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Expanded Criteria Donors

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THE SPECTRUM OF DONOR QUALITY: IDEAL, STANDARD, AND EXPANDED

The ideal deceased donor liver, a whole liver from a brain dead donor less than 40 years of age who died of trauma, is well defined. The standard graft and the expanded liver graft are, in contrast, relative concepts that may evolve with time. A standard liver connotes an organ of average quality relative to the spectrum currently utilized for transplantation, while an expanded liver connotes an organ of lower than average quality, coming from a donor with characteristics known to be associated with suboptimal transplant outcomes. There is general consensus that the criteria fall into 2 categories of risk: (1) graft dysfunction and (2) disease transmission.

Donor Risk Factors for Graft Dysfunction

Older donor age—Although the young adult donor is widely recognized as ideal, utilization of livers from older donors represents a logical means to expand the donor pool. In the nontransplant setting, the liver's physiologic function remains well preserved throughout life, likely a result of its unique regenerative capacity.¹ However, in the transplant setting, liver grafts from older donors are associated with a higher risk of graft failure and mortality.^{2–11} Although there is marked heterogeneity in the age cut-offs used to define an older donor, decreased patient and graft survival rates have been reported regardless of the age cut-off used: 50, 60, or 70 years.^{4–7} From 2008 to 2012, 1-year unadjusted graft survival for recipients of grafts from donors younger than 40 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years and older was 88%, 86%, 84%, 85%, and 82%, respectively ($P < .001$).¹²

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There are at least 2 probable mechanisms for this age-related increased risk of liver allograft failure. First, older hepatic parenchyma has increased vulnerability to ischemia/reperfusion injury owing to relatively fewer hepatocytes and decreased regenerative capacity.¹ In mouse models, older livers demonstrate significantly more necrosis and neutrophil accumulation¹³ and lower hepatic expression of heat shock proteins that protect hepatocytes from cellular injury.¹⁴ A second, and potentially synergistic, mechanism is the increased burden of medical comorbidities in older donors. Obesity, diabetes, hypertension, and dyslipidemia may lead to hepatic steatosis and atherosclerotic disease,^{8,15,16} further increasing susceptibility to injury.

The vulnerability of livers from older deceased donors manifests in multiple pathways of allograft dysfunction or failure. Several studies have shown that older donor livers are associated with primary nonfunction (PNF), defined as initial poor function requiring retransplantation or causing death within 7 days of transplantation.^{11,17–19} Recipients of older livers have increased rates of hepatic artery thrombosis^{16,20,21} and more severe ischemia reperfusion injury.^{9,13,14} Higher rates of biliary complications and cholestasis have also been reported among recipients of livers from donors at least 60 years of age.^{5,7} Finally, longer transplant hospitalization length of stay, higher transplant costs, and increased resource utilization are strongly associated with livers with a higher donor risk index, a metric of donor quality dominated by donor age.^{22–24}

Interestingly, donor age exerts a differential impact on recipients with chronic hepatitis C virus (HCV) infection. Studies have consistently shown an interaction between older donor age and positive recipient HCV status that predisposes to fibrosing cholestatic hepatitis, more rapid fibrosis, post-transplant infections, graft failure, and mortality.^{10,19,25–34} Although age cut-offs defining an older donor for HCV recipients has varied, the negative impact appears to begin at 40 years of age. In an analysis of data on all adult primary, single-organ liver transplants from 1995 to 2001, there was a statistically significant increase in graft loss for every decade increase in donor age starting at 40 years among HCV-infected recipients but not until 60 years in non-HCV-infected recipients (**Fig. 1**).¹⁰

Utilization of livers from deceased donors of advanced age continues to rise throughout the world,^{35–38} and there is currently no consensus on an upper age limit for liver donors. One strategy to minimize risk is to have a lower biopsy threshold. A second strategy is to minimize cold ischemia time (CIT).^{6,16,39} This can be accomplished through careful recipient selection, avoiding candidates expected to require protracted dissection, and through careful coordination between organ procurement and initiation of recipient surgery. In 1 Italian study of 178 patients who received livers from donors at least 60 years of age, grafts transplanted with less than 7 versus 7 or more hours of CIT demonstrated significantly higher graft survival at 1 year (84% vs 71%) and 3 years (76% vs 54%) [$P < .005$].³⁹ Lastly, experts have generally agreed that HCV-infected recipients are suboptimal candidates for older donor livers. This belief is likely to evolve with the availability of increasingly effective and tolerable direct-acting antiviral agents against HCV.

Donation after cardiac death status—Donation after cardiac death (DCD) refers to the recovery of organs from a donor who has experienced circulatory arrest after withdrawal of

life-sustaining medical interventions. Hypoperfusion during the donor's demise—a period termed warm ischemia—represents an additional injury phase that worsens post-transplant outcomes.^{3,40–51} Compared with liver grafts from donors after brain death (DBD), DCD liver grafts were associated with a 51% increased risk of graft failure (95% confidence interval [CI], 19%–91%). A meta-analysis of 11 studies reported that DCD recipients (n 5 489) experienced higher rates of biliary complications (odds ratio [OR] 5 2.4, 95% CI 5 1.8–3.4), ischemic cholangiopathy (OR 5 10.8, 95% CI 5 4.8–28.2), and PNF (OR 5 3.6, 95% CI 5 2.1–6.4), but not hepatic artery thrombosis (OR 5 1.0, 95% CI 5 0.6–1.8) when compared with DBD recipients (n 5 4455). The odds of 1-year patient (OR 5 1.6, 95% CI 5 1.0–2.5) and graft (OR 5 2.1, 95% CI, 1.5–2.8) survival were also significantly worse.⁴⁰

Despite their worse outcomes, DCD utilization has steeply increased, accounting for 4.5% of all liver transplants in the United States in 2008 compared with 0.5% in 1999.³⁴ Several approaches have been developed to lessen the ischemic injury, both cold and warm, to improve outcomes.^{52,53} Rapid surgical procurement technique and stringent thresholds of 20 to 30 minutes for organ acceptance together limit warm ischemia time, whereas selection of surgically straightforward recipients and early initiation of recipient surgery together limit CIT.^{52,53} These strategies, in combination with selection of low-risk recipients (age <60 years, primary transplantation, serum creatinine <2 mg/dL, not on hemodialysis, and not on ventilator support) have yielded comparable graft survival at 1 (81% vs 80%) and 3 years (67% vs 72%) [$P = .23$] for DCD relative to DBD livers.⁵¹ With careful management, DCD liver transplantation can offer survival benefit to well-selected recipients with Model for End-Stage Liver Disease (MELD) greater than 20 and patients with hepatocellular carcinoma (HCC) without MELD exception points.⁵⁴

Steatosis—Hepatic steatosis refers to the accumulation of lipid droplets in hepatocytes and is an important risk factor for PNF and other post-transplant complications. Upon initial evaluation, aminotransferases in donors with fatty livers are generally normal or near normal but increase markedly after transplantation, suggesting that ischemia/reperfusion injury is the key to graft dysfunction in fatty livers.^{55–57} In mouse models of ischemia/reperfusion injury, livers with significant fat accumulation demonstrate increased Kupffer cell activity and decreased oxidative phosphorylation, which results in severe sinusoidal lining cell damage and compromised membrane integrity relative to livers without steatosis.^{57–60}

Hepatic steatosis occurs in 2 histologic patterns: macrovesicular and microvesicular (**Fig. 2A**). Traditionally, these patterns have referred to and become synonymous with the size of the fat droplet: macrovesicular for large droplet and microvesicular for small droplet fat. Distinguishing between the types of fat is critical, because the fats exert a differential impact on post-reperfusion outcomes. Compared with either lean mice or obese mice with microvesicular steatosis, obese mice with macrovesicular steatosis demonstrated significantly higher elevations of aminotransferases and more extensive necrosis following ischemia/reperfusion injury⁵⁵; 90% of the lean or obese mice with microvesicular steatosis survived to 14 days after reperfusion compared with 0% of the obese mice with macrovesicular steatosis ($P < .05$).⁵⁵

More recently, pathologists have increasingly recognized that microvesicular steatosis refers to the accumulation of very small, uniform lipid droplets measuring less than 1 mm (see **Fig. 2B**). Histologically, with standard light microscopy, the microvesicles themselves are difficult to discern individually but result in a characteristic foamy-appearing cytoplasm.⁶¹ True microvesicular steatosis is rare and typically associated with conditions such as Reye syndrome, acute fatty liver of pregnancy, or drug toxicity. Macrovesicular steatosis now encompasses both large and/or small fat droplets. Large droplet fat is defined as a lipid droplet that occupies greater than one-half of the hepatocyte, and as such, displaces the cell nucleus. Factors associated with macrovesicular steatosis in the general population include obesity, alcohol intake, diabetes and/or hyperglycemia.^{62–66} Unfortunately, much of the literature regarding the impact of steatosis on transplant outcomes predates these new definitions. Therefore, this article will qualify the utilization of the terms macro- and micro-steatosis with the terms large and small droplet fat, as appropriate.

There is general agreement that the overall volume of large droplet fat is the key criterion to assess the suitability of a liver for transplantation since small droplet fat has not been associated with poor early graft function.^{67,68} Typically, less than 30% volume of large droplet fat has been considered permissive of transplantation, while greater than 60% has been prohibitive, associated with PNF, severe acute kidney injury, longer transplant hospitalization, biliary complications, graft failure, and mortality.^{67–72} In the largest study to date investigating the association between steatosis and transplant outcomes using UNOS/OPTN registry data, 5051 (23%) of the 21,777 livers transplanted from 2003 to 2008 had some degree of macrovesicular (large droplet) steatosis, but only 153 livers, or approximately 30 per year nationwide, had greater than 30%.⁷² The recipients of these livers had a 71% increased adjusted risk of 1-year graft failure ($P = .007$).⁷² Although most experts agree that livers with severe macrovesicular (large droplet) steatosis should be avoided, livers with macrovesicular (large droplet) steatosis between 30% and 60% may result in acceptable outcomes in select donor–recipient combinations.^{68,69} Favorable donor factors include age younger than 40 years and CIT less than 6 hours; favorable recipient factors include age less than 60 years, no prior abdominal surgeries, and low MELD score.^{68,69}

Historically, procurement surgeons suspect significant steatosis based on the liver's appearance and perform a biopsy to determine the overall fat content and the specific volume of large droplet fat. In situ, steatotic livers often have blunted edges and, when blanched, a yellow as opposed to a reddish-brown hue that becomes more obvious ex vivo, after exsanguination. More recently, pre-procurement liver biopsies have gained popularity as knowing that there is significant large droplet fat can initiate mitigation strategies. Pre-procurement liver biopsies are typically triggered by factors such as metabolic syndrome or alcohol intake. However, abdominal imaging—either ultrasound or cross-sectional—can also suggest hepatic steatosis. Of 492 living liver donors whose ultrasound did not suggest steatosis, 61% had none (<5%); 38% had mild (5–29%), and 0.8% had moderate (30–59%) large droplet fat on liver biopsy. No one had severe (60%) large droplet fat on liver biopsy.⁶⁶ In a study of unenhanced computed tomography scan and same-day percutaneous liver biopsy, both visual grading and the liver attenuation index accurately identified large

droplet fat of at least 30% with area under the receiver operating characteristics curves of 0.93 (95% CI, 0.82–1.00) and 0.93 (95% CI, 0.88–0.98), respectively.⁷³

Although demographics, medical history, radiographic imaging, and/or visual inspection can suggest hepatic steatosis, assessment of a fresh frozen liver biopsy remains the gold standard to determine a liver's transplantability. Histologic assessment is the only method to determine the volume of large droplet fat. Unfortunately, there are several sources of inaccuracy, including insufficient sampling, misinterpretation of freezing artifact, and inter-/intraobserver variability among pathologists who are often located at donor hospitals with little experience providing a (semi-)quantitative assessment of large and small droplet fat on frozen liver biopsies.^{74,75}

Cold ischemia time—CIT is defined as the time from cardiac arrest and the initiation of in situ cold flush in the donor to removal of the organ from cold storage for implantation into the recipient. There is widespread agreement that increased CIT is associated with inferior post-transplant outcomes.^{3,34,35,72,76,77} An analysis of donor and transplant-related factors using UNOS/OPTN registry data has shown that, for every hour of CIT above 8 hours, the adjusted risk of graft failure increases by 2% (95% CI = 1–3%).³⁵ This has been confirmed in the continental European liver transplant experience; every 15-minute increase in CIT increases 1-year graft failure risk by 0.9% (95% CI = 0.5–1.3%).⁷⁶ In addition, the risk of developing nonanastomotic biliary strictures significantly increased with every hour increase in CIT (relative risk [RR] = 1.16, 95% CI = 1.04–1.29),⁷⁸ as biliary epithelium may be particularly sensitive to ischemia-induced oxidative stress after reperfusion.⁷⁹

Notably, CIT has significantly decreased in the United States from a median (interquartile range) of 7.1 (6.0–9.4) hours from 1998 to 2002 to 6.6 (5.0–8.3) hours from 2007 to 2010 ($P < .001$).³⁵ Europe and Canada have reported similar trends.^{36,76}

Donor Risk Factors for Disease Transmission

Viral hepatitis B

Hepatitis B core antibody positive donors: Utilization of organs from hepatitis B virus (HBV) surface antigen negative (HBsAg–) but hepatitis B core antibody positive (HBsAg+) donors is an accepted means of expanding the organ donor pool. This serologic profile identifies a donor who has spontaneously cleared HBV infection but who may continue to harbor covalently closed circular HBV DNA in the liver. Among 133 HBsAg+ but HBsAg– individuals in the United States, 8% had detectable HBV DNA in the liver.⁸⁰ In contrast, in a Japanese study of 22 HBsAg+ living donors with undetectable serum HBV DNA, all had detectable HBV DNA in the liver,⁸¹ suggesting that intrahepatic HBV DNA may be more frequently present with spontaneous clearance after vertical transmission compared with adult acquisition. The prevalence of HBcAb positivity among liver donors varies widely by country: 5% in the United States,³ 12% in Spain,⁸² 7% in France,⁸³ 15% in Italy,⁸⁴ and upwards of 60% in East Asian countries where chronic HBV infection is endemic.^{85,86}

Two clinically significant scenarios can ensue after transplantation of an HBsAg+ liver unless appropriate prophylaxis is administered: (1) de novo HBV infection, defined by

detection of HBsAg in a patient without previous HBV infection or (2) recurrent HBV infection, defined as HBV viremia in a recipient with previously suppressed HBV infection. Two large meta-analyses covering studies from 2 overlapping time periods (462 transplants from 1966 to 2009 and 903 transplants from 1995 to 2010) reported that de novo HBV infection occurred in 28% to 58% of HBsAg– recipients.^{87,88} Traditionally, 3 tiers of prophylaxis have substantially prevented de novo infection: (1) HBV immune globulin (HBIG) alone (19%), (2) oral nucleos(t)ide alone (2.6% for lamivudine), or (3) combination HBIG and oral nucleos(t)ide (2.8% for HBIG and lamivudine).⁸⁷ Although there is currently sparse literature regarding the efficacy of newer-generation nucleos(t)ide analogues, the high potency and resistance barriers of both entecavir and tenofovir, compared with lamivudine, telbivudine, or adefovir, predict even lower rates of de novo HBV infection.

When possible, HBsAg+ grafts should be utilized in recipients with chronic HBV who require post-transplant HBV suppressive therapy. Nine studies that evaluated this strategy of donor–recipient matching identified HBV recurrence in 11 of 80 recipients who received HBIG alone, lamivudine alone, or combination HBIG and lamivudine.^{83,89–96} One instructive study of 10 recipients with HBV DNA sequencing data from pretransplant serum/explant liver samples and post-transplant liver biopsies reported that intrahepatic HBV DNA was donor derived in 2 patients, recipient derived in 4 patients, and both donor and recipient derived in 6 patients.⁹⁶

Whether transplantation with organs from HBsAg+ versus HBcAb– donors is associated with a decrement in survival remains controversial. Among 1270 US liver transplant recipients of HBsAg+ grafts from 1994 to 2006, the adjusted hazard ratio (HR) for graft survival was 1.09 (95% CI, 0.97–1.21).⁹⁷ In contrast, a more recent analysis of all liver transplants in Italy from 2007 to 2009 revealed a significantly elevated risk of graft loss associated with livers from HBsAg+ donors (HR, 1.56; 95% CI, 1.18–2.04).⁸⁴ Interestingly, only one of these graft losses in the HBsAg+ group occurred secondary to de novo hepatitis, suggesting that HBcAb positivity may be a surrogate for suboptimal donor quality.

HBsAg+ donors—Finally and notably, there has been recent interest but limited experience in transplantation of livers without significant fibrosis from HBsAg+ donors into HBsAg+ recipients who require post-transplant HBV therapy regardless of their donor HBV status. Appropriate antiviral suppressive therapy has prevented HBV recurrence in 8 recipients at a median follow-up of approximately 2 years.⁹⁸

Viral hepatitis C—HCVAb+ donors account for 3% of the US deceased donor pool between 2007 and 2010. Because de novo HCV infection is essentially certain with transplantation of these grafts into HCV-naïve recipients, utilization of HCVAb+ livers is limited exclusively to HCV-viremic recipients.³⁵ UNOS/OPTN registry analysis has shown comparable patient and graft survival for recipients of HCVAb+ versus HCVAb– grafts from 1994 to 2008.^{99,100} Whether grafts from HCVAb+ donors are associated with more rapid HCV recurrence remains controversial. In 1 multicenter study of = US transplant centers, recipients of HCVAb+ (n = 99) compared with HCVAb– (n = 1107) liver recipients experienced a 58% increased risk of advanced fibrosis, defined as Ludwig-Batts stage 3 or 4 disease.²⁷ The increased risk of aggressive recurrent disease appears to be driven by

HCVAb+ donors older than 45 years (HR = 1.78, 95% CI, 1.10–2.88) but not by donors 45 years old or younger (HR = 1.34; 95% CI = 0.70–2.54).²⁷ In a multicenter European study, the mean [$\pm$ standard deviation (SD)] time to HCV recurrence was numerically faster but statistically similar between recipients of grafts from 63 HCVAb+ compared with 63 HCVAb– matched donors $\pm$ 12.8 months versus 13.4 ± 20 months [$P = .07$].¹⁰¹ However, when stratified by the liver's stage of fibrosis at the time of transplant, HCV recurrence occurred more rapidly in grafts with fibrosis stage 1 or greater versus no fibrosis ($P = .03$).¹⁰¹

Because donor HCV genotype is typically unknown at the time of donation, and HCV genotype 1 is the most common in the United States, transplantation with HCVAb+ grafts has traditionally been restricted to recipients with genotypes 1 or 4. This strategy avoids transmitting genotypes known to have lower sustained virologic response rates with antiviral treatment (1 and 4) into recipients with the more favorable genotypes 2 or 3. The approval of more effective and more tolerable direct-acting antiviral agents against all HCV genotypes may obviate this restriction in the near future.

Human immunodeficiency virus—In 2013, the passage of the HIV Organ Policy (HOPE) Act opened the doors to allow transplantation with organs from human immunodeficiency virus (HIV)-positive donors into HIV-infected recipients.¹⁰² This is anticipated to increase the number of organs available to HIV-infected recipients; evaluation of data from the Nationwide Inpatient Sample from 2005 to 2008 estimated that the pool of liver donors would increase by approximately 55 per year.¹⁰³ In addition, as the number of transplant centers that perform transplantation for HIV-infected recipients is currently limited, the HOPE Act may also encourage transplant centers to accept HIV-infected candidates for transplantation, thereby increasing access to HIV-infected individuals to transplant.¹⁰⁴

Centers for Disease Control and Prevention classification of donors at increased risk for infection transmission—The Centers for Disease Control and Prevention (CDC) has identified that certain donor characteristics are associated with an increased risk of transmission of HIV, HCV, and/or HBV (Box 1).¹⁰⁵ Although donors who meet one or more of these criteria are generally younger and have fewer medical comorbidities than those who do not meet any of the criteria,¹⁰⁶ unintended infection transmission is a significant public health concern. The prevalence of HIV and HCV among donors classified as at increased risk for infection transmission, adjusted for false-positive antibody test results, is 0.5% and 18.2%, respectively,¹⁰⁷ substantially higher than the 0.1% and 3.5% baseline prevalence among donors who are not classified as at increased risk.¹⁰⁷ From 2005 to 2007, when all solid organ donors were required to undergo testing for HIVAb and HCVAb,¹⁰⁵ there were 7 cases of donor-derived HIV infection from 3 donors and 9 cases of donor-derived HCV infection from = donors in the United States; eight of these transmissions resulted in active infection in the recipients, and 2 transmissions resulted in death.^{108,109}

Box 1**CDC guidelines for factors associated with an increased risk for recent HIV, HBV, or HCV infection**

1. People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
2. Men who have had sex with men (MSM) in the preceding 12 months
3. Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
4. People who have had sex in exchange for money or drugs in the preceding 12 months
5. People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
6. People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
7. A child who is less than 18 months of age and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection
8. A child who has been breastfed within the preceding 12 months, and the mother is known to be infected with, or at increased risk for, HIV infection
9. People who have injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
10. People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
11. People who have been newly diagnosed with, or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers in the preceding 12 months
12. People who have been on hemodialysis in the preceding 12 months

Data from Seem DL, Lee I, Umscheid CA, et al. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. *Public Health Rep* 2013;128:247–392.

In 2013, the CDC issued new guidelines recommending HCV nucleic acid testing (NAT) for all deceased donors and HIV NAT for those with at least 1 risk factor (see Box 1).¹¹⁰ Compared with serologic testing that requires a host's immune response to generate antiviral antibodies, NAT simply requires sufficient viral replication for viral nucleic acid to be detectable in the circulation. Because it is both more sensitive and specific, NAT significantly reduces the risk of transmission when donors have recently contracted HIV or HCV or have false-negative HIVAb or HCVAb results.^{111–114} The estimated risk of unintended infection transmission per 100,000 person-years from solid organ donors

classified at increased risk decreases from 8.5 (95% CI, 1.5–23.4) to 2.7 (95% CI, 0.5–7.4) for HIV and from 104.9 (95% CI, 56.8–170.8) to 10.5 (95% CI, 5.6–17.2) for HCV.¹⁰⁷ NAT cannot eliminate transmission risk completely, as there will always remain some time immediately after infection during which there is insufficient circulating viral nucleic acid to be detected by available assays.

Cancer—Donor tumor transmission through liver transplantation has been rare. The Israel Penn International Transplant Tumor Registry has reported 38 cases in liver transplant recipients between 1965 and 2003.¹¹⁵ In the United States, donor tumor transmission of neuroendocrine, pancreatic, adenocarcinoma, melanoma, and undifferentiated squamous cell carcinoma was documented in = liver transplant recipients between 1994 and 2000, representing 0.02% of all liver transplants¹¹⁶ and resulting in 2 deaths (neuroendocrine and melanoma). Four additional cases of donor-derived tumor transmission (hepatocellular carcinoma, lymphoma, small cell lung cancer, and melanoma [possible]) were reported in 2007.¹⁰⁸ In the United Kingdom, 15 (0.05%) reported cases of tumor transmission among 30,765 organ transplants from 2001 to 2010 resulted in a 20% mortality rate directly attributed to the donor-derived tumor.¹¹⁷

Tumor transmission in solid organ transplantation can occur and has occurred from donors with or without a history of malignancy. Acceptance of livers from donors with a known history of cancer—either current or past—is a challenging decision for both transplant surgeons and patients who must consider the estimated risk that the tumor cells have (micro)metastasized to or are within the circulation of the donor liver. At a minimum, thorough inspection of all organs at the time of organ procurement is essential with biopsy of any suspicious lesion(s).

In 2003, a diverse group of transplant experts convened to review the current understanding of tumors in transplantation and to make specific recommendations about the organ utilization from donors with a history of malignancy. At this symposium, tumors were classified by risk of post-transplant recurrence (**Table 1**).¹¹⁸ Glioblastoma multiforme, melanoma, choriocarcinoma, and lung cancer were determined to be absolute contraindications to organ donation.¹¹⁸ With respect to central nervous system tumors, in addition to glioblastoma multiforme, whose aggressive biology disrupts the blood–brain barrier, ventriculo-peritoneal shunting and invasive surgical procedures represent risk factors for tumor transmission through transplantation.^{119,120} For common cancers such as breast and colon cancers, although advanced-stage disease (colon cancer stage T3 or breast cancer T1c) was considered an absolute contraindication, early stage disease may be permissible for donation, depending on the exact tumor stage and the disease-free interval (**Table 2**).¹¹⁸

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KEY POINTS

- The expanded criteria donor graft connotes an organ with characteristics associated with suboptimal transplant outcomes that fall into 2 categories of risk: (1) graft dysfunction and (2) disease transmission.
- Graft characteristics associated with increased risk of graft dysfunction include older donor age, donation after cardiac death, large droplet steatosis, prolonged cold ischemia time.
- Donor characteristics associated with increased risk of disease transmission include positive hepatitis B core antibody, positive hepatitis C antibody, behaviors known to be associated with increased risk of human immunodeficiency virus, hepatitis B or C infection, and known history of malignancy.

Fig. 1.

Graft survival by donor age categories in patients infected with (A) chronic hepatitis C and (B) without chronic hepatitis C. The proportion of organ recipients for each donor age category is shown in parentheses. (*Adapted from* Lake JR, Shorr JS, Steffen BJ, et al. Differential effects of donor age in liver transplant recipients infected with hepatitis B, hepatitis C and without viral hepatitis. *Am J Transplant* 2005;5(3):549–57; with permission.)

Fig. 2.

(A) Macrovesicular fat, both large and small droplet. Large droplet (*arrows*) refers to fat globules that occupy greater than one-half of the hepatocyte, whereas small droplet (*arrowheads*) refers to fat globules that occupy less than one-half of the hepatocyte. (B) Microvesicular steatosis describes very small, uniform fat globules packed within hepatocytes giving the cytoplasm a characteristic foamy appearance. (*Courtesy of L. Ferrell, MD, University of California, San Francisco, San Francisco, California.*)

Table 1

Risk of post-transplant recurrence of pre-existing malignancy

Risk Group	Tumor Type	Patients (n)	Patients Treated >5 y Prior to Transplantation (%)	Overall Recurrence Risk (%)
Low	Incidental renal cell carcinoma (RCC) ^a	72	0	1
	Uterine	26	50	4
	Testicular	43	58	5
	Cervical	93	54	6
	Thyroid	54	38	7
Moderate	Lymphoma	37	76	11
	Wilm	78	33	13
	Prostate	33	34	18
	Colon	53	42	21
High	Breast	90	51	23
	Symptomatic RCC	222	22	27
	Bladder	55	22	29
	Sarcoma	17	24	29
	Skin	125	11	53

Data from Feng S, Buell JF, Chari RS, et al. Tumors and transplantation: the 2003 Third Annual ASTS State-of-the-Art Winter Symposium. Am J Transplant 2003;3(12):1481–7.

^aRefers only to tumors incidentally discovered at time of bilateral nephrectomy before or concurrent with renal transplantation.

Table 2

Recommendations for utilization of organs from donors with a history of early stage colon and breast cancer

Cancer/Stage	Specific Characteristics	Survival	Recommended Disease-Free Interval
Colon/0 = CIS		5 y: 99%–100%	0
Colon/1 = T1/T2	Caucasian male	5 y: >95%	>1 y
Colon/1 = T1/T2	Caucasian female	5 y: 90%–95%	>5 y
Colon/1 = T1/T2	African American male	5 y: <90%	Never
Breast/0 = CIS	High risk ^a = comedo histology, extensive or high-grade disease	5 y: 99%–100%	0
Breast/1 = T1a ^b or T1b ^c		10 y: 91%	10 y
Breast/T1 = 1c ^d		10 y: 78%	Never

Data from Feng S, Buell JF, Chari RS, et al. Tumors and transplantation: the 2003 Third Annual ASTS State-of-the-Art Winter Symposium. Am J Transplant 2003;3(12):1481–7.

^a Presence of these high-risk characteristics may increase risk of nodal disease from less than 1% to approximately 2%.

^b 0.1 cm < Tumor < 0.5 cm.

^c 0.5 cm < Tumor < 1.0 cm.

^d 1.0 cm < Tumor < 2.0 cm.