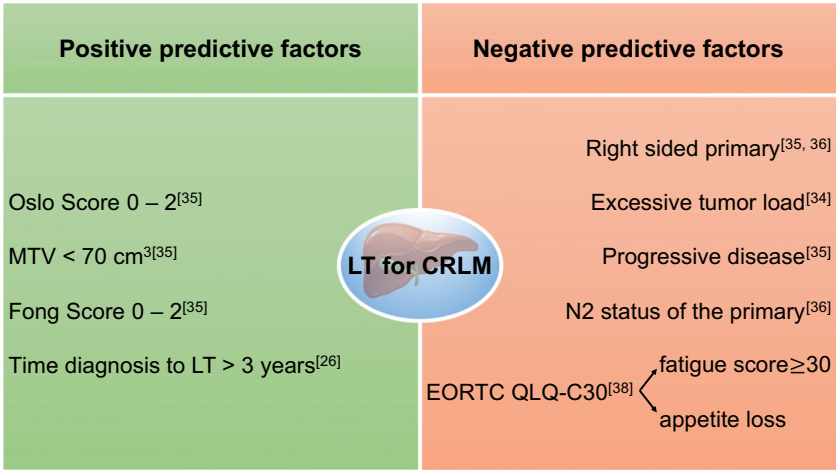

Fig. 1 Factors relevant for patient selection in liver transplantation for colorectal liver metastasis (corresponding references indicated by number). MTV, metabolic tumor volume; LT, liver transplantation; CRLM, colorectal liver metastasis; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer questionnaire version 3.0

and liver resection. In the transplant scenario, 68% were lung metastases and liver was affected only in 5% of cases. Thirteen (62%) patients had lungs as first metastatic site, and 50% of these did not develop other metastases. Both patients treated with lung resection and those not resected were alive at the end of follow-up. The 5-year survival of patients with lung recurrence after LT was 72%. By retrospectively backtracking pre-transplant thoracic CT scans, the presence of lung metastases at the time of LT did not seem to seriously affect survival negatively and immunosuppression does not seem to accelerate their growth [28]. In contrast, liver recurrence after LT was seen only as part of disseminated disease and had a very poor prognosis [27].

In liver resection cohorts, the overall recurrence rate is about 50–70% and about half of the relapses are new liver metastases [29–31]. The 5-year OS after pulmonary recurrence in resected patients has been reported to be 40% [29]. Nonetheless, treatment of recurrence has proven to improve survival after hepatic resection for CRLM [32, 33]; likewise, the same strategy is effective for relapse after LT [19, 27]. There seems to be a low correlation between DFS and OS in LT for CRLM. Consequently, DFS is not an optimal outcome parameter to assess the efficacy of LT in CRLM [20, 34].

Strategies for Improving Access to Liver Transplantation for CRLM

The limiting factor for a broader implementation of liver transplantation for CRLM remains the scarcity of liver grafts. To overcome this problem, we need to move in two directions: improve patient selection and expand the donor pool.

Essentially, improved patient selection implies a better understanding of the tumor biology to improve outcomes and avoid the futile use of liver grafts. Within the Oslo Criteria, the CEA level and the response to chemotherapy are surrogates for the biological behavior of the disease. A Fong Clinical Risk Score of 0–2 has also been shown to be associated with superior long-term survival, and this score shares some factors with the Oslo Score [5, 35]. Some other factors are distinctly associated with inferior survival: right-sided primary tumor location [35, 36] and a metabolic tumor volume (MTV) exceeding 70 cm^3 on pre-transplant 18F–FDG PET/CT [37] are both strong predictors of inferior outcome. Moreover, patients that, on quality of life assessment with European Organization for Research and Treatment of Cancer questionnaire version 3.0 (EORTC QLQ-C30) prior to transplant, display a high score, and in particularly those that have loss of appetite, have significantly worse survival [38••]. An overview of factors important to patient selection is summarized in Fig. 1.

Dependent on which criteria are applied, the impact on the transplant waiting list will vary accordingly. Based on stringent selection, calculated based on SECA-studies and Norwegian population, only 0.24 to 0.51 patient per 1 million people per year would be eligible, representing 1 to 2% of yearly liver transplants (based on US population) [35••], meaning that the required resources do not necessarily negatively impact the patients with conventional indications for LT.

Regarding the donor pool expansion, a logical solution would be to use extended criteria donors (ECDs) for CRLM patients [36••], assuming that these recipients will tolerate ECD grafts better due to the absence of hepatic failure and portal hypertension. Another, potentially promising approach is based on split liver technique and auxiliary transplantation. The novel concept of RAPID (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy) technique [39] allows maintenance of adequate metabolic liver mass during which a small auxiliary graft can regenerate to allow delayed second stage hepatectomy. Augmented regeneration of the graft is facilitated by diverting portal blood flow from the liver remnant, but importantly, this should be done under pressure guidance to avoid small-for-size syndrome (SFSS) damage to the graft [40]. As soon as the graft has obtained a size approaching 0.8% of body weight (or

Table 1 Clinical trials on liver transplantation in colorectal liver metastases

Name	NCT number	Locations	Interventions	Study design	Number to be enrolled	Endpoints
Deceased donor liver transplantation						
TRANSMET	NCT02597348	Paris, France	CTx ± LT	Allocation: randomized Intervention model: single group assignment Masking: none (open label) Primary purpose: treatment	90	5-year OS 3-year OS DFS (Arm LT+C) and PFS (Arm C)
SOULMATE	NCT04161092	Gothenburg and Stockholm, Sweden	LT vs. best alternative care	Allocation: randomized Intervention model: parallel assignment Masking: none (open label) Primary purpose: treatment	45	5-year OS 2-year OS PFS Hepatic PFS Extrahepatic RFS QoL Health economic evaluation
SECA III	NCT03494946	Oslo, Norway	LT vs. other treatment (further chemotherapy, TACE, SIRT)	Allocation: randomized Intervention Model: parallel assignment Masking: none (open label) Primary purpose: treatment	30	OS DFS
SECA II	NCT01479608	Oslo, Norway	LT vs. resection	Allocation: randomized Intervention model: single group assignment Masking: none (open label) Primary purpose: treatment	25	OS DFS
COLT	NCT03803436	Italy (multicentric)	LT vs. triplet CTx + anti-EGFR	Allocation: non-randomized Intervention model: parallel assignment Masking: none (open label) Primary purpose: treatment	22	OS PFS Complications rate
Partial Liver Segment 2/3 Transplantation Study	NCT02215889	Oslo, Norway	LT	Intervention model: single group assignment Masking: none (open label) Primary purpose: treatment	20	Percentage reaching second stage hepatectomy within 4 weeks of segment 2/3 transplantation OS DFS
Living donor liver transplantation						
Living Donor LT for Unresectable CRLM	NCT02864485	Toronto, Canada	LDLT	Intervention model: single group assignment Masking: none (open label) Primary purpose: treatment	20	OS DFS Patterns of cancer recurrence after LT
Liver-T(w)o-Heal	NCT03488953	Tuebingen and Jena, Germany	LDLT with two-staged hepatectomy	Intervention model: single group assignment Masking: none (open label) Primary purpose: treatment	40	OS 3 years after 2nd stage of hepatectomy DFS 3 years after 2nd stage of hepatectomy Morbidity of the recipient Morbidity of the donor

CTx, chemotherapy; *LT*, liver transplantation; *OS*, overall survival; *DFS*, disease-free survival; *PFS*, progression-free survival; *RFS*, relapse-free survival; *QoL*, quality of life; *TACE*, trans arterial chemoembolization; *SIRT*, selective internal radiation therapy; *EGFR*, epithelial grow factor receptor; *CRLM*, colorectal cancer liver metastasis; *LDLT*, living donor liver transplantation

35 to 40% of recipient standard liver volume), the second stage hepatectomy of the native liver remnant is completed within 3 weeks. The concept has been further developed by retrieving the left lateral graft from living donors. To date, 6 two-stage hepatectomies with auxiliary partial orthotopic liver transplantation from a living donor (named LD-RAPID) have been reported: 5 in Germany [41, 42] and 1 in Belgium [43]. The first results are promising, but still the experience with the RAPID concept is limited and does not yet allow firm conclusions.

Finally, conventional living donor liver transplantation could be an option for centers that offer this option, and studies are currently ongoing within this area (Table 1).

Conclusion

Selected patients with CRLM with low Oslo score or low Fong Clinical risk score at listing can be offered liver transplantation with survival outcomes comparable to conventional indications for liver transplantation. Stringent selection criteria are important to avoid futile use of grafts. Expansion of the donor pool may be obtained through increased use of ECD grafts, the RAPID technique, and living donor liver transplantation. To further improve the outcomes based upon shared best practices, all transplants for this indication should be part of prospective clinical trials.

Acknowledgements Open Access funding provided by University of Oslo (incl Oslo University Hospital).

Code Availability Not applicable.

Authors' Contributions All authors contributed to the study conception and design. Jacopo Lanari performed the literature search and wrote the first draft of the manuscript. Pål-Dag Line and Svein Dueland critically revised the work. All authors read and approved the final manuscript.

Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest Jacopo Lanari, Svein Dueland, and Pål-Dag Line declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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