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Review

# LIVING DONOR LIVER DONATION IN THE ONCOLOGICAL FIELD: WHAT'S NEW

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**Summary**

Liver transplantation is emerging as a promising strategy to treat several malignancies, in selected patients.

However, expanding the indication for LT to oncologic indication exacerbates the persisting shortage of grafts. Living donor liver transplantation (LDLT) appears as a useful solution to enlarge the donor pool to meet this need. This review aims to comprehensively explore the current indications for LDLT in the context of hepatic malignancies, emphasizing reported outcomes and presenting future perspectives. A particular attention will be devoted to ethical considerations. The review will focus on the role of LDLT for hepatocellular carcinoma (HCC), for intrahepatic and perihilar cholangiocarcinoma (iCCA and pCCA), and for colo-rectal liver metastases (CRLM). Lastly, we will present new techniques of living transplantation using small left lateral grafts, namely RAPID Resection And Partial Liver segment II-III transplantation with Delayed total hepatectomy) and dual-graft transplantation (DG-LDLT).

**Key words**: liver transplant, living donors, liver tumours

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Liver transplantation is emerging as a promising strategy to treat several malignancies, in selected patients [1,2].
However, expanding the indication for LT to oncologic indication exacerbates the persisting shortage of grafts. Living donor liver transplantation (LDLT) appears as a useful solution to enlarge the donor pool to meet this need. This review aims to comprehensively explore the current indications for LDLT in the context of hepatic malignancies, emphasizing reported outcomes and presenting future perspectives. A particular attention will be devoted to ethical considerations. The review will focus on the role of LDLT for hepatocellular carcinoma (HCC), for intrahepatic and perihilar cholangiocarcinoma (iCCA and pCCA), and for colo-rectal liver metastases (CRLM). Lastly, we will present new techniques of living transplantation using small left lateral grafts, namely RAPID Resection And Partial Liver segment II-III transplantation with Delayed total hepatectomy) and dual-graft transplantation (DG-LDLT).

## LDLT FOR HCC

Liver transplantation (LT) offers excellent long-term outcome and has been widely accepted as the most effective treatment for selected patients with hepatocellular carcinoma (HCC). LT radically treats the tumor while concurrently addressing the underlying liver disease and decreasing the risk of de novo tumors.

HCC is becoming one of the leading indications for LT worldwide [3]. However, access to LT is limited by the shortage of available organs in many settings, leading to potentially long waitlist times, risk of disease progression and waitlist dropout [4].

Organ allocation differences reflect geographical disparities in terms of organ availability and donation patterns. In Asian countries living donor liver transplantation (LDLT) accounts for most cases (90%) of LT for HCC, due to the serious shortages of deceased donors and high incidence of cirrhosis, mainly for viral infection [5]. In Western countries most LT are deceased donors liver transplantations (DDLT). However, in several settings, current deceased donation rates fail to meet the demands for LT, with an estimated 20-25% waitlist mortality over the past decades. Nonetheless, LDLT only accounts for only 4.5% of total LT performed in the United States and 15.6% of transplants in Canada in 2019. Aggregated data from multiple national LT registries spanning 2010-2014 revealed similar trends across Europe, ranging from less than 1% of total LTs in French transplant centers to approximately 8% in Germany [6].

Patients with access to LDLT experience reduced or even absent waiting times, resulting in a lower dropout risk, and do not add any competitive harm to the list of patients who are waiting for a DDLT.

Initial experiences reported higher rates of HCC recurrence among LDLT recipients compared to DDLT. A 2012 North American multicenter study showed 38% recurrence rate in LDLTs against 11% among DDLTs (p 0.0004; HR 2.35), mainly related to differences in tumor characteristics and pre-transplant management [7]. A 2013 meta-analysis [8] (comprising 633 LDLTs and 1232 DDLTs) showed an increased risk for HCC recurrence following LDLT with a 1.59 hazard ratio (95% CI, 1.02-2.49).

Proposed explanations for these findings included the expedited evaluation process (fast-track approach), which may limit a thorough assessment of tumor biological characteristics, the parenchymal regeneration of the partial graft, possibly promoting tumor growth and dissemination, and the potential persistence of residual tumor due to inferior vena cava preservation [9].

However, recent studies involving more homogeneous LDLT and DDLT populations from Eastern and Western experiences have shown similar, or even better, results after an LDLT. In 2019, the group from Toronto [10], comparing 219 LDLTs with 632 DDLTs, reported a substantial reduction of the risk of death in HCC patients in an intention-to-treat analysis (HR, 0.67; 95% CI, 0.53-0.86) for those with potential live donors at listing. This was attributed to shorter waiting periods (4.8 *vs* 6.2 months, p = 0.02) and lower dropout rates (14.6% *vs* 27.5%, p < 0.001). The reported 1-, 3- and 5-year intention-to-treat survival rates were 86%, 72% and 68% in the LDLT *vs* 82%, 63% and 57% in the DDLT group (p = 0.02). A multicenter analysis [11] of North-American experiences with 360 LDLT for HCC between 1999 and 2019 noted that, despite its limited diffusion, LDLT yielded equivalent post-transplant outcomes as DDLT. Patients within Milan criteria (MC) had a 1-,5-, and 10-year post-transplant survival rate of 90.9, 78.5, and 64.1%, while the survival of patients outside Milan criteria was 90.4, 68.6, and 57.7% (p = 0.20), rsepectively. For patients within the UCSF criteria, respective post-transplant survival rates were 90.6, 77.8, and 65.0%, while that of patients outside UCSF were 92.1, 63.8, and 45.8% (p = 0.08). Notably, patients who exceeded both the MC and UCSF achieved 5-year post-LDLT survival (68.6 and 63.8%, respectively) that exceeded the minimum recommended threshold of 60%, as proposed by recent expert consensus for LDLT in HCC [12].

A meta-analysis [13] involving more than 5000 patients revealed that LDLT was associated with better 5-year intention-to-treat patient survival rates (relative risk, 1.11; 95% CI, 1.01-1.22; p = 0.04), with similar 5-year recurrence rates (relative risk, 0.85; 95% CI, 0.56-1.31; p = 0.47).

A multicenter cohort study [14] with an intention-to-treat design analyzed the survival benefit among a large international population comprising centers in Europe, Asia, and North America. This study encompassed nearly 4000 patients treated with LDLT for HCC from 2000 to 2017. LDLT emerged as an independent protective factor, reducing the intention-to-treat risk of overall mortality in patients with HCC who were on a waiting list for a liver transplant by 33 to 49% (HR, 0.51; 95% CI, 0.36-0.71; p < .001). Moreover, LDLT did not entail an increased risk of HCC recurrence, even when some centers employed more liberal criteria regarding tumor burden in cases of live donor availability.

Regarding donor risk, a global survey [15] involving 11.553 liver donors reported a mortality rate of 0.2%, a transplant rate of 0.04% due to donor liver liver failure, and an overall donor morbidity of 24%. An overall donor complication rate below 27%, with less than 6% Clavien-Dindo grade 3/4 complications, has been deemed acceptable in a benchmark study, although improved outcomes remain desirable.

The expansion of the donor pool through LDLT may reduce the risk of waitlist mortality and broadened patient eligibility for LT, transcending the limitations of a MELD-dependent graft allocation system. Moreover, the elective nature of LDLT offers a timing advantage, enabling patients to undergo surgery after preoperative medical optimization but prior to becoming critically ill from liver failure.

Live donor grafts are not a public resource, and their use does not impact the standing waiting list for DDLT recipients. Therefore, the risk of HCC recurrence, recipient survival prospects, and the wishes of the donor can be singularly taken into account, without compromising the essential double equipoise in LDLT, which aims to ensure both acceptable recipient outcomes and donor safety. Owing to the inherent risk of donor morbidity and mortality careful consideration must be exercised when extending the criteria for LT to patients with HCC, even in the context of LDLT. There is a

need for a concerted effort to develop predictive models that incorporate tumor biology into selection criteria, combining tumor burden, biomarkers, molecular, or radiological criteria [5,12,16]. HCC patients may benefit from LDLT, especially in areas where DDLT rates are low. The transplant benefit [17] concept, blended with that of dual equipoise [16] must serve as a pivotal framework for decision making in LDLT.

## LDLT FOR CCA

### Perihilar cholangiocarcinoma (pCCA)

Perihilar Cholangiocarcinoma (pCCA) is a rare tumor of the liver, associated with dismal prognosis even for patients amenable to surgery, with a five-year survival around 40% and a median 45 months survival after radical resection [18]. For unresectable cases, the combination of gemcitabine and cisplatin yields a median overall survival of 11.7 months [19].
Liver transplantation (LT) allows complete excision of the tumor, reducing the risk of positive margins or residual disease. At the same time it substitutes the liver, which might be damaged by aggressive preoperative treatments or may be affected by cancerogenic factors, such as primary sclerosing cholangitis (PSC).
The Mayo Clinic proposed a protocol [20] for LT for unresectable pCCA, with strict inclusion and exclusion criteria and an extensive preoperative chemo and radiotherapy treatment, achieving excellent results. The latest report from this group on 211 patients treated with LT for pCCA reported 1, 5, and 10 years survival rates after LT of 91, 69, and 62% respectively. A significantly better outcome was observed in patients with PSC-associated pCCA compared to de novo pCCA, with reported 1, 5 and 10 years survival rates of 92, 76, and 70% in the PSC group and 90, 58, and 49% in the de novo group [21].
LT for pCCA is now performed in several transplant centers in the setting of scientific trials with rigorous criteria and neoadjuvant regimens. Living donor liver transplantation (LDLT) has been utilized for patients with pCCA to avoid prolonged waiting time for a deceased donor liver.
A retrospective analysis [22] by the group of the Mayo Clinic compared 73 cases of LDLT for pCCA with 173 LDLT performed for other indications between 2000 and 2017. Forty-nine (66.2%) patients had PSC-associated-pCCA; the remainder had de novo-pCCA. The pCCA group had higher need of arterial or portal vein reconstruction, and Roux-en-Y choledocho-jejunostomy. The incidence of early hepatic artery thrombosis was similar in the two groups (5.4 *vs* 7.6%, $p = 0.54$). Late arterial (18.9 *vs* 4.1%, $p < 0.001$) and portal (37.8 *vs* 8.7%, $p < 0.001$) complications were more common in pCCA group, but did not affect long-term survival. Anastomotic biliary complications were less common in the pCCA group (39.2 *vs* 54.1%, $p = 0.032$). The five-year OS among patients with pCCA was 66.5% (75.9% in PSC and 47.5% in de novo pCCA), with an incidence of tumor recurrence of 12.3%. Therefore, LDLT stands as a viable alternative to deceased donor liver transplantation (DDLT) for pCCA within the confines of stringent study protocols. Nonetheless, the elevated incidence of vascular complications associated with neoadjuvant radiation poses a particular challenge in the context of LDLT.

### Intrahepatic cholangiocarcinoma (iCCA)

Liver resection is the first treatment option for iCCA, but liver transplantation has been proposed as a viable alternative, and its role is actually under scrutiny [2].
A meta-analysis by Ziogas et al. [23] reported 1-, 3- and 5-year survival of 75, 56 and 42 after LT for iCCA, with a variable recurrence rate depending on tumor size: very early iCCA (< 2 cm) had a recurrence rate of 15%, whereas the recurrence rate of advanced iCCA was 51%. The benefit of LT for patients with early stages of iCCA was confirmed in an international collaborative study [24]. Among 48 patients with iCCA, the 5-year cumulative risk of recurrence was 18% for those with very early iCCA and 61% for those with more advanced disease ($p = 0.01$). The 5-year OS rate among the very early iCCA and advanced iCCA was 65 and 45%, respectively ($p = 0.02$).
The role of LDLT in liver transplantation for iCCA has not been specifically studied, but among reported case series, the proportion of LDLTs ranges from 6 to 16% [25].

## LDLT FOR CRLM

Colorectal cancer is a leading cause of cancer-related death worldwide, and more than half of patients develop liver metastases (CRLM) [26]. The combination of surgery and systemic chemotherapy can offer a chance of cure with a 5-year survival rate of 50%. However, only 15% to 20% of patients are suitable for upfront resection owing to multiple bilobar tumors and insufficient future liver remnant. On the other hand, in patients with unresectable CRLM on palliative chemotherapy the median OS decreases to 5–10% [27,28]. Aggressive surgical approaches, hypertrophy-inducing procedures and locoregional and systemic therapies for downstaging disease, have expanded the definition of resectable liver-only CRLM and improved outcome [29].
Despite historically dismal survival rates (12-20% 5 years OS) [30] and high recurrence rates, total hepatectomy and liver transplantation is emerging as a viable strategy for unresectable liver-only CRLM. This follows the reports of Norwegian SECA-1 and SECA-2 prospective studies, applying stringent selection criteria and effective chemotherapy regimens, which demonstrated 5-year OS rates of 60 and 83%, respectively, albeit with 95 and 65% 5-year recurrence rate [31,32]. A comparative study between liver transplantation (LT) and liver resection (LR) for CRLM

with a high tumor load (tumor burden score ⩾ 9) and low Oslo score (⩽ 2) revealed significantly superior 5-year OS (69% LT *vs* 15% LR, p = 0.002) and disease-free survival (23% LT *vs* 0% LR, p = 0.005) for the LT group [33].

However, the scarcity of deceased-donor allografts mandates caution in expanding eligibility criteria for DDLT [34]. Living-donor LT provides an alternative without further burdening the organ-scarce liver waiting list. In addition, LDLT is open to a more flexible planification, allowing time to discontinue systemic or locoregional therapies before transplantation and scheduling elective surgery by taking into the account the potentially short therapeutic window [35]. Nevertheless, LDLT must be judiciously employed, balancing the potential benefits for the recipient against the risks of donor morbidity and mortality, by selecting patients who are most likely to have long-term benefit. Until more efficient clinical and molecular biomarkers emerge, surrogates for disease biology, such as the Oslo Score, the Clinical Risk Score, and sustained clinical response to systemic therapy, remain pivotal filters for selecting patients with adequate prospects for long-term cancer control, thereby justifying the risk to a living donor [36,37].

A prospective study [38] by three North American transplant centers, reported results of 10 LDLT performed between December 2017 and May 2021. Patients were affected by unresectable CRLM with low Oslo Scores and Clinical Risk Scores and demonstrated sustained response to systemic and local therapies, suggestive of favorable tumor biology. Patients had received extensive oncologic treatments before transplantation, including liver resection, hepatic artery infusion chemotherapy, and tumor ablation. For these 10 LDLTs, eight right lobe grafts and two left lobe grafts were directly implanted. Recurrence-free and overall survival at 1.5 years after LDLT were 62% and 100%, respectively.

The Toronto group published [39] a compelling study involving 81 patients referred to their center for LDLT for unresectable bilobar CRLM between 2016 and 2023. After uniform re-assessment of resectability, they divided the patients in three groups: transplanted with LDLT (7), resected (22), and control on systemic chemotherapy (48). No significant difference in overall survival was observed between the transplanted and resected populations (1-year 100 *vs* 93.8%; 3-year 100 *vs* 43.3%, p = 0.17). However, recurrence-free survival was markedly superior in the LDLT group (1-year 85.7 *vs* 11.4; 3-year 68.6 *vs* 11.4%, p = 0.012). The control group of patients not meeting criteria for LDLT nor resection, had the worst outcome with a 3-year survival of 16%.

A recent retrospective study [40] from the University of Pittsburgh reported 10 LDLTs for CRLM, performed between 2019 and 2022. All patients underwent pre-transplant chemotherapy and some were subjected to surgical resection (60%), hepatic-artery infusion pumping (50%), and/or radiofrequency ablation (50%). Mean overall survival was 3 years, recurrence-free survival was 2.2 years and 30% of patients suffered a recurrence. Interestingly, this study includes both patients referred for oncologic indication and patients referred for severe liver dysfunction or biliary complications secondary to oncologic treatment, as confirmed by models for end-stage liver disease scores as high as 32, in addition to pathology reports demonstrating cirrhosis or fibrosis [35].

## LEFT-LATERAL SECTION (LLS) GRAFTS LDLT: RAPID AND DUAL-GRAFT

Living donor liver transplantation widespread utilization is limited by the fear of exposing donors to excessive risk, especially in case of right lobe donation. In contrast, donor risk can be significantly lowered if a small left lateral section (LLS) is selected, with low risk of post-operative liver insufficiency and significantly better donor tolerance compared to a right hepatectomy [41]. However, using such small grafts (< 1% of the recipient's body weight) may lead to small-for-size syndrome (SFS) and recipient death [42]. To overcome such obstacles, several groups have devised techniques to induce graft's hypertrophy in the setting of a two-stage transplantation (RAPID) or chose to simultaneously transplant two LLS grafts (dual-graft).

### RAPID

The Oslo group described a novel technique of two-stage liver transplantation named RAPID [43] (Resection And Partial Liver segment II-III transplantation with Delayed total hepatectomy), combining the concept of auxiliary partial orthotopic liver transplantation (APOLT) with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). A left lateral graft from living or deceased donors is implanted orthotopically after a left hepatectomy of the native liver; portal flow is diverted to the implanted graft, to stimulate fast regeneration, and once optimal volume is achieved, native liver hepatectomy is completed as in ALPPS.

The Norwegian group proposed RAPID for patients with nonresectable CRLM using LLS splits from deceased donors [43]. Subsequently, the Tubingen group suggested extending this technique to left-lateral live donor donation (LD-RAPID) [44]. Their first case was a 49 years old woman with unresectable CRLM. After a left hepatectomy and right portal vein ligation she received a left-lateral lobe transplantation. Completion hepatectomy was performed two weeks later. The donor postoperative course was uneventful, while the recipient developed a slight post-operative small for size syndrome and, five months after surgery showed evidence of micrometastases in bones and lungs.

A French group [45] reported two RAPID procedures for patients affected by HCC on liver cirrhosis. Both patients underwent a left-lateral resection without banding of the

right portal vein, and subsequent auxiliary transplantation using laparoscopically procured LLS grafts. Grafts growth was effective (112% in 1 week), but only one patient proceeded to completion hepatectomy, as the second developed biliary stenosis and received a standard liver transplantation a year later.

A recent retrospective multicentric study46 reported 23 noncirrhotic patients treated with RAPID between 2015 and 2022 in 6 European centers (20 with grafts from living donors and 3 after deceased donation). The main indication was unresectable CRLM, in one case was unresectable liver metastases of neuroendocrine tumor and in another case was -catenin–mutated unresectable liver adenomatosis. This study demonstrated positive early outcomes, with no donor mortality, low donor morbidity (4.3%), and acceptable recipient morbidity (43% ⩾ IIIb Clavien-Dindo) and mortality (4.3%) rates. Graft hypertrophy was rapid, with a mean volume increase of 107% and a median interstage time of 14 days. One year OS was 90% while recurrence-free survival was 66,7%, with a median follow up of 696 days.

The LD-RAPID has several advantages, for both donors and recipients. LLS donation minimizes donor morbidity through a minor resection [41]. The risk of liver failure is extremely unlikely and the procedure can be performed with a laparoscopic approach, with consequent faster recovery. Furthermore, the use of LLS, regardless of graft volume, broadens the pool of potential living donors, including those excluded for insufficient volume or anatomical anomalies [47].

On the recipient's side, the native right liver functions as a metabolic backup, aiding the initially small functional graft during its regenerative period. In the event of a graft failure, this prevents acute liver insufficiency and the need for a second emergency liver transplantation [45].

The primary concerns involve the technical complexity and the interplay during the interstage period between the tumor-affected right residual liver and the regenerating LLS graft. Similar to the ALPPS setting, minimizing the time interval between both steps can mitigate the risk of interstage tumor progression, although further studies are imperative due to the unique context of immunosuppression.

The low living donor risk associated with left lateral donation, coupled with the absence of harm on the waiting list, maximize the overall transplant benefit of RAPID and exemplifies optimal ethical equipoise in transplantation [46]. On one hand this technique can address chronic graft scarcity for accepted indications, such as cirrhotic patients with HCC and low MELD score, at risk for tumor progression while on the waiting list. On the other hand, it may allow the expansion to other non- established transplantation indications like CRLM. However, unresolved issues, including technical complexities and oncologic implications of leaving metastatic disease in an immunocompromised patient, necessitate further exploration.

## Dual graft LDLT

An alternative strategy for using small grafts in an adult to adult LDLT without risking small for size syndrome, is simultaneously transplanting two grafts obtained from two living donors, the so-called dual-graft (DG) LDLT [48].

The initial concept centered on utilizing two LLS grafts to minimize the risk to each donor and provide sufficient graft volume to the recipient, but in the last decade several graft combinations have been experimented. When using two LLS grafts, one is transplanted ortothopically, while the other must be positioned heterotopically in the right-upper quadrant, after being rotated 180° on a sagittal plane, to adjust the location of vascular structures. In some cases, a right graft and left graft from two donors have been procured and transplanted orthotopically in a single recipient, with a consequently easier implantation process.

The largest case series was published in 2017 by the group of the Asan Medical Center in Korea [49]. They reported 3887 LDLTs performed between 2000 and 2014, with 400 (11.7%) being dual graft (DG) LDLTs. Notably, donors in the DG group had higher age, body mass index, and steatosis, reflecting the fact that those donors would have probably been refuted for single-graft LDLT. In the DG group, mean operative time was longer (18.7 *vs* 13.9 hours; $p < 0.001$) and need for blood transfusion was higher (18.2 *vs* 11.4 units; $p < 0.001$). The surgical complication rate was significantly higher in the DG group (53.7 *vs* 28.5%; $p < 0.001$), as well as the in-hospital mortality rate (7.0 *vs* 4.0%). Overall donor morbidity rate was very low (1.7%), primarily consisting of Clavien I or II complications.

Patient survival rates at 1, 5, and 10 years for DG LDLT were 89.2, 85.5, and 80.2%, respectively. In a propensity-matched cohort, no significant differences in survival outcomes were observed between DG and single-graft LDLT. The principal impediment to widespread adoption of DG LDLT is its technical complexity, manifested in significantly prolonged operative and ischemic times. Given the doubling of vascular and biliary anastomoses, the inherent rise in surgical complication rates in DG LDLT is evident. The technical complexity of this procedure is further compounded by geometrical and positional challenges associated with implanting two grafts.

Using two grafts, putting at risk two healthy donors to save a single life, furtherly challenges the ethical dilemma of live donation. However, doubling the donors at risk is counterbalanced by a lower individual risk, and both risks must be weighted against the transplant benefit of the recipient. The equilibrium may be more favorable when the likelihood of receiving a deceased donor graft is low because of the scarcity of organs (particularly in Asian countries) or when dealing with non-established indications (such as CRLM), but the expected transplant benefit is high.

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*Ethical consideration*

The present work is a review of the literature and does not involve patients' data. Ethical evaluation is not required.

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