Review Article

Living donor liver transplantation for colorectal liver metastasis: a narrative review

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Abstract: Colorectal cancer (CRC) is a spread disease worldwide. Most of the patients with CRC will develop liver metastases along the time and more than 75% of them are unresectable (uCRLM). In this case, despite the actual modern chemotherapy, the 5-year overall survival (OS) is lower than 10%. In the recent ten years liver transplantation (LT) for uCRLM experienced a "comeback" with excellent results in terms of OS at 5 years ranging from 60% to 100% according to different selection criteria, notwithstanding high recurrence rates (mainly extrahepatic). These promising results are based on a global population of almost 50 patients who underwent a DDLT. In times of organ paucity and still critical indication, standard DDLT will not find any place outside of studies. Additionally, the use of extended criteria donors (ECD) showed recently poor results in this context. Therefore, one way out of this dilemma may be represented by the use of Living-Donor liver transplantation (LDLT). In this review, we report about LDLT for uCRLM. In addition to a report of initial experience (i.e., global amount of 25 cases), we mainly focused on ethical, technical and oncological aspects of the procedure and proposed future applications as well. In summary, in times of scarcity of organs, LDLT for uCRLM may represent a valid alternative to DDLT with minimal donor risk and maximal recipient benefit in selected cases.

Keywords: Colorectal cancer (CRC), Colorectal Liver Metastases, liver transplantation (LT); Living Donor

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Introduction

Colorectal cancer (CRC) is a worldwide spread disease (third most commonly diagnosed cancer) (1,2). More than 75% of CRC will develop colorectal liver metastases (CRLM of which 15–25% are synchronous and 25–50% metachronous) (3).

Unfortunately, more than 75% of CRLM are unresectable (uCRLM) and the respective overall survival rate (OS) at 5 years is about 10% despite the actual modern drugs and therapeutic strategies like antibodies and ablative procedures (4,5). Longer median OS has been obtained in selected patients with (I) good performance status (i.e., Eastern Cooperative Oncology Group 0–1), (II) no (K) RAS or BRAF mutations, and (III) left-sided primary tumors (6,7). In this context, liver transplantation (LT) has been proposed as the only treatment to achieve long term survival for uCRLM. In the recent 10 years LT for uCRLM experienced a "comeback" with excellent results in terms of OS at 5 years ranging from 60% to 100% according to different selection criteria (*Table 1*) (8).

These data are mainly based on the results of SECA

I (n=21), SECA II study (n=15) and Compagnons Hepatobiliares experience (n=12) (a total amount of 48 patients) (6,11,12). In spite of high rates of tumor recurrence (>80% and mainly extrahepatic, i.e., pulmonary), the Oslo group showed that excellent OS rates could be reached provided that maximal treatment of recurrent disease has been performed (surgery and aggressive chemotherapy) (6,10,13-15). In this context, it is important to keep in mind that after LT in case of extrahepatic recurrence the prognosis in terms of long-term OS is good (because of natural history and possibility to treat it surgically or systemically). On the opposite, in case of intrahepatic tumor recurrence the prognosis is very poor (16,17).

Lastly, it has been recently reported that immunosuppressive therapy seems not to negatively influence the post-transplant tumor progression. On the opposite, in case of low immunosuppression the risk of rejection may even increase up to 40% (15).

The above-mentioned results (SECA I, SECA II and Les Compagnons) support the recently proposed recommendations of the ILTS consensus conference on 'Transplant Oncology' recently held in Amsterdam 2019: LT for uCRLM does represent a viable option in highly selected patients with only liver involvement with very good survival outcomes comparable to those for conventional indications (6,8,18-21).

In this regard, different studies are presently under way. The aim is to confirm the outstanding results of LT for CRLM, results that are better than the ones of LT for standard indications (oncologic and non-oncologic ones) (*Table 2*).

Table 1 Prognostic scores actually used for selection of recipients for LT for uCRLM (6)

Oslo Score [0–4] (8)
• Tumor Diameter >5.5 cm
• CEA >80 μg/L
• <2-year interval between primary resection and LT
• Progressive disease at time of LT
Fong Clinical Risk Score [0–5] (9)
• Largest Tumor >5 cm
• CEA >200 μg/L
• Synchronous disease (primary to liver recurrence <12 months)
• Node-positive primary
Metabolic tumor volume (MTV) (10)
• >1 liver metastasis
• Cut-off: 70 cm^3

CEA, carcinoembryonic antigen; LT, liver transplantation.

Table 2 Clinical trials in patients undergoing LT for uCRLM: DDLT and LDLT studies (updated June 2020)

Trial Protocol	Clinical trial Identifier	Country	Protocol timeline	Study design
Deceased donor liver transplantation (DDLT)				
SECA II	NCT01479608	Norway	2011–2027	LT *vs.* Surgical Resection
SECA III	NCT03494946	Norway	2016–2027	LT *vs.* CTx or ablation
TRANSMET	NCT02597348	France	2015–2027	CTx + LT *vs.* CTx
COLT	NCT03803436	Italy	2019–2024	CTx + LT *vs.* CTx
SOULMATE	NCT04161092	Sweden	2020–2029	CTx + LT with ECD *vs.* CTx
RAPID	NCT02215889	Norway	2014–2028	Liver resection and partial section 2-3 transplantation with two-stage hepatectomy
Living donor liver transplantation (LDLT)				
Toronto Protocol	NCT02864485	Canada	2016–2023	CTx + LDLT *vs.* CTx
LIVER-T(W) O-HEAL	NCT03488953	Germany	2018–2023	LDLT with two-stage hepatectomy

LT, liver transplantation; uCRLM, unresectable colorectal liver metastasis; DDLT, Deceased donor liver transplantation; LDLT, Living donor liver transplantation; CTx, chemotherapy; ECD, extended donor criteria.

In spite of the excellent and promising results, the actual situation shows following limitations:

(I) All these data are coming from small and selected populations with a grand total of almost 50 cases (6,11,12).

(II) According to different grades of selection, only 1-2% of all uCRLM seem to be eligible for LT (13).

(III) Although no mortality has been reported, relevant perioperative complications have been described in SECA I and SECA II Study (6,11,15).

(IV) The major limitation is represented by the fact that the source of liver grafts in all the above-mentioned studies is exclusively represented by deceased donors (DD) (standard or extended criteria). LT for uCRLM is at the present time still considered an experimental procedure. Most importantly it is not considered a curative intervention in view of the high recurrence rate. Consequently, because of the scarcity of organs, Deceased-Donor Liver Transplantation (DDLT) for uCRLM has been considered ethically unfair since it takes away a life-saving opportunity for a patient fulfilling the standard indications (22). Additional limitation for such an intervention is due to the nature of LT and the fact that the DD cannot be available at exactly the right time, for example during a chemotherapy free window. This fact might have an impact on the uniform application of the protocol and ultimately on the outcome of the patients.

Therefore, it might be impossible to offer LT as standard therapy for patients with uCRLM in countries with limited DD organ supply and large waiting lists. Possible alternatives to standard whole DDLT are represented by: DDLT by using extended criteria donors' livers (ECD), DD-RAPID procedure and Living-Donor Liver Transplantation (LDLT) (classic right/left or LD-RAPID).

We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-91).

LT with ECD

Although it would be possible to use extender criteria livers (up to which DRI and kind of ECD criteria including DCD should be defined), one should consider the fact that the SECA I and SECA II study showed relevant perioperative complications even by not using ECD organs (15). Therefore, using marginal grafts for such "extended indications" may furtherly increase the risk of postoperative complications (15). At this regard, Smedman *et al.* recently reported the results of SECA II arm D group using DDLT with ECD grafts: the authors showed very poor results, with very short OS opening a discussion regarding the feasibility of this strategy (23).

DD-RAPID

As possible alternative to standard whole DDLT, the Oslo Group recently introduced the RAPID-procedure (i.e., resection and partial liver segment 2–3 transplantation with delayed total hepatectomy) (24), which consists in use of left lateral grafts from split-DD, which could not be allocated to patients with standard indication. The RAPID is a sort of fusion of the APOLT (auxiliary partial orthotopic liver transplantation) (25) and ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) concepts (26,27). It consists mainly of a two-step procedure: in step 1 a left hepatectomy with ligature of right portal vein is performed in the recipient's liver. This is followed immediately by an auxiliary orthotopic transplantation of the left lateral lobe as a split graft from DD. As soon as the transplanted graft has reached sufficient volume and function (28), the 2nd step of the procedure will be performed, and, similarly to step 2 of ALPPS, the residual metastasized right liver lobe is removed (24,29). To date 3 patients have undergone the DD-RAPID within the DD-RAPID trial (NCT02215889) (30).

Even though the DD-RAPID seems to be an excellent alternative to standard whole DDLT, the basic problem of scarcity of organs from DD and specifically of organs that can be split, remains. Moreover, the possibility of using left lateral grafts for uCRLM will require drafting specific policies defining the characteristics of the liver donors eligibility to the split and the proper allocations of these left lateral segments, with specific attention not to deplete an already scarce supply and not to further diminish the chances of transplantation for pediatric and small adult patients. Lastly, appropriate informed consents should be given to the recipients of these otherwise perfect livers, who, by accepting a split organ, by definition might encounter an increased risk of complications.

LDLT

The LDLT may represent a possible solution to the above-mentioned problems i.e., limited availability of DD grafts (31),

but is mainly conditioned by the basic dilemma of LDLT: the risk for the donor. For the specifics of LDLT for uCRLM do the recipient's benefits justify the donor's risks according to the concept of "double equipoise" for LDLT" (32-35).

Related to this, the LDLT community should establish a priori the primary goals in terms of OS rates according to benchmarks as well as social and ethical aspects. Clavien *et al.* established that a LT for oncological reason should guarantee at least OS rates >65% at 5 years (36). Lieber *et al.* proposed that, when extending the oncological indications, the transplant community should accept LDLT, when the risk-benefit ratio is reasonable and not when it is unreasonable (31). In this regard Lieber *et al.* suggested a 40% likelihood of 5-year OS as a cut-off for LDLT. According to the recent results reported by the Oslo group, these criteria would be completely fulfilled (i.e., 5-year OS rates 60-100% according to different selection criteria) (8,13).

Therefore, it is essential to accurately select the potential recipient (8) and avoid compassionate LT for uCRLM (which would end with poor results) (12).

Recently, the Oslo group proposed to select and stratify the prognosis of the patients through 3 different prognostic score systems [i.e., Fong Score (9), Oslo Score and Metabolic Tumor Volume (8) in addition to clinical and biological parameters (e.g., metachronous/synchronous disease, location of the primary tumor, BRAF/KRAS mutation)].

If from one side incorporating these variables may yield an even higher expected OS, on the other side it can lead to exclusion of >70% of patients who would also benefit sufficiently to justify LT (6,8,13).

Based on such strict selection, it has been calculated that 0.24 to 0.51 patients per 1 million people per year would be eligible, representing 1% to 2% of yearly liver transplants in the United States. At the moment, more than 14,000 people are waiting for a LT in the U.S., and yet only about 8,000 transplants are performed on a yearly basis (37,38). Considering this, it seems obvious that the best card one could play in this scenario is the LDLT one. Additionally, on the opposite to DDLT, LDLT offers the main advantage of plannability and consequently performing LT at the right time when the tumor is stable within a chemotherapy free-window.

The donor's risks and burdens must be perceived as the complex assortment of potential physical (fatal risk), social and psychological outcomes (non-fatal risk) (39). More precisely, the main donor's risks include the general risks associated with the organ procurement surgery and physical consequences related to loss of a part of the liver. Furthermore, psychological and emotional risks related to the recovery and aftermath of surgery as well as the effects on the relationship between donor, recipient and others should be also considered (31,40-42).

The medical risk for the donor includes the general surgical risk and additionally the risk of hepatectomy. The latter increases proportionally with the mass of the tissue removed. Altogether these risks do occur in less than 2% of procedures (31,43-45). The mortality risk for the donor is usually very low and decreased significantly with increasing experience. According to the latest reports, the total risk is 0.1% for the left-lateral segments and 0.5% for right hepatectomy (43,46,47). Psychological problems have been described before and after living donation. Pre-donation burdens can arise from the care of the organ recipient especially with very close emotional ties and with acutely life-threatening disease. After donation, different psychosomatic disorders have been reported (48-57).

Therefore, in the ethical considerations, it is important not only to include mortality and morbidity, but also quality of life, psychological and social considerations related to the two parties (20,58). In this regard, Pomfret *et al.* described a similar critical scenario of a hypothetical case of LDLT for recipients with Hepatocellular carcinoma (HCC) beyond the standard inclusion criteria (58). Although the risk of HCC recurrence was 100% and the procedure had a clear palliative intent, the authors demonstrated that weighing the risk to the donor against the benefit to the recipient (including psychosocial benefits for the recipient and the family members) moved the case from ethically questionable to ethically acceptable provided that both donor and recipient are adequately informed about the long term of results in terms of OS and DFS.

Similarly, in context of LDLT for uCRLM, one should consider the social and psychological benefits for families even if there is a high chance of recurrence of disease (8) and consequently also respect the donor's autonomy to perform a living donation to a beloved one in the knowledge that it might not be a curative therapy at all.

One additional major point of debate is, if it is ethically correct to offer the possibility of a re-transplantation with a DDLT to a patient with early graft failure after LDLT for extended oncological indications. Clavien *et al.* reported about the international consensus conference on LT for HCC and concluded that "based on utility, justice, and equity, they did not support re-transplantation for patients

Table 3 Reported cases of LDLT for uCRLM (published and through personal communication)

Center	n	Graft type (right *vs.* left *vs.* left-lateral)	RAPID-Concept Y/N
Ankara, Turkey*	n=1	Right (n=1)	N
Bologna, Italy (63)	n=2	Left-Lateral (n=1)	Y (n=1)
		Left (n=1)	N (n=1)
Brussels, Belgium (64,65)	n=3	Left-Lateral (n=1)	Y (n=1)
		Left (n=2)	N (n=2)
Cleveland, U.S.*	n=2	Right (n=2)	N (n=2)
Jena, Germany (66)	n=6	Left-Lateral (n=6)	Y (n=6)
Les Compagnons Hepatobiliares (12)	n=1	Not reported	N (n=1)
Padua, Italy*	n=1	Left (n=1)	Y (n=1)
Rio de Janeiro, Brazil (67)	n=1	Right (n=1)	N
Rochester, U.S.*	n=3	Right (n=3)	N
Toronto, Canada*	n=2	Right (n=2)	N
Tübingen, Germany (68)	n=2	Left-Lateral (n=1)	Y (n=1)
		Left (n=1)	N (n=1)
Zagreb, Croatia (69)	n=1	Right (n=1)	N
TOTAL	25	Right = 10; Left = 5; Left-Lateral = 9	RAPID: n=10

*, reported by personal communication.

who were beyond the standard eligibility criteria, because these patients would not have qualified for DDLT in the first place" (36). One could argue that using a deceased organ from the common pool to transplant a patient who was determined to be ineligible for that organ would be unjust. In fact, it would deny the transplant to another patient who, having been placed on the waiting list based on standard diagnosis for LT, would derive a great benefit and long term survival from that liver. Therefore, despite the emotional burden of withholding the opportunity for re-transplantation following organ failure, transplant teams should not offer a deceased organ to a living donor recipient with acute graft failure given the injustice to others on the transplant list (31). It becomes then essential to obtain an adequate informed consent focused on risk, benefits and outcome benefits for both donor and recipient (59,60). In any living donor situation, the harms and burdens to the donor are justified by the significant benefit to the recipient. This means that the organ donor needs to have a robust understanding of the risks and burdens involved and the capacity to consider them in the context of the values and priorities that the donor finds most salient (31,61,62).

At the moment, the worldwide experience with LDLT for uCRLM is very limited to 25 cases (*Table 3*) (67,69).

The Toronto group recently started a clinical trial with standard LDLT (usually right grafts) for patients with uCRLM and who have shown no disease progression on standard chemotherapy. The study aims at evaluating the 5-year outcomes in terms of OS, DFS and quality of life after CTx and LDLT (NCT02864485). At the moment two patients have been included in the study (personal communication). Few additional standard LDLT have been performed worldwide (*Table 3*).

Recently Königsrainer *et al.* introduced the concept of LD-RAPID aimed to further reduce the medical risks taken by the donor (3,30,68). Principally it consists in the same RAPID technique described originally by Line *et al.* (24) with the main difference that the source of left lateral graft is represented by a living donor (24,30).

At the moment seven LD-RAPID procedures have been performed within the Liver-Two-heal study (30,66). Other similar procedures have been performed outside of clinical trials (Brussels, Padua, Bologna) and minimal changes of the original technique have been proposed [e.g.,

laparoscopic donor hepatectomy in Padua, laparoscopic removal of remnant right liver lobe in Brussels (64,65) or even heterotopic graft implantation in the splenic fossa by the group in Bologna (63,70)].

The LD-RAPID procedure is technically very demanding. From pure technical/surgical point of view, the key of success of this technique is based on the possibility to use a very small graft in absence of portal hyperflow and portal hypertension. It may represent a valid alternative in terms of safety and efficacy only when applied in selected patients and performed by very experienced hepato-biliary-pancreatic (performing ALPPS procedures) and LT centers with both experience in DDLT and LDLT including pediatric LT.

Following criticisms have been raised regarding the LD-RAPID procedure:

(I) It has been argued that leaving the right lobe with the liver metastases in loco until the left graft is regenerated and under immunosuppressive therapy may influence the oncological outcome of these patients. Line *et al.* recently showed that this hypothesis may not be true since CRLM grow at a similar rate in the immunosuppressed patients compared to immunocompetent patients (13,71).

(II) Although there is lack of strong data to support one approach over the other, the question arises whether it would be more beneficial and safer to perform a high demanding technique like LD-RAPID, that similarly to an ALPPS procedure can also be associated to a complicated postoperative course, or instead favor a straight forward left liver lobe LD, avoiding the second stage hepatectomy that might be more prone to complications.

A last topic of debate is the question if LDLT should also be offered to patients with resectable CRLM who usually undergo complex liver resections (e.g., Two-stage hepatectomy, ALPPS) without a true benefit (i.e., high complications rates and early intrahepatic tumor recurrence >70% within 1 year with a mean OS of 30 months and 5-year OS <40%) (72). Considering that, the pattern of recurrence after LT for uCRLM is 68–75% in the lung and 38% of them are resectable. Consequently, it would make sense to go for LDLT for these "extremely" resectable patients with definitively better long term results (13).

In conclusion, LT for uCRLM seems to be a promising tool and to offer excellent OS rates notwithstanding high recurrence rates. DDLT is an option in very few countries, because of organ scarcity and competition with standard indications, and should anyhow be still performed within a research protocol. In selected cases and with the proper donor and recipient preparation and approach LDLT (standard or LD-RAPID) may represent a valid alternative as long as the donor risks are kept to a minimum and the indications in the recipient are tightly set to allow for maximal benefit. Last but not least LDLT may be also considered as a good alternative to extremely aggressively marginally resectable CRLM.

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