

ORIGINAL ARTICLE

Use of preprocurement biopsy in donation after circulatory death liver transplantation

Alexandra C. Bolognese¹ | David P. Foley¹ | Carrie J. Sparks² |
Adam K. Schneider² | Anthony M. D'Alessandro^{1,2} | Nikole A. Neidlinger^{1,2}

¹Division of Transplantation, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

²UW Organ and Tissue Donation, Madison, Wisconsin, USA

Correspondence

Alexandra C. Bolognese, Division of Transplantation, Department of Surgery, University of Wisconsin School of Medicine and Public Health, 600 Highland Ave, Madison, WI 53792, USA.
Email: bolognese@surgey.wisc.edu

Abstract

We perform routine preprocurement image-guided percutaneous liver biopsies on potential donation after circulatory death (DCD) liver donors. The purpose of this study was to examine the impact of preprocurement liver biopsy on the use of livers from DCD donors. We retrospectively reviewed demographics, liver histology, and disposition of DCD liver donors within a single organ procurement organization (OPO) who underwent preprocurement liver biopsy from January 2000 through December 2019. A total of 212 potential donors underwent prerecovery biopsy. No donors were lost as a result of complications of biopsy. Of these, 183 (86.3%) had acceptable biopsies: 146 (79.8%) were successfully transplanted and 37 (20.2%) were deemed not suitable for transplant. In contrast, of 120 DCD livers recovered with the intent to transplant that were not biopsied prior to recovery, 59 (49.2%) were successfully transplanted, and 61 (50.8%) were deemed not suitable for transplant. A total of 14 donors were ruled out for transplant based on prerecovery histology. Successfully transplanted livers that underwent preprocurement biopsy were more likely to come from donors aged older than 50 years or with body mass index more than 30 kg/m² compared with successfully transplanted livers without a prerecovery biopsy. Biopsy excluded 6.6% of DCD donor livers for transplant prior to recovery and facilitated the successful recovery and transplant of two-thirds of potential DCD donor livers. Livers intended for transplant at the time of recovery that did not undergo preprocurement biopsy were more likely to not be recovered or to be discarded. Preprocurement biopsy provides additional histologic information prior to deploying resources and helps to identify usable livers that might otherwise be declined for transplant. Consideration of liver biopsy in this group benefits OPOs and transplant centers by maximizing organ use and optimizing resource deployment.

Abbreviations: BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death; HCV, hepatitis C virus; IRB, institutional review board; NAT, nucleic acid test; OPO, organ procurement organization; WIT, warm ischemia time.

SEE EDITORIAL ON PAGE 1699

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INTRODUCTION

The transplant community is perpetually faced with a growing waiting list and increasing waitlist deaths as a result of the organ shortage. One way to increase transplantation is the use of organs from donation after circulatory death (DCD) donors.^[1] Transplantation of livers from DCD donors increased in the mid-1990s, but initial enthusiasm was tempered by the recognition of increased rates of complications in recipients from these donors, especially ischemic cholangiopathy.^[2,3] It is now recognized that DCD livers can be transplanted with good outcomes when donor and recipient selection are optimized.^[2,4]

Preprocurement liver biopsies are regularly performed by a majority of organ procurement organizations (OPOs) at a rate of 5%–10% of donation after brain death (DBD) donors; the most common indications are advanced age, obesity, history of alcohol use, positive hepatitis serologies, imaging results, candidacy as single-organ liver donor only, or transplant center request.^[5] In contrast, it is uncommon for OPOs to obtain preprocurement biopsies from DCD liver donors, although their use could positively impact organ and resource use and the timely allocation of livers to appropriate recipients for optimal outcomes. Although prerecovery biopsies of DCD donors has not been documented in the literature, a recent article reviewed pretransplant pathology findings in livers from DCD donors. The authors' analysis demonstrated decreased graft survival rates in livers with pretransplant biopsies demonstrating macrosteatosis equal to or greater than 20% or sinusoidal neutrophilic infiltrates, but all of these biopsies were performed postmortem.^[6] Another study analyzing pretransplant biopsies from DCD livers using the Organ Procurement and Transplantation Network database demonstrated an impact of both macrosteatosis (<15%) and microsteatosis (<10%) on outcomes after DCD liver transplant, including an increased risk of both graft failure and patient mortality, although these biopsies were presumably taken postmortem as well.^[7]

We routinely perform preprocurement image-guided liver biopsies on potential DCD liver donors to aid in the decision-making process for organ acceptance. The purpose of this study was to examine the impact of preprocurement liver biopsy on use of livers from DCD donors.

MATERIALS AND METHODS

During a 20-year period from January 2000 to December 2019, our OPO recovered organs from 600 controlled DCD (Maastricht Class III) donors. In this context, "DCD donor" indicates an individual who deteriorated to circulatory death after a terminal extubation and donated at least one organ with the intent to

transplant. All 113 donor hospitals within our donor service area allow bedside liver biopsies for the purpose of evaluation for transplant.

As premortem biopsies were done on living patients, consent was obtained from a legal surrogate at the time of authorization for DCD donation. Surrogates were approached by a donor support specialist from our OPO at the time of referral for donation. If the family wished to proceed with donation after circulatory death, consent was obtained for prerecovery evaluation and procedures to facilitate the successful recovery of organs for transplant, including placement of arterial and central lines, groin cut-down for the purpose of vessel cannulation, bronchoscopy in the case of potential lung donation, bedside liver biopsy in the case of potential liver donation, transesophageal echocardiogram and coronary angiogram in the case of potential heart donation, and the administration of medications including premortem heparin.

Percutaneous liver biopsies were performed at the donor hospital using image guidance and a single pass of an 18-gauge needle. In the majority of cases, they were then read by pathologists at the donor hospital. When resources and technical expertise were unavailable, samples were sent back to our tertiary care center and read by an experienced liver pathologist, although this was the exception. All centers were provided a "Liver Biopsy Consultation Report" form to focus pathologic evaluation (Figure 1). Evaluation was performed on frozen sections and focused on macro- and microvesicular fat content (total percentage), degree of fibrosis, hepatitis, necrosis, and portal infiltrates. Trichome staining was not performed.

Results were then available to the medical director of the OPO (a transplant surgeon) within 1 h of biopsy to allow for a determination regarding the appropriateness of allocation. In general, we deemed livers suitable for recovery with any level of microsteatosis, 30% or less macrosteatosis, and Grade 0 or 1 fibrosis. Transplant centers had access to the liver biopsy report at the time of organ evaluation. Additional tissue was fixed for permanent section and pathologic review; if these results were available at the time of organ offer, they were also provided to transplant centers.

Exceptions to biopsies included young (aged <30 years) and lean (body mass index [BMI] <25 kg/m²) individuals without risk factors for or signs of liver disease; inability to biopsy because of a lack of family consent or time constraints or contraindications to biopsy, including intractable coagulopathy (international normalized ratio >1.2 or platelet count <100,000 per microliter); livers ruled out for donation based on donor characteristics, including age, known cirrhosis, malignancy, or injury; or the absence of a qualified practitioner to perform the biopsy. Biopsies were reviewed and scored by independent pathologists at the

TO BE COMPLETED BY STAFF COLLECTING BIOPSY SAMPLE

Biopsy performed by: _____

Signature: _____ Date/Time _____

Biopsy performed:

- Bedside
 Interventional radiology
 Intra-operatively

Type of Liver Biopsy:

- Needle core right side
 Needle core left side
 Wedge
 Other Specify _____

TO BE COMPLETED BY PHYSICIAN EVALUATING THE BIOPSY SAMPLE

The physician signing below represents that the information provided in this report is accurate. The physician provides this consultation in support of the effort to transplant the liver but makes no representation as to whether the liver is suitable for transplant. The transplant program is solely responsible for determining whether the liver is suitable for transplant.

Biopsy interpreted by: _____ Date/Time _____

% Macro vesicular fat: _____ % Micro/ intermediate vesicular fat: _____

Fibrosis:

- No Fibrosis
 Fibrous expansion of SOME portal areas, with or without short fibrous septa
 Fibrous expansion of MOST portal areas, with or without short fibrous septa
 Fibrous expansion of most portal areas, with OCCASIONAL portal to portal bridging
 Fibrous expansion of portal areas, with marked bridging (portal to portal as well as portal to central)
 Marked Bridging with occasional nodules (incomplete cirrhosis)
 Cirrhosis, probable or definite

Hepatitis:

- None
 Steatohepatitis
 Acute hepatitis - microabscesses
 Chronic - portal and/or interface

Necrosis:

- None
 Centrilobular
 Periportal
 Midzonal
 Panlobular
 Random

Portal Infiltrates:

- None Noted
 Mild, some or all portal areas
 Mod, some/ all portal areas
 Moderate/Marked
 Marked, all portal areas

Comments:

Pathologist Signature: _____ Date/Time: _____

FIGURE 1 Liver biopsy consultation report.

donor hospital or at our tertiary care hospital when possible.

We received a minimal-risk institutional review board (IRB) exemption through the University of Wisconsin Health Sciences IRB. Demographics are presented as mean and range for continuous variables and as total number and percentage of total for categorical variables. We used a two-sided *t*-test to compare means between groups for continuous variables, and Fisher's exact test to compare categorical variables between groups. $p < 0.05$ was considered to be statistically significant.

RESULTS

Of 600 DCD donors during this 20-year period, 332 were considered for potential liver donation (Figure 2). The remaining 268 were excluded as liver donors based on known comorbidities, age, lack of consent, or time constraints. Among the 332 donors being considered for liver donation, 212 (63.9%) underwent prerecovery biopsy and 120 (36.1%) did not. There was a 100% consent rate for eligible potential donors. No donors were lost as a result of complications of biopsy.

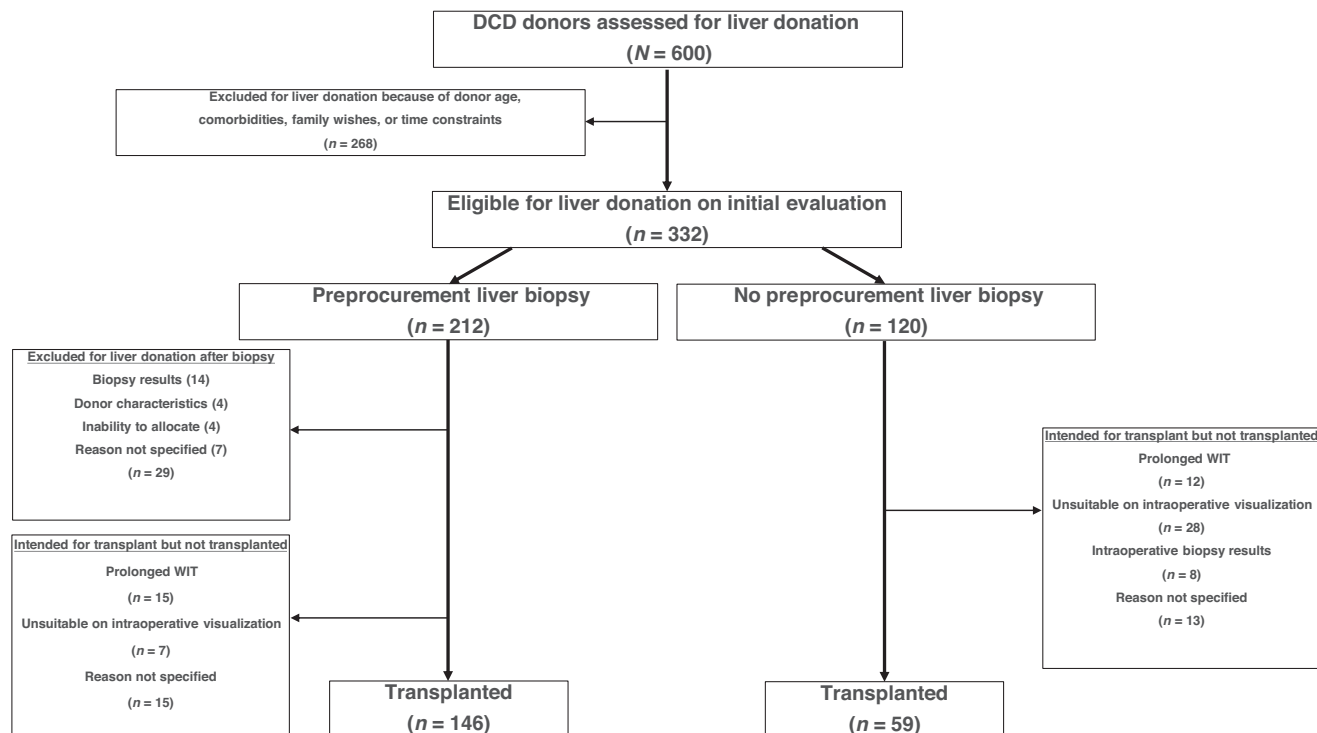


FIGURE 2 Outcomes of DCD donors considered for liver donation.

TABLE 1 Characteristics of DCD donors eligible for liver donation

DCD donor livers intended for transplant, n = 303	Biopsied, n = 183	Not biopsied, n = 120
Transplanted	146 (79.8)	59 (49.2)
Intended for transplant but not transplanted	37 (20.2)	61 (50.8)
Prolonged WIT	15 (8.2)	12 (10.0)
Unsuitable on intraoperative visualization	7 (3.8)	28 (23.3)
Unsuitable on intraoperative biopsy	0 (0.0)	8 (6.7)
Not transplantable for unspecified reason	15 (8.2)	13 (10.8)

Note: Parentheses indicate percentage of total donors transplanted or intended for transplant.

Abbreviations: DCD, donation after circulatory death; WIT, warm ischemia time.

A total of 14 donors (6.6%) were ruled out for transplant based on prerecovery histology. Of the donors, 3 (21.4%) were aged younger than 50 years, and 5 (35.7%) had a BMI <30 kg/m² (data not shown). A total of 15 additional biopsied livers were not recovered for transplant based on donor characteristics (n = 4), an inability to allocate (n = 4), or unspecified reasons (n = 7).

Of 183 livers with an acceptable histology on biopsy, 146 (79.8%) were successfully transplanted and 37 (20.2%) were not transplanted (Table 1). Regarding the 37 not used for transplant, 15 were as a result of

TABLE 2 Age and BMI of DCD donors of transplanted livers

Donors	Transplanted DCD donor livers, N = 205		p value
	Biopsied, n = 146	Not biopsied, n = 59	
Age, years	42 (10–64)	34 (1–58)	<0.001
<18	3 (2.1)	7 (11.9)	
18–49	101 (69.2)	41 (69.5)	0.01
≥50	42 (28.8)	11 (18.6)	
BMI, kg/m ²	27.9 (14.5–46.5)	25.2 (15.1–43.8)	0.01
<25	52 (35.6)	33 (55.9)	
25–30	47 (32.2)	17 (28.8)	0.01
>30	47 (32.2)	9 (15.3)	

Note: Values are presented as mean (range) and total number (percentage of total).

Abbreviations: BMI, body mass index; DCD, donation after circulatory death.

prolonged warm ischemia time (WIT; 8.2%), seven were deemed unsuitable based on intraoperative visualization (3.8%), and 15 (8.2%) were deemed not transplantable for an unspecified reason.

In contrast, there were 120 livers intended for transplant that were not biopsied prior to recovery; 59 (49.2%) were successfully transplanted and 61 (50.8%) were not transplanted. Of these, 12 (10.0%) were because of prolonged WIT, 28 (23.3%) were unsuitable at intraoperative visualization, 8 (6.7%) were excluded after

intraoperative biopsy, and 13 (10.8%) were deemed not transplantable for an unspecified reason. Of the eight that were deemed unable to transplant after an intraoperative biopsy, histological findings were as follows: moderate iron deposition ($n = 1$), bridging fibrosis ($n = 2$), greater than 45% macrosteatosis ($n = 3$), 30%–40% macrosteatosis with portal fibrosis ($n = 1$), and 25% macrosteatosis ($n = 1$).

Successfully transplanted livers that underwent preprocurement biopsy came from older donors (42 vs. 34 years; $p < 0.001$) with higher BMIs (27.9 kg/m² vs. 25.2 kg/m²; $p = 0.01$) compared with those from donations that were not biopsied (Table 2). In addition, a greater percentage of successfully transplanted biopsied livers came from donors aged older than 50 years (28.8% vs. 18.6%) or those with BMIs more than 30 kg/m² (32.3% vs. 15.3%) compared with successfully transplanted livers without prerecovery biopsies.

A total of 10 donors eligible for liver donation had positive hepatitis C virus (HCV) serologies. Eight were biopsied; five of these were successfully transplanted (one was also HCV nucleic acid test [NAT] positive), and the remaining three were declined prerecovery based on biopsy findings ($n = 2$) or donor characteristics ($n = 1$; also HCV NAT positive). Two HCV antibody-positive donors did not undergo preprocurement liver biopsy; both were declined for transplant (one also HCV NAT positive after visualization in the operating room and one for an unspecified reason after recovery). No potential liver donors had positive human immunodeficiency virus or hepatitis B virus serologies.

CONCLUSIONS

In this review of 600 DCD donors during a 20-year period, more than half were considered for liver donation, and a majority of these underwent preprocurement liver biopsies. Biopsy findings excluded 6.6% of DCD donor livers prior to recovery and facilitated the successful recovery and transplant of two-thirds of potential DCD donor livers. Livers intended for transplant at the time of recovery that did not undergo preprocurement biopsy were more likely to not be recovered or to be discarded.

A precedent exists for the use of prerecovery biopsies in donors declared dead by neurologic criteria. Of 49 OPOs surveyed, 40 currently perform percutaneous liver biopsy prior to organ recovery in DBD donors.^[5] It is demonstrated to be a safe and reliable practice.^[8,9] Prerecovery liver biopsy in extended-criteria DBD donors was found to be safe and can lead to decreased futile liver recovery without decreasing rates of transplantation. Its use in liver-only donors was especially likely to improve resource use and efficient organ

allocation.^[10] In our experience, there were no donors or organs lost as a result of the prerecovery biopsy in DCD donors. Nonetheless, there certainly exist potential risks associated with preprocurement liver biopsy in the DCD donor population, including bleeding and pneumothorax, either of which may precipitate donor instability necessitating additional procedures or expedited recovery and possible decreased organ use. The evaluation of such complications is unfortunately limited by our study design, as postbiopsy bleeding events necessitating an expedited recovery or noted on incision at the time of the recovery were not tracked during this time period nor were other potential complications, including pneumothorax or hollow viscus injury. We have changed our practice to now track these complications prospectively and hope in the future this will inform the risk–benefit discussion of premortem biopsy. At present, we can at best extrapolate from the existing data in DBD donors. In a case–control study of DBD donors from two OPOS, Oliver et al. studied postbiopsy complication defined as a composite of hemoglobin decrease greater than 2g/dl, mean arterial pressure decrease greater than 20mm Hg, or a blood transfusion following biopsy and found no significant difference in complication rate between those donors who underwent prerecovery biopsy compared with those who did not.^[11] Interestingly, however, they found a decreased risk of aborted liver recovery when prerecovery biopsy was obtained.

These risks carry with them potential undue stress and pain to the living potential donor. In our practice, consent for preprocurement procedures, including percutaneous biopsy, is obtained from a surrogate decision maker. Risk of harm to the potential DCD donor and his or her family must not be taken lightly and is to be considered in the context of maximizing organ use and the donor or surrogate's wishes for organ donation.^[12]

We attribute our ability to successfully employ premortem biopsies for the purpose of organ evaluation for transplant to a long-standing collaborative relationship between our OPO and our donor hospitals that was established 40 years ago. Our donor support specialists are highly trained and experienced in working with families of potential donors to adequately outline expectations for the donation process such that the wishes of donors and their families may be fulfilled in the case of DCD. Relationships with providers and pathologists at donor hospitalists allow for biopsies to be read and interpreted expeditiously. Although a focused liver pathologist was not routinely consulted, they were available as needed at our tertiary care center in difficult cases.

Regarding organ use, preprocurement liver biopsy may facilitate the allocation of livers that otherwise may not be placed prior to recovery. In our study, we found that biopsied livers were more likely to come from older donors with higher BMIs. Although half of

the livers not biopsied preprocurement were turned down for transplant at the time of recovery, this was the case for only 20% of biopsied livers. Furthermore, almost a quarter of the livers intended for transplant that were not biopsied were turned down after intraoperative visualization compared with less than 4% in the biopsied group. Although in DBD donors the luxury for biopsy and pathological evaluation often exists and provides for successful allocation prior to cross-clamp in the setting of any concerning findings on donor history or visualization, biopsy at the time of recovery from DCD donors adds cold ischemia time that may preempt successful allocation and transplantation in addition to increasing the risk of complication in potential recipients.^[4] In fact, in our review there were eight such livers that did not undergo pre-mortem biopsy and had a biopsy performed at the time of recovery that ruled the organ out for transplant. Premortem histological information in these cases may have saved recovery resources or even allowed for timely organ reallocation to a more appropriate recipient.

It should be noted that suitability for transplant can be quite subjective and varies based on center experience and practice as well as recipient characteristics. During the first 13 years of our study, very few centers outside of our own institution were accepting livers for transplant from DCD donors, so the assessment of suitability for transplant based on evaluation by a liver transplant surgeon at our own institution was adequate. However, as organs continue to be more widely shared, and more transplant centers routinely use DCD organs for transplant, the utility of pre-mortem biopsy may have even more relevance, and the subjectivity of “suitability” should be taken into account in an OPO’s decision to allocate such organs.

Another factor complicating liver recovery and transplant from DCD donors is the presence of positive hepatitis serologies. Despite evidence demonstrating excellent outcomes after transplantation of solid organs from HCV-positive individuals, hesitance still exists in the acceptance of these organs for transplant from some recipients and providers.^[13,14] In kidney transplantation, concerns exist among providers regarding the inferiority of transplant outcomes from HCV NAT-positive donors.^[15,16] Many potentially useable HCV-positive liver allografts are not being transplanted each year, with a majority of those that are being transplanted occurring at a small number of centers.^[17–19] The “double hit” of HCV and DCD may therefore preclude the use of these allografts, especially at smaller centers with less experience using grafts from HCV-positive donors. In our review, 50% of biopsied livers from HCV antibody-positive donors were recovered and transplanted. Preprocurement biopsy may present a potential avenue for expanding the use of grafts from HCV-positive donors after circulatory death by

providing additional pathologic insight prior to organ recovery.

From an organizational standpoint, preprocurement liver biopsy can help to optimize human and equipment resources. In the case of a liver-only potential donor, a preprocurement biopsy may prevent the unnecessary deployment of resources for a nontransplantable organ. In the evolving era of machine perfusion of liver allografts and the increasing use of normothermic regional perfusion, having pathologic information available prior to recovery can further optimize resource allocation and the use of marginal grafts.^[20]

There are a number of limitations to the current study primarily owing to its design as a retrospective review of a limited database, including the lack of tracking of biopsy-related complications outside of lost donors as described previously and an inability to correlate recipient outcomes after transplant from biopsied versus not-biopsied livers. In addition, our review included only donors—that is, those individuals who deteriorated to death with at least one organ recovered with intent to transplant. Not included are those potential donors who did not die within a time frame suitable even for kidney donation or patients referred as potential donors who were excluded from donation; data on these individuals and intent for transplant prior to recovery would give us a better idea of the impact of preprocurement biopsy in this setting. Moreover, data entered at the time of recovery are primarily in preset categories and variables; lack of granularity for some variables (e.g., those organs deemed not transplantable for an unspecified reason) limits our review. However, frequency of organs deemed not transplantable either for WIT or for an unspecified reason was relatively low and similar between the biopsied and not-biopsied groups.

As mentioned previously, the subjectivity of “suitability” based on pathologic criteria presents another limitation, as does the lack of detail regarding the pathologic findings of organs that were used versus those that were not transplanted. Interestingly, a prior examination of pretransplant liver biopsy in grafts from DCD donors demonstrated macrovesicular steatosis greater than or equal to 20% and sinusoidal neutrophilic infiltrate to be independent risk factors for graft survival and may inform the use of grafts from these donors when the data are available on prerecovery biopsy.^[6]

As biopsies were performed and read primarily at donor hospitals off of frozen sections, there are necessarily variations in processing and interpretation. Our liver biopsy consultation form is designed to streamline the evaluation and focus on pertinent pathologic characteristics that may influence suitability for transplant. Although the lack of a liver-focused pathologist may increase the variability in the interpretation of these specimens, this may not be practical given the time constraints of processing and evaluating frozen sections for the purposes of organ evaluation for

transplant. As discussed previously, our relationship with our donor hospitals during the past 40 years has allowed us to use premortem biopsy in DCD liver transplantation, and pathologists at these donor institutions have been critical to its success.

Preprocurement biopsy allows the surgeon to rule out unsuitable donors prior to deploying resources and to identify usable livers that might otherwise be ruled out for transplant based on donor age, BMI, or serologies. Consideration of liver biopsy in this group benefits OPOs and transplant centers by maximizing organ use and optimizing resource deployment.

CONFLICT OF INTEREST

Nothing to report.

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