

Expanding Donor Selection and Recipient Indications for Living Donor Liver Transplantation



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KEYWORDS

• Living donor • Liver transplant • Extended criteria • Transplant oncology

KEY POINTS

- Living donor liver transplantation (LDLT) can play a significant role in increasing the national donor pool.
- Donor selection criteria are being expanded with the help of surgical innovation, increasing technical expertise, and novel outcomes data.
- Donor organ pool expansion requires a structured and robust initiative promoting public awareness and education.
- The growth of LDLT programs nationally will help meet the organ demand created by expansion of recipient indications (eg, HCC outside of Milan, cholangiocarcinoma, metastatic colorectal cancer).

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INTRODUCTION

Each year in the United States, only about 8000 of the 14,000 patients awaiting transplantation receive a liver transplant.¹ Nearly 25% of patients die while awaiting liver transplantation and another 10% get delisted² because of disease progression. A significant shortage of deceased donor organs is the prime reason for waitlisted patients not receiving a transplant. The shortfall between the number of patients listed for liver transplantation and the available grafts can potentially be addressed by living donor liver transplantation (LDLT). LDLT is an effective and safe method that increases the donor pool, improves the likelihood of timely transplants, and extends the survival of patients. Despite the proven benefits of LDLT,³ uptake in the United States has been slow,⁴ and widespread implementation of LDLT has been limited, because of concerns about donor risk. In addition, there is a perception that healthy individuals will not be willing to donate and therefore many programs are challenged with identifying and enrolling living donors.

However, some programs in the United States and globally have successfully adopted LDLT.^{3,4} Growth in LDLT volume has led to an increase in LDLT surgical expertise, which in turn has paved the path for technical innovation in LDLT at these centers.⁴ Success, in the form of decreased transplant list waiting time and waitlist mortality, has prompted expansion of recipient indications for LDLT. Now, traditional donor selection criteria are also being challenged and expanded, while trying to balance donor safety with recipient and graft survival.

In this article, we present the current knowledge of donor selection criteria and recipient indications for LDLT, and describe the recent advances made on these fronts. We also present a comprehensive patient support program that may serve as a model for programs trying to expand LDLT, by supporting recipients in identifying their own donor.

EXPANDING DONOR SELECTION CRITERIA

Donor Body Mass Index and Hepatic Graft Steatosis

With the rising prevalence of obesity, increasing body mass index (BMI) of potential donors has become a real obstacle to LDLT. A higher BMI frequently, but not always, correlates with hepatic steatosis. In a 2001 study with 33 potential live donors, no donor with a BMI less than 25 had histologic evidence of hepatic steatosis, but 76% of the donors with a BMI greater than 28 had steatosis on liver biopsy.⁵ At some transplant centers, potential donors who are obese (BMI >30), or those who have hepatic steatosis on imaging, might undergo a liver biopsy as part of the donor evaluation. Donors with BMI greater than 35 are frequently excluded at the outset. Potential donors with macrovesicular steatosis of greater than 10% on biopsy are also excluded, whereas microvesicular steatosis is less of a concern.^{6,7}

The reason for this practice is the body of literature that has demonstrated that moderate to severe steatosis in the graft can lead to primary nonfunction, reduced graft survival, ischemia-reperfusion injury, and biliary strictures.^{8,9} However, a more recent systematic review of 3226 recipients demonstrated that even though short-term outcomes were unfavorable, longer-term outcomes, such as 1-year mortality, were similar to control subjects without moderate-severe hepatic steatosis.¹⁰ Another recent study in recipients of right-lobe grafts showed that after matching for age, Model for End-Stage Liver Disease (MELD), and graft recipient weight ratio (GRWR), the short-term outcomes of graft function, postoperative morbidity, hospital stay, and 30-day mortality were similar for grafts with less than 10% steatosis and grafts with 10% to 20% steatosis.¹¹

Knaak and colleagues¹² from Toronto, asked the important question of whether donor obesity without hepatic steatosis has an independent impact on transplant outcomes. They found that right-lobe donation from donors with a BMI greater than or equal to 30 but with hepatic steatosis of less than 10% and no other comorbidity had similar donor and recipient outcomes including recipient graft function, surgical complications, and hospital stay.¹² Overall, it has become clear that there is a complex interplay of multiple donor and recipient factors in the decision to use a graft from an obese donor. Even so, the key factors that are pushing the boundaries of donor BMI are the growing surgical expertise in LDLT and the rapidly advancing science of medical management of LDLT donors and recipients.

Donor Age

Donor age is a well-known prognosticator of outcomes in liver transplantation. The impact of donor age on recipient survival in adult-to-adult LDLT has been studied. In a study by Kubota and colleagues,¹³ donors from age 20 to 67 years were studied. Donor age was divided into five groups: 20s, 30s, 40s, 50s, and 60s. Not surprisingly, this study demonstrated that recipient survival is the best with the youngest group of donors (20s). However, what this study does not answer one might argue is the more critical question: Does recipient survival differ between those with a donor in their 50s versus 60s? In extrapolating from this study, at 1 year, 67 of 94 (71%) recipients were alive when they received a graft from a donor in their 50s, whereas 25 of 32 (78%) recipients were alive at 1 year when they received a graft from a donor in their 60s.¹³ The clinical significance of these numbers is unclear but suggest that pushing the age limits for donor may be one safe way to increase the donor pool.

Although most of the focus has largely been on the appropriateness of older recipients, some have pushed the envelope in terms of accepting younger donors. The hesitation in accepting younger donors for centers focuses on the concern that the young donors (age <18) lack a deep understanding of the possible complications that may arise and their long-term implications. Nonetheless, a standard age cutoff might be deemed somewhat arbitrary because maturity is starkly different in two persons of the same age. Teenagers are allowed to drive at the age of 16, knowing that there is a significant risk of fatal car crashes in this group, nearly 1.5 times higher than in those just 2 years older.¹⁴ The University of Toronto has tested this idea after getting to know a 16-year-old son and allowing him to donate to his mother at the age of 17; and now has the policy that persons older than the age of 16 can be evaluated as donors.¹⁵

Although we acknowledge the importance of center guidelines for age limits, we believe that each potential donor deserves individual consideration. The level of maturity of young donors should be rigorously assessed by members of the multidisciplinary transplant team before arriving at a consensus. In addition, when considering older donors, protocols need to be developed for performing a sound physiologic assessment rather than simply a chronologic one. The age limits for LDLT require continued exploration as ways to increase the donor pool are examined.

Graft Recipient Weight Ratio

Compared with the full-size grafts of deceased donors, the smaller volume of single-lobe grafts from live donors has frequently garnered concern regarding outcomes, especially during LDLT in sicker recipients. A GRWR of at least 0.8 has been generally considered a prerequisite for right lobe LDLT, based on initial LDLT literature from Asia. Several transplant centers still use this cutoff, even though subsequent research has shown good outcomes with smaller grafts.¹⁶ A 2009 study from Toronto

compared outcomes in LDLT recipients with a GRWR of 0.59 to 0.79, LDLT recipients with a GRWR of greater than or equal to 0.8, and deceased donor liver transplant recipients with full-sized grafts. The study demonstrated similar patient outcomes of reperfusion injury (peak aspartate aminotransferase and alanine aminotransferase), graft function, complications, and graft and patient survival across all three groups. This study challenged the safe lower limit of GRWR for LDLT.¹⁶ A more recent study investigated the use of absolute graft weight rather than a GRWR of 0.8. The study found that a cutoff value of 643 g for the right lobe provided the highest positive predictive value (94%) for a good outcome in recipients with GRWR less than 0.8; with 15 (19.4%) deaths in the group with absolute graft weight less than 643 g and only 5 (7.1%) deaths in the group with absolute graft weight greater than or equal to 643 g.¹⁷

Wong and colleagues¹⁸ published a study in 2020 that concluded that the incidence of small-for-size-syndrome (SFSS; defined as GRWR <0.8) could be kept low even with a GRWR of 0.6, if meticulous care was taken with recipient selection, surgical technique including the use of portal flow modulation, and perioperative management. Their findings were in agreement with a meta-analysis of 1821 LDLT recipients that showed inferior medium-term (3-year) but comparable long-term (5-year) graft survival with SFSS, with the use of appropriate flow modulatory measures,¹⁹ once again highlighting the importance of scrupulous surgical protocols for improving patient outcomes.

ABO Incompatibility

ABO incompatibility is usually thought of as a relative contraindication to transplantation because of a fear of humoral or antibody-mediated rejection. The susceptibility to rejection is thought to be driven by antigens expressed on the vascular endothelium and bile ducts driving hyperacute rejection and biliary complications.^{20,21} Although the early outcomes for ABO-incompatible (ABOi) transplant were poor,^{22,23} ABOi liver transplantation was not abandoned.²⁴ The need to expand the donor pool, particularly in Asian centers, drove the improvement of clinical protocols.^{24,25}

To overcome the initial poor outcomes in ABOi transplants, high-dose immunosuppression, splenectomy, and plasmapheresis were instituted with little change in the initial outcomes.^{26,27} With the addition of rituximab to the surgical conditioning regimen, the outcomes of ABOi LDLT have shown similar survival rates to ABO-compatible LDLT.²⁸ In a study by Egawa and colleagues,²⁸ 381 ABOi LDLT in the pre-rituximab and postrituximab era were studied and an increase in 3-year survival from 30% to 80% from the pre-rituximab era and the postrituximab era. A meta-analysis by Yadav and colleagues²⁹ suggests that there is no significant difference in 1-, 3-, and 5-year survival in ABO-compatible versus ABOi liver transplants with rituximab prophylaxis. However, increased rates of cytomegalovirus infection, antibody-mediated rejection, and biliary complications emphasize the importance of a formal desensitization protocol and careful consideration of the donor characteristics when selecting recipients for ABOi LDLT.^{29,30} Another consideration to overcome the issue of ABO-incompatibility is the possibility of a paired organ exchange or swap, which allows for recipients to swap donors for compatibility.³¹ If such a swap negating the issue of ABO incompatibility is available, it is preferred. If a swap is not available, ABOi LDLT remains a viable option in selected recipients.

Dual-Graft Adult Living Donor Liver Transplantation

A novel surgical technique that was developed to overcome the issue of SFSS while ensuring donor safety is the dual-graft technique, first described by Lee and colleagues³² in 2001. This technique uses smaller grafts from two living donors into

one recipient, thus ensuring adequate residual liver in the donor while avoiding SFSS in the recipient; and has been successfully adopted in selected cases of LDLT, especially in Asia in the past few years.^{33–35} As rising obesity in the recipient population is balanced with optimal BMI donors, the dual-graft technique is expected to gain popularity in the western world.

In summary, it is fair to say that this is an exciting time where the boundaries for selection of living donors are being pushed more than ever before. The limits of donor BMI, age, and graft steatosis are expanding not only because of vigorous outcomes research, but also because of major advances in technical innovation and increasing expertise in LDLT surgery. In the next several years, the driving forces for donor criteria expansion will be the multidisciplinary teams supporting the LDLT enterprise, including but not limited to transplant hepatology, transplant infectious disease, psychiatry, and physical therapy.³⁶

EXPANDING THE DONOR ORGAN POOL

Living Donor Champion Program

LDLT is a lifesaving option for many patients but finding a living donor can serve as a significant barrier to surgery. To overcome the challenge of finding a donor, Johns Hopkins created a Live Donor Champion Program for kidney transplantation in 2010³⁷ that has subsequently been adapted across the country. Expanding this model to liver transplantation, the University of Pittsburgh created the Living Donor Champion Program in June 2017.^{3,38} Recognizing that much of the burden for finding a donor typically falls on the patient, the program attempts to alleviate that burden.

The first step in the program asks the patient to identify a surrogate (champion) to advocate for them. The champion is the recipient's primary advocate in identifying a living donor using the program's multipronged strategy and resources. This allows the patient to concentrate on the management of their liver disease while their surrogate champions their cause. The next part of the process is raising public awareness regarding live donation through public education efforts, such as town hall style meetings, our program Web site, social media outreach via Twitter and a Facebook support group, and radio and television commercials. Lastly, we provide an additional level of personal support to the recipient and their champion by providing one-on-one support of a transplant team member we call the Live Donor Ambassador. All of these efforts together (Fig. 1) have created successful and sustained growth in the LDLT program at the University of Pittsburgh (Fig. 2).

Anonymous Live Donation

Unrelated LDLT has been considered over the last two decades as a response to the national organ shortage. This involves donation to a recipient from someone with no biologic connection or prior relationship.³⁹ The donation may be directed (preidentified) or nondirected, often referred to as altruistic donation. This form of transplantation is allowed in some countries including the United States, Canada, Saudi Arabia, and the Netherlands and prohibited in other countries, such as Poland, Italy, and France suggesting that controversies surrounding the ethics of unrelated donation still persist.³⁹ In a recent study, the Toronto group led by Goldaracena and colleagues⁴⁰ described their 12-year experience with anonymous donation. The group explored anonymous donor characteristics, drivers for donation, and patient outcomes. Most donors in this study reported feeling compelled to perform a kind act or good deed after an appeal from potential recipients. In addition, this study suggested that anonymous donation can have a sustainable impact on the growth of the donor pool,

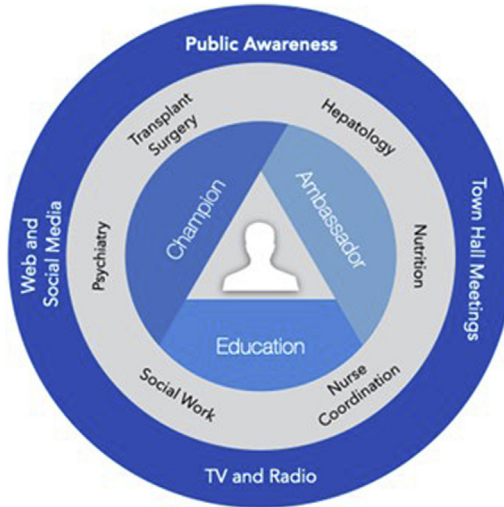


Fig. 1. Elements of the Living Donor Champion program.

representing 6.7% (50/743) of the total number of LDLTs performed by the Toronto group over the 12 years, and 2.5% (50/2037) of the total number of liver transplants. The overall donor and recipient outcomes were excellent, with 1-year recipient survival of 91% for adult recipients and 98% for children, no donor deaths, and only one Dindo-Clavien grade 3 donor complication with complete resolution.⁴⁰ The possible impact of anonymous live donation is summarized best by the authors when they point out that if 1 in every 17,000 US citizens between the ages of 18 and 65 years anonymously donated there would be no liver transplant waiting list.⁴⁰ The controversies

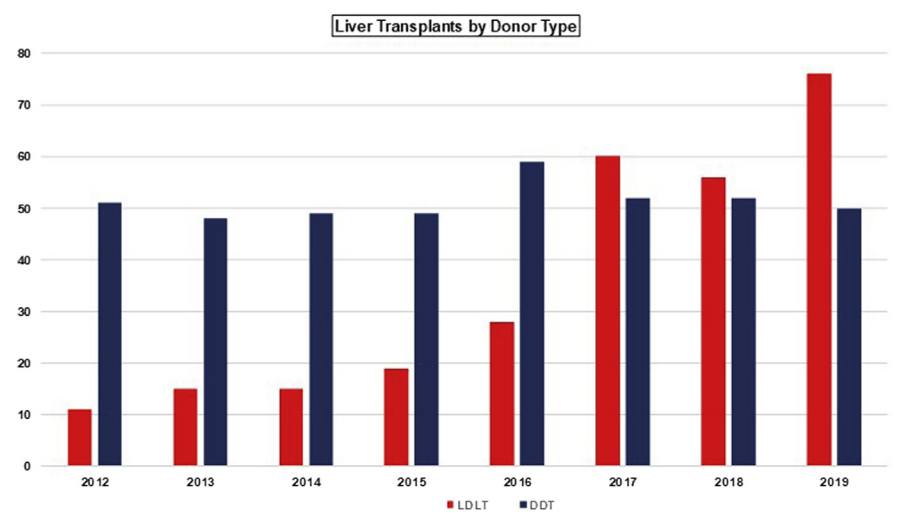


Fig. 2. Number of adult-to-adult LDLT and deceased donor liver transplants (DDT) at the University of Pittsburgh (2012–2019).

surrounding anonymous live donation will continue but this study helps to understand the possible impact of anonymous donation on increasing the size of the donor pool.

EXPANDING RECIPIENT INDICATIONS

LDLT helps all patients that may benefit from liver transplantation but more notably, presents a unique opportunity to offer timely liver transplants to patients who fall outside of the conventional United Network for Organ Sharing criteria. In this section, we explore some of the extended recipient indications that have a reasonable chance of success with LDLT. LDLT is the avenue to test the outcomes of liver transplantation in this population where drawing organs from the limited deceased donor pool cannot be currently justified. Over time, if LDLT proves successful, new vistas of management for these patients will have been opened.

Metastatic Colorectal Carcinoma

Transplantation as a modality for treatment of colorectal liver metastasis (CLM) was first attempted in the initial cohort of human liver transplants,⁴¹ abandoned because of poor outcomes, and then revisited years later.^{42,43} One of the seminal investigations in this area was a small prospective study (SECA trial) conducted in 2013 to assess survival in patients with CLM following liver transplantation.⁴⁴ For the 21 patients without extrahepatic disease in the SECA trial, median survival was 27 months and the 1-, 3-, and 5-year survival was 95%, 68%, and 60%, respectively.⁴⁴ Notably, this trial had no standardized protocol for the administration of neoadjuvant or adjuvant chemotherapy. The study demonstrated that median time to recurrence for patients transplanted for CLM was 6 months. However, if recurrence of disease was outside the liver, primarily pulmonary, 5-year survival was 72%.⁴⁵

Such studies on liver transplantation for CLM have made an increasingly compelling argument for consideration of liver transplantation for patients with CLM given the improvement in patient survival compared with standard chemotherapy alone.⁴⁶ There are no prospective data on liver transplantation compared with modern chemotherapeutic agents or multimodal treatments, but trials are ongoing⁴⁷ to answer these questions. Nevertheless, the current literature clearly suggests that select patients with CLM benefit from transplantation. These patients are often disadvantaged by low MELDNa scores, making them noncompetitive on the transplant wait-list. CLM is therefore, an indication well-suited for LDLT.

Hepatocellular Carcinoma Outside Milan Criteria

The original Milan criteria for liver transplantation in patients with hepatocellular carcinoma (HCC) were published nearly 30 years ago.⁴⁸ In their 1996 *New England Journal of Medicine* paper, Mazzaferro and colleagues⁴⁹ defined the criteria that are still considered the gold standard in many transplant centers around the world. Fifteen years later, they published a meta-analysis confirming a statistically significant survival benefit with liver transplantation for patients with HCC within the Milan criteria as compared with patients with HCC exceeding the Milan criteria on explant pathology, with a hazard ratio of 1.68.

However, over time, many centers found the Milan criteria too restrictive, and attempted to use less stringent criteria for transplantation. Of these, the most well-known are the University of San Francisco criteria that were published in 2001.⁵⁰ These criteria increased the tumor size limit while maintaining comparable 1-year and 5-year survival rates to the Milan criteria. The next major advance came a decade later, with the extended Toronto Criteria.⁵¹ Research had shown that imaging findings

frequently understage or overstage HCC, and that tumor size and number did not always go hand-in-hand with tumor biology.^{52–55} The Toronto group studied patients with HCC who met Milan criteria (M; n = 189) and exceeded Milan criteria (M+; n = 105) and underwent liver transplantation between 1996 and 2008. They found no difference in the 5-year overall or recurrence-free survival between the 2 groups. However, excluding patients with poorly differentiated tumors and aggressive pre-transplant bridging therapies significantly improved overall survival in the M+ group. Hence, the extended Toronto Criteria advocated for a protocol biopsy to rule out aggressive features in the largest tumor, but had no limitations on the size or number of tumors present.⁵¹ They also noted that serum α -fetoprotein greater than or equal to 400 ng/mL associated with poorer recurrence-free survival.⁵¹

Several other attempts have since been made to expand transplant criteria for HCC (Table 1). Many of these criteria successfully captured a subset of patients outside of the Milan criteria for whom one could still expect outcomes similar to those within the Milan criteria. These criteria have pushed the limits of tumor size and number, refined patient selection by factoring in key laboratory tests, and included patients with segmental portal vein thrombosis.^{56–59} Over the years, multiple studies have validated several of the criteria.^{49,60–64} However, the quest for refining the criteria continues, with the ultimate aim of being most inclusive and still producing the most acceptable transplant outcomes. For a cancer where the only curative treatment today is transplantation, this quest is a noble one.

Severe Acute Alcoholic Hepatitis

After many years of US transplant programs defaulting to the 6-month rule for sobriety, the issue of transplantation in severe acute alcoholic hepatitis again gained attention with the paper by Mathurin and colleagues⁶⁵ in 2011. This study looked at the benefit of early transplantation in severe acute alcoholic hepatitis and demonstrated a survival benefit in those patients who underwent early transplantation (<2%) versus matched control subjects ($77 \pm 8\%$ vs $23 \pm 8\%$). Patients who did not undergo early transplantation were typically excluded because of “unfavorable social or familial profiles.”⁶⁵

Despite the clear survival benefit, transplantation for severe alcoholic hepatitis is still controversial. Given their acute severity of illness, these patients are immediately placed at a high priority for transplantation ahead of other waitlist candidates. This apparent inequity in transplant allocation would be less controversial if graft availability was a nonissue. Indeed, LDLT resolves the issue of organ supply and allows patients to be considered for transplantation without altering the deceased donor pool. In addition, willingness of family or friends to donate may be the best indicator of social support, an important predictor of transplant outcomes. Thus, for several reasons, LDLT may prove to be a lifesaving option for patients with severe alcoholic hepatitis.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common primary hepatobiliary malignancy following HCC. Hilar CCA represents two-thirds of the cases of CCA and has dismal overall survival. Despite the curative intent of resection, it is often achieved in only 25% to 40% of patients.^{66–68} After original exploration of neoadjuvant chemoradiation by Sudan and colleagues,⁶⁹ the Mayo Clinic (2002) created a protocol that would serve as the standard of treatment before transplantation in CCA. This study along with the Nebraska study⁶⁹ supported the idea that for selected patients with early disease (stages I and II) durable long-term survival was possible with the combination for neoadjuvant chemoradiation followed by transplantation. Later in 2004, the original study was updated and reported overall 1-, 3-, and 5-year survival for

Table 1
HCC criteria for transplantation

Name of Criterion		Criterion Characteristics
1996	Milan	Single tumor ≤ 5 cm in diameter, or up to 3 tumors, each ≤ 3 cm in diameter; plus absence of nodal or vascular tumor invasion
2001	University of San Francisco	Single tumor ≤ 6.5 cm in diameter, or up to 3 tumors with largest tumor ≤ 4.5 cm in diameter, along with total tumor diameter of ≤ 8 cm
2007	5–5 rule (Tokyo)	Up to 5 tumors, with a maximum tumor size ≤ 5 cm
2007	10–5 rule (Kyoto)	Up to 10 tumors, all ≤ 5 cm in diameter, and PIVKA II ≤ 400 mAU/mL
2008	Asan Medical Center	Up to 6 tumors, with largest tumor diameter ≤ 5 cm, and no gross vascular invasion
2009	Up-to-seven	Sum of the size of the largest tumor in cm and the total number of tumors ≤ 7
2011	Extended Toronto Criteria	Protocol biopsy to rule out aggressive features in the largest tumor No limitations on the size or number of tumors
2014	Samsung Medical Center	Maximal tumor size ≤ 6 cm, tumor number < 7 , and/or AFP levels < 1000 ng/mL
2015	Hangzhou	Tumor stratification as type A or B; A has better outcomes Type A = tumor burden ≤ 8 cm, or tumor burden > 8 cm with AFP ≤ 100 ng/mL Type B = tumor burden > 8 cm with AFP 100–400 ng/mL
2016	Seoul National University	PVTT that has not spread to the main portal vein, and a low AP score ($\leq 20,000$)
2017	Seoul St. Mary's hospital	Only segmental PVTT not lobar, plus AFP < 100 ng/mL
2017	Soonchunhyang University Seoul Hospital	PVTT less than the Vp4 type per the Liver Cancer Study Group of Japan staging (Vp4 = presence of tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe, or both), and good biologic response to downstaging by radiotherapy
2019	5-5-500 rule	Nodule size ≤ 5 cm in diameter, nodule number ≤ 5 , and AFP ≤ 500 ng/mL

Abbreviations: AFP, α -fetoprotein; AP score, AFP \times PIVKA II score; PIVKA II, protein induced by vitamin K absence/antagonist-II; PVTT, portal vein tumor thrombus.

transplanted patients as 92%, 82%, and 82%, respectively, compared with 82%, 48%, and 21%, for those who underwent resection alone.⁷⁰

Intrahepatic CCA (iCCA) is a contraindication to transplantation at most centers. Early studies demonstrated very poor post-transplant outcomes for patients transplanted for iCCA.⁷¹ However, one study found that the overall 5-year survival in patients with iCCA following transplant was greater than 50%. More importantly, the study demonstrated that patients with small tumors (<2 cm) had a long-term disease-free survival of 73%, and better outcomes compared with patients with more advanced disease (either tumor >2 cm or multifocal disease).⁷²

For hilar cholangiocarcinoma and iCCA, similar to CLM, the MELDNa score provides no advantage in their listing for a deceased donor organ. This raises the importance of considering early intervention with LDLT in this population who may achieve durable long survival.

Low Model for End-Stage Liver Disease and Other Considerations

The MELD score currently determines liver transplant waitlist position. However, it does not always capture the true severity of disease, especially with cholestatic diseases. Physicians must step away from objective data and weigh the benefit of transplantation for each individual patient based on what is known about the natural trajectory of their individual disease. LDLT gives this opportunity. In fact, Goldberg and colleagues⁷³ showed that LDLT has superior graft survival compared with deceased donor liver transplantation in autoimmune and cholestatic diseases.

SUMMARY

There is a significant organ shortage for transplantation throughout the world. LDLT is a viable option for meeting the shortfall in available organs. The process of increasing the number of living donor transplants must be thoughtful and must maintain donor safety as the top priority. To improve implementation of LDLT, we have three recommendations:

1. Educate more transplant programs on the benefits of LDLT and demonstrate that donor safety is improving with each procedure performed.

There is an urgent need for lifesaving measures, and valuable opportunities are being missed. Transplant programs need to invest in establishing LDLT programs and health care systems. Over time, advances in transplant technology and continued improvements in LDLT protocols will progressively decrease donor risk and increase post-transplant longevity for recipients. Therefore, as the number of LDLTs is increased throughout the world, it is critical to document and disseminate longitudinal data on outcomes.

2. Encourage transplant programs to adopt the Living Donor Champion model.

To help overcome the barriers of public perception and also take the responsibility of finding a donor out of the patient's hands, comprehensive educational and patient advocacy programs, such as the Living Donor Champion model, must be implemented. The widespread adoption of such programs will help increase the living donor pool and address the nation's unmet needs.

3. Expand LDLT access to a larger group of potential transplant recipients while continuously testing the boundaries of donor selection criteria.

Such conditions as HCC outside of Milan, CCA, CLM, and low MELD should be considered for transplantation. This, along with safe expansion of donor criteria, will offer lifesaving treatment while simultaneously improving the

transplantation process leading to new guidelines, protocols, and technologies to accelerate advancements in the effectiveness and safety of LDLT.

CLINICS CARE POINTS

- Donors with BMI >30 but with hepatic steatosis of <10% can potentially be considered for LDLT if they have no other relevant comorbidities, and there is both surgical and medical expertise for LDLT care at the center.
- Careful assessment of emotional maturity in younger donors and rigorous physiological assessment in older individuals can safely expand donor age criteria in both directions.
- Absolute graft weight of more than or equal to 643g may be a better predictor of outcomes than a GRWR of 0.8 SFSS incidence can be low even with GRWR of <0.8 with meticulous recipient selection, and well-defined surgical protocols including appropriate portal flow modulation.
- Although ABOi LDLT is a viable option in selected recipients, a paired organ exchange or swap should be considered to eliminate the issue of ABO incompatibility altogether.
- The Living Donor Champion Program allows the patient to focus on the management of their medical condition while their surrogate 'champions' their cause to help find a live donor.
- Selected patients with colorectal metastases to the liver may benefit from LDLT, however, no studies have compared survival post-LDLT with modern chemotherapeutic or multi-modal treatments.
- LDLT for severe acute alcoholic hepatitis remains controversial, but social support in the form of a friend or a family member willing to donate could receive favorable consideration.
- The combination of neoadjuvant chemoradiation and transplantation can improve survival in hilar CCA with careful consideration of the role of tumor size in long term outcomes.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. OPTN Database. Available at: <http://optn.transplant.hrsa.gov>. Accessed July 21, 2020.
2. Cullaro G, Sarkar M, Lai JC. Sex-based disparities in delisting for being "too sick" for liver transplantation. *Am J Transplant* 2018;18(5):1214–9.
3. Humar A, Ganesh S, Jorgensen D, et al. Adult living donor versus deceased donor liver transplant (LDLT versus DDLT) at a single center: time to change our paradigm for liver transplant. *Ann Surg* 2019;270(3):444–51.
4. Abu-Gazala S, Olthoff KM. Status of adult living donor liver transplantation in the United States: results from the adult-to-adult living donor liver transplantation cohort study. *Gastroenterol Clin North Am* 2018;47(2):297–311.
5. Rinella ME, Alonso E, Rao S, et al. Body mass index as a predictor of hepatic steatosis in living liver donors. *Liver Transpl* 2001;7(5):409–14.
6. Soin AS, Chaudhary RJ, Pahari H, et al. A worldwide survey of live liver donor selection policies at 24 centers with a combined experience of 19 009 adult living donor liver transplants. *Transplantation* 2019;103(2):e39–47.

7. Andert A, Ulmer TF, Schöning W, et al. Grade of donor liver microvesicular steatosis does not affect the postoperative outcome after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2017;16(6):617–23.
8. Chu MJ, Dare AJ, Phillips AR, et al. Donor hepatic steatosis and outcome after liver transplantation: a systematic review. *J Gastrointest Surg* 2015;19(9):1713–24.
9. Frongillo F, Liroso MC, Sganga G, et al. Graft steatosis as a risk factor of ischemic-type biliary lesions in liver transplantation. *Transplant Proc* 2014;46(7):2293–4.
10. Wu C, Lu C, Xu C. Short-term and long-term outcomes of liver transplantation using moderately and severely steatotic donor livers: a systematic review. *Medicine (Baltimore)* 2018;97(35):e12026.
11. Bhangu P, Sah J, Choudhary N, et al. Safe use of right lobe live donor livers with up to 20% macrovesicular steatosis without compromising donor safety and recipient outcome. *Transplantation* 2020;104(2):308–16.
12. Knaak M, Goldaracena N, Doyle A, et al. Donor BMI >30 is not a contraindication for live liver donation. *Am J Transplant* 2017;17(3):754–60.
13. Kubota T, Hata K, Sozu T, et al. Impact of donor age on recipient survival in adult-to-adult living-donor liver transplantation. *Ann Surg* 2018;267(6):1126–33.
14. Available at: <https://aaafoundation.org/rates-motor-vehicle-crashes-injuries-deaths-relation-driver-age-united-states-2014-2015/>.
15. Aulakh R. Too young to save his mother's life? Hospital changes policy for teen. Available at: https://www.thestar.com/life/health_wellness/news_research/2011/07/12/too_young_to_save_his_mothers_life_hospital_changes_policy_for_teen.html. Accessed July 21, 2020.
16. Selzner M, Kashfi A, Cattal MS, et al. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. *Liver Transpl* 2009;15(12):1776–82.
17. Agarwal S, Selvakumar N, Rajasekhar K, et al. Minimum absolute graft weight of 650 g predicts a good outcome in living donor liver transplant despite a graft recipient body weight ratio of less than 0.8. *Clin Transplant* 2019;33(10):e13705.
18. Wong TC, Fung JYY, Cui TYS, et al. The Risk of Going Small: Lowering GRWR and Overcoming Small-For-Size Syndrome in Adult Living Donor Liver Transplantation. *Ann Surg* 2020. [Epub ahead of print].
19. Ma KW, Wong KHC, Chan ACY, et al. Impact of small-for-size liver grafts on medium-term and long-term graft survival in living donor liver transplantation: a meta-analysis. *World J Gastroenterol* 2019;25(36):5559–68.
20. Kawagishi N, Satomi S. ABO-incompatible living donor liver transplantation: new insights into clinical relevance. *Transplantation* 2008;85(11):1523–5.
21. Egawa H, Oike F, Buhler L, et al. Impact of recipient age on outcome of ABO-incompatible living-donor liver transplantation. *Transplantation* 2004;77(3):403–11.
22. Pratschke J, Tullius SG. Promising recent data on ABO incompatible liver transplantation: restrictions may apply. *Transpl Int* 2007;20(8):647–8.
23. Stewart ZA, Locke JE, Montgomery RA, et al. ABO-incompatible deceased donor liver transplantation in the United States: a national registry analysis. *Liver Transpl* 2009;15(8):883–93.
24. Kim JM, Kwon CH, Joh JW, et al. ABO-incompatible living donor liver transplantation is suitable in patients without ABO-matched donor. *J Hepatol* 2013;59(6):1215–22.
25. Egawa H, Teramukai S, Haga H, et al. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology* 2008;47(1):143–52.
26. Gugenheim J, Samuel D, Reynes M, et al. Liver transplantation across ABO blood group barriers. *Lancet* 1990;336(8714):519–23.

27. Farges O, Kalil AN, Samuel D, et al. The use of ABO-incompatible grafts in liver transplantation: a life-saving procedure in highly selected patients. *Transplantation* 1995;59(8):1124–33.
28. Egawa H, Teramukai S, Haga H, et al. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. *Am J Transplant* 2014;14(1):102–14.
29. Yadav DK, Hua YF, Bai X, et al. ABO-incompatible adult living donor liver transplantation in the era of rituximab: a systematic review and meta-analysis. *Gastroenterol Res Pract* 2019;2019:8589402.
30. Kim JM, Kwon CH, Joh JW, et al. Case-matched comparison of ABO-incompatible and ABO-compatible living donor liver transplantation. *Br J Surg* 2016;103(3):276–83.
31. Lo AL, Sonnenberg EM, Abt PL. Evolving swaps in transplantation: global exchange, vouchers, liver, and trans-organ paired exchange. *Curr Opin Organ Transplant* 2019;24(2):161–6.
32. Lee S, Hwang S, Park K, et al. An adult-to-adult living donor liver transplant using dual left lobe grafts. *Surgery* 2001;129(5):647–50.
33. Song GW, Lee SG, Moon DB, et al. Dual-graft adult living donor liver transplantation: an innovative surgical procedure for live liver donor pool expansion. *Ann Surg* 2017;266(1):10–8.
34. Jwa EK, Choi DL, Kim JD. Feasibility of dual living donor liver transplantation from donors with complex portal vein variations. *Transplant Proc* 2020;52(6):1791–3.
35. Vinayak N, Ravi M, Ankush G, et al. Dual graft living donor liver transplantation: a case report. *BMC Surg* 2019;19(1):149.
36. Rockstroh JK, Gonzalez-Scarano F. Living donor liver transplant from an HIV-positive individual to an HIV-negative individual: could this become a new reality? *AIDS* 2018;32(16):2423–4.
37. Garonzik-Wang JM, Berger JC, Ros RL, et al. Live donor champion: finding live kidney donors by separating the advocate from the patient. *Transplantation* 2012;93(11):1147–50.
38. Hughes CB, Humar A. Liver transplantation: current and future. *Abdom Radiol (NY)* 2020. [Epub ahead of print].
39. Duvoux C. Anonymous living donation in liver transplantation: squaring the circle or condemned to vanish? *J Hepatol* 2019;71(5):864–6.
40. Goldaracena N, Jung J, Aravinthan AD, et al. Donor outcomes in anonymous live liver donation. *J Hepatol* 2019;71(5):951–9.
41. Starzl TE. The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955–1967). *J Am Coll Surg* 2002;195(5):587–610.
42. Foss A, Adam R, Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. *Transpl Int* 2010;23(7):679–85.
43. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. *Transpl Int* 2008;21(12):1107–17.
44. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013;257(5):800–6.
45. Hagness M, Foss A, Egge TS, et al. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg Oncol* 2014;21(4):1323–9.
46. Glinka J, Ardiles V, Pekolj J, et al. Liver transplantation for non-resectable colorectal liver metastasis: where we are and where we are going. *Langenbecks Arch Surg* 2020;405(3):255–64.

47. Adam R. Curative potential of liver transplantation in patients with definitively unresectable colorectal liver metastases (CLM) treated by chemotherapy: a prospective multicentric randomized trial. Available at: <https://clinicaltrials.gov/ct2/show/NCT02597348>. Accessed July 21, 2020.
48. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334(11):693–9.
49. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl* 2011;17(Suppl 2):S44–57.
50. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33(6):1394–403.
51. DuBay D, Sandroussi C, Sandhu L, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Ann Surg* 2011;253(1):166–72.
52. Zavaglia C, De Carlis L, Alberti AB, et al. Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. *Am J Gastroenterol* 2005; 100(12):2708–16.
53. Jonas S, Bechstein WO, Steinmüller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001;33(5):1080–6.
54. Shah SA, Tan JC, McGilvray ID, et al. Accuracy of staging as a predictor for recurrence after liver transplantation for hepatocellular carcinoma. *Transplantation* 2006;81(12):1633–9.
55. Sotiropoulos GC, Malagó M, Molmenti E, et al. Liver transplantation for hepatocellular carcinoma in cirrhosis: is clinical tumor classification before transplantation realistic? *Transplantation* 2005;79(4):483–7.
56. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007;25(4):310–2.
57. Lee KW, Suh SW, Choi Y, et al. Macrovascular invasion is not an absolute contraindication for living donor liver transplantation. *Liver Transpl* 2017;23(1):19–27.
58. Choi JY, Yu JI, Park HC, et al. The possibility of radiotherapy as downstaging to living donor liver transplantation for hepatocellular carcinoma with portal vein tumor thrombus. *Liver Transpl* 2017;23(4):545–51.
59. Choi HJ, Kim DG, Na GH, et al. The clinical outcomes of patients with portal vein tumor thrombi after living donor liver transplantation. *Liver Transpl* 2017;23(8):1023–31.
60. Bonadio I, Colle I, Geerts A, et al. Liver transplantation for hepatocellular carcinoma comparing the Milan, UCSF, and Asan criteria: long-term follow-up of a Western single institutional experience. *Clin Transplant* 2015;29(5):425–33.
61. Kaido T, Ogawa K, Mori A, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery* 2013;154(5):1053–60.
62. Patel SS, Arrington AK, McKenzie S, et al. Milan criteria and UCSF criteria: a preliminary comparative study of liver transplantation outcomes in the United States. *Int J Hepatol* 2012;2012:253517.
63. Unek T, Karademir S, Arslan NC, et al. Comparison of Milan and UCSF criteria for liver transplantation to treat hepatocellular carcinoma. *World J Gastroenterol* 2011;17(37):4206–12.

64. Sapisochin G, Goldaracena N, Laurence JM, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology* 2016;64(6):2077–88.
65. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365(19):1790–800.
66. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001;234(4):507–17 [discussion: 517–9].
67. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245(5):755–62.
68. Kimura N, Young AL, Toyoki Y, et al. Radical operation for hilar cholangiocarcinoma in comparable Eastern and Western centers: outcome analysis and prognostic factors. *Surgery* 2017;162(3):500–14.
69. Sudan D, DeRoover A, Chinnakotla S, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002;2(8):774–9.
70. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005;242(3):451–8 [discussion: 458–61].
71. Robles R, Figueras J, Turrión VS, et al. Liver transplantation for peripheral cholangiocarcinoma: Spanish experience. *Transplant Proc* 2003;35(5):1823–4.
72. Sapisochin G, Rodríguez de Lope C, Gastaca M, et al. Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? *Am J Transplant* 2014;14(3):660–7.
73. Goldberg DS, French B, Abt PL, et al. Superior survival using living donors and donor-recipient matching using a novel living donor risk index. *Hepatology* 2014;60(5):1717–26.