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MINIREVIEWS

Role of liver transplantation in the management of colorectal liver metastases: Challenges and opportunities

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Abstract

The liver is the most common site of colorectal cancer metastasis. Complete resection of the metastatic tumor is currently the only treatment modality available with a potential for cure. However, only 20% of colorectal liver metastases (CRLM) are considered resectable at the time of presentation. Liver transplantation (LT) has been proposed as an alternative oncologic treatment for patients with unresectable CRLM. This review summarizes the published experiences of LT in the setting of unresectable CRLM from the previous decades and discusses the challenges and future horizons in the field. Contemporary experiences that come mostly from countries with broader access to liver grafts are also explored and their promising findings in terms of overall survival (OS) and disease-free survival (DFS) are outlined along with their study design and methods. The rationale of establishing specific patient selection criteria and the dilemmas around immunosuppressive regimens in patients undergoing LT for CRLM are also highlighted. Additionally, this review describes the findings of studies comparing LT *vs* chemotherapy alone and LT *vs* portal vein embolization plus resection for CRLM in terms of OS and DFS. Last but not least, we present current perspectives and ongoing prospective trials that try to elucidate the role of LT for CRLM.

Key Words: Colorectal cancer; Colorectal liver metastases; Liver transplantation;

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Core Tip: Despite the discouraging results of the previous decades, reports from the recent era showed promising results and reemerged the idea of liver transplantation (LT) for colorectal liver metastases (CRLM). Documentation of patient selection criteria and stronger evidence from ongoing prospective trials may reinforce the implementation of LT as an oncologic treatment for CRLM.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancer entities worldwide, ranking third in terms of incidence, and second in terms of cancer-related death[1]. The overall survival of the patients with CRC depends primarily on cancer staging[2-4]. The liver is the most common site of CRC metastasis, mainly due to its anatomical association with the portal circulation[3]. Published data indicate that approximately 20% of patients with CRC present with concomitant liver metastasis at the first medical consultation, while another 50% develops liver metastasis within the first 3 years after primary tumor diagnosis[2,3,5,6]. The life expectancy of patients with colorectal liver metastasis (CRLM) who do not receive any type of treatment ranges from 12 to 15 mo, and the 5-year survival is less than 5%[2]. Implementation of chemotherapy as the only treatment modality for CRLM results in a median patient survival of approximately 25 mo[7]. Complete tumor resection is currently the only potentially curative treatment with a 5-year and 10-year overall survival (OS) of 38% and 26%, respectively[8]. Yet, only 20% of patients present with a hepatic lesion that can be managed surgically with a curative intent[9-11]. Additionally, what constitutes a surgically resectable CRLM is a matter of debate among surgeons[12,13]. Recent advances in surgical techniques[14] combined with the emergence of newer chemotherapeutic drugs[15,16] have increased the proportion of CRLM amenable to resection. Unfortunately, disease recurrence is still reported in 40%-70% of patients within the first 3 years after surgical excision[17,18] due to the presence of micro-metastatic disease, resulting in a median OS of 10-38 mo for patients relegated to palliative chemotherapy[19,20].

This has led to the consideration of liver transplantation (LT) as an oncologic treatment for patients with CRLM isolated to the liver[9,21]. The aim of this review is to delineate the rationale and outcomes of LT in the setting of unresectable CRLM, and to outline the potential benefits, future perspectives, and ethical dilemmas about this treatment modality.

EARLY EXPERIENCE

LT was historically first attempted in patients with malignant liver tumors (including patients with CRLM)[22]. However, poor survival and high recurrence rates quickly led to restriction of LT utilization to early-stage hepatocellular carcinoma (HCC). The experience gained through the years along with advances in surgical technique and neoadjuvant modalities have broadened the spectrum of malignant indications for LT including advanced HCC, hilar cholangiocarcinoma, as well as metastatic liver tumors (*e.g.*, neuroendocrine metastasis)[23]. This motivated some groups in 1990s to re-assess the role of LT for unresectable CRLM.

The first report of LT for CRLM was from Medical University of Vienna, Austria [24]. Mühlbacher *et al*[24] reported a series of 25 patients who underwent LT for CRLM between 1982-1994 (all patients had lymph node negative disease). In this study, the 1-,

3-, and 5-year post-LT OS was 76% (19/25), 32% (8/25), and 12% (3/25), respectively [19,24]. It should be acknowledged, that after retrospective histological examination of the excisional specimens, lymph node micro-metastases were observed in 15 out of 21 patients who were initially classified as having negative lymph node status. This finding was associated with a decreased post-LT median survival of 28 mo compared to a median survival of 118 mo in patients without micro-metastases[24-26]. Another early experience was published in 1991 by Penn *et al*[27] from University of Cincinnati reporting on 10 patients undergoing LT for CRLM (eight of them due to unresectable tumor and two of them due to chemotherapy adverse effects) with a 70% recurrence rate. Additionally, Pichlmayr *et al*[28] published another series of patients undergoing LT in Germany during 1972-1995, and amongst the reported cases there were 4 patients who underwent LT for CRLM. Two of these patients died in the early post-operative period (one due to acute graft rejection), while the other two patients died from disease recurrence at 11 mo and 33 mo follow-up[28]. The discouraging results from these studies in addition to the lack of standardized criteria for patient selection led to CRLM being established as a formal contraindication for LT over the next decades.

RECENT ERA

The broader access to deceased donor liver grafts in Norway led a group from Oslo University Hospital to investigate the outcomes of well-selected LT candidates with unresectable liver-only CRLM[9,21,29,30]. The first prospective study (SECA-I) was published in 2013 and included 21 patients who had undergone LT from 2006 to 2011 [30]. Inclusion criteria were total resection of the primary tumor, ECOG score 0 or 1, at least 6 wk of neoadjuvant chemotherapy, and absence of extrahepatic disease[30]. Liver resection prior to LT had been performed in 3 patients. The median follow-up time was 27 (range, 8-60) months and the 1-, 3-, and 5-year OS was 95%, 68%, and 60%, respectively. All patients received sirolimus for immunosuppression and none of them received adjuvant chemotherapy. Disease free survival (DFS) was 35% at 1 year[30]. Another publication from the same group reported a total of 19 recurrences in 21 patients (16 were single-site and 3 were multiple-sites at first presentation)[29]. Thirteen of the 16 recurrences were isolated to the lung and patients with isolated pulmonary metastases had a 5-year survival of 72% after recurrence was diagnosed [29]. Notably, there was no isolated hepatic recurrence at initial presentation[29]. However, seven patients developed metastasis to the transplanted liver on subsequent follow-up and six out of those seven patients eventually died from metastatic disease.

Although the results from SECA-I were encouraging, the high recurrence rates led to more stringent candidate selection criteria in SECA-II. SECA-II included 15 patients who had undergone LT for unresectable liver-only CRLM from 2012 to 2016[9]. Similar to the SECA-I trial, all patients received sirolimus for immunosuppression and none of them received adjuvant chemotherapy. The stricter selection criteria required that isolated liver-only CRLM was confirmed by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) scan and patients had more than one year time span from diagnosis of CRC to LT. Additionally, at least 10% response on chemotherapy (according to RECIST-criteria) was a prerequisite for inclusion in the SECA-II study[9]. Resection prior to LT was performed in 4 patients. Median follow up was 36 mo. Compared to SECA-I, the more restrictive selection criteria led to improved 1-, 3-, and 5-year OS of 100%, 83%, and 83%, respectively. However, median DFS remained low at 13.7 mo. Overall, 8 patients were reported to have disease recurrence after LT and 6/8 presented with isolated pulmonary metastasis. On follow-up, 13 patients were alive, and 2 patients died 26 mo after LT due to disease recurrence. The main limitations of this study were the small sample and the relative short follow-up time, but the encouraging results drove the investigators from Oslo to conduct an additional enrollment to the SECA-II study using grafts from extended criteria donors[21]. This study (D-arm of SECA-II) included both patients with synchronous CRLM (within 1 year of primary colorectal tumor diagnosis) and those with concomitant resectable pulmonary metastases or with previously resected pulmonary metastases[21]. Moreover, the investigators did not consider response to chemotherapy as a prerequisite for recruitment[9,21]. Ultimately, 10 patients were included between 2014-2018. The median follow up was 23 mo, the median OS was 18 mo, and the median DFS was 4 mo. Disease recurrence was noted in 8/10 patients with isolated pulmonary metastasis seen in six patients. Overall, five patients were still alive on follow-up with two of them having no relapse at 23 mo and

26 mo after LT[21]. These outcomes established that LT could be considered in patients with unresectable liver-only CRLM only under strict selection criteria.

An international, multicenter, retrospective study of 12 patients was published by Toso *et al*[31] in 2017. Eleven of the patients had received chemotherapy prior to LT. The median follow-up time was 26 mo and the 1-, 3-, and 5-year OS was 83%, 62%, and 50%, respectively, while the 1-, 3-, and 5-year DFS was 56%, 38%, and 38%, respectively. Disease recurrence was noted in six patients with five of them presenting with pulmonary metastasis, while 5 out of the 11 patients were reported to be alive and without evidence of relapse at the end of the follow-up[31]. However, due to the nature of the study patients were not selected according to homogeneous criteria and they were not managed with the same interventions. Despite the limitations, this report demonstrated that LT for CRLM can provide a survival benefit in carefully selected patients, but additional refinement is necessary prior to the broader application of LT as an oncologic treatment for CRLM.

A recent worldwide systematic review and pooled analysis of 110 patients undergoing LT for CRLM reported that the 1-, 3-, and 5-year OS rates were 88.1%, 58.4%, and 50.5%, respectively[32].

Study characteristics and findings for the early experience and recent studies on LT for CRLM are shown in Table 1.

RISK STRATIFICATION CRITERIA

Similar to prior reports establishing specific selection criteria for other liver malignancies (Milan criteria for HCC and Mayo Clinic criteria for hilar cholangiocarcinoma)[33,34] the SECA studies introduced the Oslo score which was used a surrogate marker for favorable prognosis[9,21,30]. One point was assigned for each of the following characteristics: (1) Lesion larger than 5.5 cm; (2) Pre-LT plasma carcinoembryonic antigen (CEA) level above 80 μg/L; (3) Time from primary tumor resection to LT less than 24 mo; and (4) Disease progression while on pre-LT chemotherapy. Each of these factors was significantly associated with poorer OS and the five patients who possessed all four factors comprised five of the six mortalities in the SECA-I trial[30]. Risk stratification was also done utilizing the Fong Clinical Risk Score (FCRS)[35], in which one point was given for the following: (1) Synchronous CRLM (less than 12 mo from diagnosis); (2) Primary tumor with positive lymph nodes; (3) More than one lesion; (4) Tumor larger than 5 cm; and (5) CEA level higher than 200 μg/L. FCRS of 1-2 at the time of diagnosis was associated with significantly increased DFS compared to FCRS of 3-4[9].

The importance of stricter patient selection was also highlighted by the differences in OS and DFS between SECA-I and SECA-II studies, where 5-year OS was 60% and the 1-year DFS was 35% for SECA-I, while the 5-year OS was 83% and the 3-year DFS was 35% for SECA-II[9,29]. Smedman *et al*[21] attributed the poorer outcomes in terms of survival and disease recurrence of the D-arm of SECA-II in the significantly higher Oslo and FCRS scores of the patients compared to the patients of SECA-I and primary SECA-II trials[9,21,29,30]. Therefore, it is apparent that strict patient selection criteria and risk stratification are essential for the broader adoption of LT as a life prolonging oncologic treatment for liver-only CRLM.

IMMUNOSUPPRESSION

Immunosuppression is a controversial topic regarding LT for metastatic diseases in terms of achieving a balance between the risk of graft rejection and the risk of disease recurrence[19,32]. That is because attenuation of the native immune response from immunosuppression is essential to prevent graft rejection, however, it may contribute to unfavorable post-LT outcomes in patients with disseminated malignant disease, as it could facilitate disease recurrence. A study that assessed the impact of sirolimus post-LT for HCC, documented that immunosuppression improved the outcomes in the first few years post-LT and had no effect in DFS or OS beyond 5 years post-LT[36]. Notably, sirolimus was the immunosuppressive regimen used in the SECA trials[9,21,29,30]. Data from a study that compared the growth of pulmonary metastasis in patients enrolled in the SECA trials *vs* patients with CRC and lung metastasis who did not receive immunosuppression, reported that there was significant difference between the two groups in terms of the time needed to double tumors' diameter and volume[37]. Moreover, the same study reported that there was no association between

Table 1 Study characteristics and findings

A. Early experience

Author, Yr	Study period	Number of patients	Clinical outcomes
Mühlbacher *et al*[24], 1991	1982-1994	25	1-yr OS: 76%, 3-yr OS: 32%, 5-yr OS: 12%
Penn *et al*[27], 1991	N/A	10	70% recurrence rate
Pichlmayr *et al*[28], 1997	1972-1995	4	2 post-operative mortalities, 2 late mortalities due to recurrence

B. Recent era

Author, Yr	Study period	Number of patients	Follow-up	1-yr OS, %	3-yr OS, %	5-yr OS, %	DFS
Hagness *et al*[30], 2013	2006-2011	21	27 mo	95	68	60	35% at 1st year
Dueland *et al*[41], 2020	2012-2016	15	36 mo	100	83	83	13.7 mo
Smedman *et al*[21], 2020	2014-2018	10	23 mo	N/A	N/A	N/A	4 mo
Toso *et al*[31], 2017	1995-2015	12	26 mo	83	62	50	56% at 1st year

All values reported for continuous variables are expressed in median. OS: Overall survival; DFS: Disease free survival, N/A: Not available.

sirolimus plasma levels and DFS or growth of pulmonary metastases[37]. However, the current level of evidence is relatively low, and future high-quality studies are required to draw solid conclusions for immunosuppressive therapies after LT for CRLM.

LIVER TRANSPLANTATION VERSUS CHEMOTHERAPY

In 2015, Dueland *et al*[38] published a study aiming to outline the differences in OS of patients with CRC and nonresectable CRLM treated by LT or chemotherapy. The investigators compared the SECA-I study with the NORDIC VII study, which was a multicenter randomized three-arm trial investigating the efficacy of cetuximab added to bolus fluorouracil/folinic acid and oxaliplatin[39]. The 21 patients from SECA-I study were compared with the 47 patients from the NORDIC VII study, in terms of DFS and OS. DFS was 8 to 10 mo in both groups[38]. However, the 5-year OS was 56% in patients undergoing LT compared to 9% in patients receiving chemotherapy[38]. The authors attributed this difference to the pattern of disease recurrence. While small and slow growing lung metastases were the most common recurrence pattern in the LT group, patients in the chemotherapy group presented with progression of the nonresectable CRLM, which has a less favorable prognosis[38].

LIVER TRANSPLANTATION VERSUS PORTAL VEIN EMBOLIZATION PLUS LIVER RESECTION

Emerging surgical advances have been proposed to increase the pool of patients with CRLM that can be subjected to liver resection. Implementation of portal vein embolization (PVE) could render initially nonresectable CRLM amenable to resection [40]. Dueland *et al*[41] compared 50 patients enrolled to SECA studies with a matched group of 53 intention-to-treat patients who have undergone PVE to expand the future liver remnant (FLR) and were planned to undergo liver resection (15 patients did not proceed to liver resection due to inadequate FLR or disease progression). Although the data for the whole LT cohort are not presented to clearly appreciate differences compared to the PVE cohort, the authors mentioned that the two groups had similar selection criteria. Additionally, patients were subclassified in two subgroups; the high tumor load (HTL) group was defined as patients having ≥ 9 metastatic tumors or largest tumor diameter ≥ 5.5 cm, while patients with CRLM below the aforementioned limits were included in the low tumor load (LTL) group[41]. The 5-year OS for patients with HTL was 33.4% in the LT arm (n = 29) compared to 6.7% in the PVE arm (n = 15) of the study without any between-group differences regarding tumor burden score. The 5-year OS for patients with LTL was 72.4% in the LT arm (n = 21) compared to 53.1% in the PVE arm (n = 30), while the tumor burden score was significantly higher

in the LT arm. Accounting that there are no randomized controlled trials comparing LT to PVE plus resection in patients with extensive liver-only CRLM, as well as the fact that these two modalities may not necessarily be applicable to the same pool of patients, this study provides some evidence that LT has promising future perspectives in the field of oncologic treatments for CRLM.

CURRENT AND FUTURE PERSPECTIVES

The International Liver Transplantation Society Transplant Oncology Consensus Conference recommendations, based on the findings of SECA trials, suggested that LT could be implemented in patients with unresectable CRLM with only liver involvement and with a maximum tumor diameter ≤ 5.5 cm, pre-LT CEA ≤ 80 μg/L, response to pre-LT chemotherapy, and time interval from diagnosis to LT ≥ 1 years [42]. However, worldwide liver graft scarcity poses an ethical dilemma which is summarized as follows: How will the distribution of existing grafts to patients with CRLM impact patients with imperative need for a graft? In the United States, the Model for End-Stage Liver Disease score is used to prioritize patients for LT based on severity of liver derangements. However, patients with non-resectable CRLM have no portal hypertension or liver disease and thus are handicapped for access to deceased donors. Such patients could be good candidates for living donor liver transplantation (LDLT). Consequently, considering a long-term OS in the order of 60%, LDLT could offer a very good therapeutic alternative to this group of patients without jeopardizing the cadaveric donor pool.

Several trials attempting to elucidate the role of LT in CRLM are currently ongoing. In addition to the SECA-I (NCT00294827 - active, not recruiting: estimated study completion date May 2023) and SECA-II (NCT01479608 - active and recruiting: estimated study completion date December 2027), the Oslo group is also working on the SECA-III study, which aims to assess the efficacy of LT *vs* other therapies (chemotherapy and surgical resection) with a primary outcome of 2-year OS, and the RAPID (NCT02215889) trial, which aims to evaluate the outcomes of recipient left lateral segmentectomy and implantation of donor segments 2 and 3 followed by removal of the remaining recipient liver segments (second stage hepatectomy) at 4 wk post-LT. The LIVERT(W)OHEAL trial (NCT03488953) will evaluate the outcomes of LDLT in both the donors and the recipients. The largest ongoing trial, estimated to eventually enroll approximately 90 patients, is the TRANSMET (NCT02597348) phase III randomized controlled trial and will evaluate the 3-year OS and disease recurrence or progression in patients with CRLM undergoing LT plus chemotherapy *vs* chemotherapy only. Finally, a trial conducted by the Toronto group (NCT02864485), the COLT trial (NCT03803436), the TRIPLETE trial (NCT03231722), and the Swedish SOULMATE trial (NCT04161092) are also ongoing trials that investigate the utilization of LT as an oncologic treatment for CRLM.

Several other perspectives on the assessment for candidacy should also be incorporated into future studies. FDG is widely used to stage and monitor treatment response in metastatic CRC and the use of PET/CT scan to stage patients, as well as to assess response to therapy has been raised as a parameter of interest. Mutational profiling of CRC has been shown to have an impact on patient outcomes[43], and thus the role of selecting patients for LT based on mutational profiling will need to be addressed. Finally, the use of neoadjuvant radiotherapy to the native liver prior to LT to reduce intraoperative shedding of tumor cells during hepatectomy is also under consideration.

CONCLUSION

The SECA studies from Oslo have demonstrated promising results in prolonging survival with the use of LT as an oncologic treatment for carefully selected patients with unresectable liver-only CRLM. Further evidence is currently awaited from ongoing prospective trials in order to better define the role of LT for unresectable CRLM. The addition of unresectable CRLM as an indication for LT represents a paradigm shift and further confirms versatility of the emerging field of transplant oncology.

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