Prevention and Management of Donor-transmitted Cancer After Liver Transplantation: Guidelines From the ILTS-SETH Consensus Conference

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Abstract. As with any other intervention in health, liver transplantation (LT) entails a variety of risks, including donor-transmitted cancers (DTCs). At present, 2%–4% of used deceased organ donors are known to have a current or past history of malignancy. The frequency of DTCs is consistently reported at 3–6 cases per 10 000 solid organ transplants, with a similar frequency in the LT setting. A majority of DTCs are occult cancers unknown in the donor at the time of transplantation. Most DTCs are diagnosed within 2 y after LT and are associated with a 51% probability of survival at 2 y following diagnosis. The probability of death is greatest for DTCs that have already metastasized at the time of diagnosis. The International Liver Transplantation Society-Sociedad Española de Trasplante Hepático working group on DTC has provided guidance on how to minimize the occurrence of DTCs while avoiding the unnecessary loss of livers for transplantation both in deceased and living donor LT. The group endorses the Council of Europe classification of risk of transmission of cancer from donor to recipient (minimal, low to intermediate, high, and unacceptable), classifies a range of malignancies in the liver donor into these 4 categories, and recommends when to consider LT, mindful of the risk of DTCs, and the clinical condition of patients on the waiting list. We further provide recommendations to professionals who identify DTC events, stressing the need to immediately alert all stakeholders concerned, so a coordinated investigation and management can be initiated; decisions on retransplantation should be made on a case-by-case basis with a multidisciplinary approach.

(*Transplantation* 2022;106: e12–e29).

INTRODUCTION

Liver transplantation (LT) has altered the natural history of end-stage liver disease and is now the most effective therapy for a number of acute and chronic liver diseases. In 2019, 35 784 liver transplants were reported by 70 countries to the Global Observatory on Donation and Transplantation.[1] LT provides benefits in terms of lifespan and quality of life.[2,3] As with any other intervention in health, LT entails a variety of risks, including the transmission of diseases from donor to recipient.

Donor-transmitted cancers (DTCs) must be differentiated from donor-derived cancers (DDCs). In DTC, the cancer is present in the graft at the moment of transplantation, whereas in DDC, the cancer is not present in the graft at transplantation but develops from transplanted donor cells thereafter (eg, a hepatocarcinoma in a liver graft several years after the transplant). Although the first implies a risk shared among all recipients of organs from the same donor, this is not the case in DDCs. Though conceptually different, the distinction between the 2 may be challenging in daily practice. In this article, we focus on DTC.

The frequency of DTC is reported to be low in solid organ transplantation. This frequency may increase as donor age expands. The need to expand the donor pool

Received 29 June 2021. Revision received 30 September 2021.

Accepted 19 October 2021.

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All authors contributed to research design, performance of research, data analysis, and writing of the article. B.D.-G., F.D., K.M., and C.W. performed a critical review of the article. All authors approved the final version of the article.

The authors declare no funding or conflicts of interest.

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ISSN: 0041-1337/20/1061-e12

DOI: 10.1097/TP.0000000000003995

also entails better characterization of the risk of DTC through transplantation and avoidance of unnecessary loss of organs whenever a donor cancer is identified. In addition, improvements in the treatment of cancer may lead to increasing numbers of potential donors who have survived after being diagnosed with a type of cancer traditionally associated with a poor prognosis.

DTC has devastating consequences from a number of perspectives: the health of patients concerned, the mental well-being of professionals involved (second victims), and the reputation of the transplantation program (third victim). It is essential to adopt procedures for proper characterization and evaluation of potential donors with regard to malignancy. Such procedures may vary depending on whether the donor is deceased or living, because in deceased donation, the diagnostic opportunities are limited by time constraints. Donor characterization, which involves interventions before, during, and after organ recovery, allows individual assessment of the risk of DTC. Such risk will depend on a number of factors and will need to be balanced against the risk of patients dying or deteriorating on the waiting list (WL). Although some donor cancers are associated with a minimal risk of transmission and would be acceptable for any patient on the liver WL, cancers considered to bear a high risk of transmission may only be acceptable for recipients with an imminent risk of death or breaching suitability criteria or may not be acceptable for donation at all (eg, metastasized cancers).

Finally, clinicians may need to care for patients at risk of DTC or who have developed DTC. Management of these patients must be part of concerted actions taken by the different stakeholders concerned, along with those responsible for alerting others and initiating investigation and management.

In this International Liver Transplantation Society–Spanish Society of Liver Transplantation (ILTS-SETH) Consensus Conference working group, we analyze (1) the epidemiology of DTC in LT, (2) the procedures to characterize and evaluate liver donors with regard to the risk of DTC and the criteria to assess the risk of transmission, (3) the specificities in the characterization and evaluation of the living liver donor, (4) the risk of DTC in LT for different cancer types, and (5) the management of DTC events.

The final recommendations resulting from this Consensus Conference working group are displayed in Table 1. The aim of these recommendations is to provide guidance for the prevention and management of DTC in LT. The methodology of the Consensus is reviewed in detail in the introductory article.[4]

TABLE 1.

2021 ILTS-SETH Recommendations on donor-transmitted cancers in liver transplantation

1. Epidemiology of donor-transmitted cancer in liver transplantation	
1.1. Patients waitlisted for LT should be informed of the low but nonzero risk of DTC. They should be informed of the possibility of receiving LT from a donor with a known history of cancer and the likelihood of transmission vs the risk of death on the WL. This information should be provided periodically, attending to the clinical status of the patient on the WL, because the decision to receive LT from a donor with cancer may change over time. When accepting such an organ, documentation of risk–benefit analysis should be provided.	Strength of recommendation: strong; quality of evidence: low
1.2. To enable a realistic estimation of the risk of DTC and better understand the implications of DTC, it will be essential to: (1) include detailed donor cancer data in national registries; (2) establish robust national biovigilance systems to properly compile information on cancers identified in the donor and on suspected and confirmed cases of DTC; and (3) define a basic data set and link international data while respecting the sensitivity of the reported data.	Strength of recommendation: strong; quality of evidence: low
2. Minimization of the occurrence of donor-transmitted cancer in liver transplantation	
2.1. A careful review of the clinical history should be performed, and a complete and careful physical examination should be conducted in every potential donor to identify a past or present malignancy.	Strength of recommendation: strong; quality of evidence: low
2.2. All potential donors must undergo conventional laboratory tests to check for specific diseases that may bear a risk of transmission.	Strength of recommendation: strong; quality of evidence: low
2.3. Universal determination of tumor markers is not recommended given the risk of false-positive results that may lead to the unnecessary loss of otherwise suitable potential liver donors.	Strength of recommendation: weak; quality of evidence: low
2.4. β-HCG levels should be determined in women of childbearing age who die as a result of an unexplained intracranial hemorrhage.	Strength of recommendation: strong; quality of evidence: low
2.5. All radiological examinations that have been performed during the admission of the potential donor to the hospital must be reviewed. At the time of donation, a chest X-ray and an abdominal ultrasound are recommended.	Strength of recommendation: strong; quality of evidence: low
2.6. Other imaging, such as CT, may be indicated in selected cases (high suspicion of cancer, risk factors, and history of cancer).	Strength of recommendation: strong; quality of evidence: moderate
2.7. Tumors or intracranial metastases in donors with intracranial bleeding should always be excluded, especially if there is no history of high blood pressure or arteriovenous malformations.	Strength of recommendation: strong; quality of evidence: low
2.8. Any malignancy in the donor history should be properly documented based on written reports.	Strength of recommendation: strong; quality of evidence: low
2.9. Any suspicious lesions, found during or after organ recovery, should be analyzed immediately through frozen sections, preferably by an expert pathologist.	Strength of Recommendation: strong; quality of evidence: low

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TABLE 1. (Continued)

2021 ILTS-SETH Recommendations on donor-transmitted cancers in liver transplantation

2.10. It is crucial to stratify donor risk to guide decisions and adequately inform potential recipients and their legal representatives.	Strength of recommendation: strong; quality of evidence: low
2.11. Allocation of livers from donors with a past or present history of malignancy should be based on an individualized risk–benefit analysis, considering the risk of transmission vs the risk of death or drop-out from the WL in the following days or weeks.	Strength of recommendation: weak; quality of evidence: low
3. Special considerations for the living liver donor with regard to donor-transmitted cancer	
3.1. Living liver donor candidates should undergo cancer screening consistent with updated clinical practice guidelines that are in accordance with the donor candidate's age, sex, and ethnicity, as well as with family and personal history.	Strength of recommendation: strong; quality of evidence: moderate
3.2. Living liver donors should ideally be subject to lifelong follow-up as a standard of care for their own well-being, but also to identify any event that may place the recipient at risk of developing a DTC.	Strength of recommendation: strong; quality of evidence: low
3.3. Donor candidates with any history of cancer should usually be excluded from donation. In some recipients for whom no other donor candidates are available (eg, medical urgency, logistic reasons), they might be acceptable under strict criteria: (1) the risk of transmission or recurrence is low, which can only be determined by complete histopathological cancer staging with sufficient recurrence-free period depending on the type of tumor; and (2) prior treatment of malignancy does not significantly increase the operative risk of hepatectomy.	Strength of recommendation: strong; quality of evidence: low
3.4. In general, donor candidates with active cancer should be excluded from donation. In some recipients where no other donor candidates are available (eg, medical urgency, logistic reasons), they might be acceptable under strict criteria: (1) the risk of transmission or recurrence is low; and (2) there is a clear management plan (either concurrent with donation or sequential) that does not predispose the donor to an increased risk of hepatectomy or lower the chance of cure.	Strength of recommendation: strong; quality of evidence: low
4. Risk of donor-transmitted cancer in liver transplantation for different cancer types	
4.1. In situ carcinomas	
• Most in situ carcinomas are associated with a minimal risk of transmission through LT.	Strength of recommendation: strong; quality of evidence: low
• High-grade in situ carcinomas of breast, colon, and lung and in situ melanoma are considered to have a low to intermediate risk of transmission through LT.	Strength of recommendation: strong; quality of evidence: low
4.2. Breast cancer	
• Liver donation in the context of newly diagnosed breast cancer poses an unacceptable risk.	Strength of recommendation: strong; quality of evidence: low
• Breast cancer stage 1A (T1, N0)[5] with curative surgical treatment and >5 y of disease-free survival is associated with a low to intermediate risk of transmission through LT.	Strength of recommendation: strong; quality of evidence: low
• In other cases of invasive breast cancer, with curative treatment and complete remission of >5 y, liver donation might be accepted for selected recipients, depending on the initial stage and E/P and HER2/neu+ receptor expression. The possibility of late metastases must be taken into consideration.	Strength of recommendation: strong; quality of evidence: low
• All other tumor stages are associated with a high risk of transmission regardless of the disease-free interval.	Strength of recommendation: strong; quality of evidence: low
4.3. Colorectal cancer	
• The risk of lymph node and distant metastases is difficult to assess at organ recovery. pT1 tumors can be considered for highly selected recipients assuming a high risk of transmission, particularly in the case of LT. Donors with higher stages of newly diagnosed colorectal cancer should be considered an unacceptable risk of transmission in LT.	Strength of recommendation: strong; quality of evidence: low
• pT1/pT2 colorectal cancer without lymph node or distant metastases, after adequate treatment and disease-free interval >5 y can be considered of low transmission risk in LT. This risk increases with stage and shorter disease-free intervals.	Strength of recommendation: strong; quality of evidence: low
4.4. CNS neoplasia	
• WHO 1 and 2 CNS tumors are considered of minimal risk of transmission through liver transplantation.	Strength of recommendation: strong; quality of evidence: moderate
• The transplantation of livers from donors with a WHO 3 CNS tumor can be considered of low transmission risk (~1%). This risk is raised to intermediate by the presence of a ventricular shunt.	Strength of recommendation: strong; quality of evidence: moderate
• The transplantation of livers from donors with a WHO 4 CNS tumor should be considered of intermediate risk of transmission (2%–10%). The presence of a ventricular shunt raises the risk.	Strength of recommendation: strong; quality of evidence: moderate

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TABLE 1. (Continued)

2021 ILTS-SETH Recommendations on donor-transmitted cancers in liver transplantation

4.5. Lung cancer	
• A patient with active lung cancer bears an unacceptable risk of transmission through LT.	Strength of recommendation: strong; quality of evidence: low
• Liver donors with a previous history of lung cancer are assumed to be associated with a high transmission risk. This may decrease with an increasing disease-free interval.	Strength of recommendation: strong; quality of evidence: low
• Livers from donors with a history of lung carcinoma should only be accepted with a high level of caution, taking into account the histological type of lung cancer and the disease-free interval, and after discussion of the transmission risk and consequences with the recipient, balanced against the risk of death on the WL.	Strength of recommendation: strong; quality of evidence: moderate
• Early stages may be acceptable after adequate therapy and a disease-free interval of at least 5, better 10 y. A patient with metastatic disease is unacceptable for donation.	Strength of recommendation: strong; quality of evidence: low
4.6. Prostate adenocarcinoma	
• Donors with intraprostate carcinoma (≤pT2) Gleason score ≤6 should be considered as minimal risk of transmission, Gleason score 7 as low to intermediate and Gleason score >7 as high risk of transmission.	Strength of recommendation: strong; quality of evidence: low
• Donors with extraprostatic extension should be considered as unacceptable risk of transmission.	Strength of recommendation: strong; quality of evidence: low
• Donors with a past history of prostate cancer ≤pT2 Gleason score ≤6 might be considered as minimal risk if they received curative treatment (or were under active surveillance) and were regularly followed for this tumor.	Strength of recommendation: strong; quality of evidence: low
• Donors with a past history of prostate cancer of higher stages or grade require an individual risk assessment.	Strength of recommendation: strong; quality of evidence: low
• Only if previous PSA values are available, current PSA testing should be performed to check for possible progress or recurrence.	Strength of recommendation: strong; quality of evidence: low
4.7. Renal cell carcinoma	
• Risk of RCC transmission with LT is considered minimal in pT1a (<1 cm), low in pT1a (1–4 cm), and intermediate in pT1b (4–7 cm), always with Fuhrman grade I/II.	Strength of recommendation: strong; quality of evidence: moderate
• pT2 RCC (>7 cm, limited to the kidney) with Fuhrman grade I/II and pT1/pT2 RCC Fuhrman grade III/IV are considered to be of high transmission risk.	Strength of recommendation: strong; quality of evidence: low
• RCC with extension beyond the kidney (pT3, pT4, and N^+ or M^+) are considered a contraindication (unacceptable risk) for LT.	Strength of recommendation: strong; quality of evidence: low
• In potential deceased donors with a past history (<5 y) of adequately treated and followed RCC, risk categories correspond to those stated above (RCC diagnosed during donor procurement) if there is no suspicion of tumor recurrence in the donor. After these 5 y, the risk of advanced stages may decrease.	Strength of recommendation: strong; quality of evidence: low
5. Management of donor-transmitted cancer events	
5.1. In case of identifying a DTC event, all relevant stakeholders should be immediately alerted and the relevant health authorities or delegated bodies be notified to activate a collective and coordinated investigation and management of the case.	Strength of recommendation: strong; quality of evidence: low
5.2. Investigation of DTC entails: (1) review of donor characterization and procurement; (2) detailed characterization of the tumor and reassessment of the risk of DTC; (3) assessment of imputability, based on clinical history, histology, situation of other recipients at risk, and genetic studies.	Strength of recommendation: strong; quality of evidence: low
5.3. Recipients at risk of DTC should be informed and the message be balanced according to likelihood of transmission and aggressiveness.	Strength of recommendation: strong; quality of evidence: low
5.4. Staging in the recipient should include chest and abdomen CT or MRI, and PET.	Strength of recommendation: strong; quality of evidence: low
5.5. Retransplantation is not a guarantee of no tumor transmission and is questionable for tumors of low transmission risk.	Strength of recommendation: weak; quality of evidence: moderate
5.6. Efforts should be made to minimize immunosuppression with CNIs levels in the lower range.	Strength of recommendation: weak; quality of evidence: low
5.7. It is generally recommended to stop MMF or azathioprine, but this recommendation is not supported by clear evidence of lower risk of transmission or slower tumor progression.	Strength of recommendation: weak; quality of evidence: low
5.8. The efficacy of mTOR inhibitors in DTC is unknown but switching from CNIs to mTOR inhibitors is an option for their potential anticancer properties.	Strength of recommendation: weak; quality of evidence: low
5.9. Surveillance depends upon the nature of the tumor and likelihood of DTC. A total body CT is the easiest way to screen for DTC, particularly for malignancies with high risk of transmission. Screening beyond 5 y is only justified for aggressive tumors.	Strength of recommendation: strong; quality of evidence: low

AJCC, American Joint Committee on Cancer; CNI, calcineurin inhibitor; CNS, central nervous system; CT, computed tomography; DTC, donor-transmitted cancer; E/P, estrogen/progesterone; HCG, human chorionic gonadotropin; HER2, human epidermal growth factor receptor 2; ILTS-SETH, International Liver Transplantation Society-Sociedad Española de Trasplante Hepático; LT, liver transplantation; MMF, mycophenolate; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin; PET, positron emission tomography; PSA, prostate-specific antigen; RCC, renal cell cancer; WHO, World Health Organization; WL, waiting list; β-HCG, beta-human chorionic gonadotropin.

EPIDEMIOLOGY OF DONOR-TRANSMITTED CANCER IN LIVER TRANSPLANTATION

The frequency of DTC in solid organ transplantation and LT needs to be assessed on the basis of comprehensive registry data.[6] The Israel Penn International Transplant Tumor Registry was conceived to report cases of malignancies developing after transplantation, including DTC. As a voluntary registry, lacking appropriate denominators, the risk of DTC was likely overestimated in different reports.[7-8] Information on the risk of DTC is more robust when derived from mandatory registries, where both numerator and denominator are known, though they lack the granularity necessary to better understand the details of DTC cases. Bearing in mind these limitations, this section presents data obtained from registry studies and extracts information to assess the frequency of donors with cancer and that of cancers transmitted through solid organ transplantation and LT. A summary of this information is displayed in Table 2 (Organización Nacional de Trasplantes, unpublished data, 2020).[11-29] A recent systematic literature review identified a total of 92 LT recipients diagnosed with a DTC in 67 studies.[30]

The transplantation of organs from donors with a past or current history of neoplasia has become frequent, representing 2%–4% deceased donors. Most of these cancers are associated with a low transmission risk, given the histology or disease-free interval before organ recovery. Still, solid organ transplantation and LT procedures have been occasionally performed with organs obtained from donors with tumors traditionally considered of a high transmission risk (particularly World Health Organization [WHO] grades 3–4 central nervous system [CNS] cancers), with a low occurrence of DTCs. It is likely that, following a risk/benefit assessment, the decision was made to proceed with transplantation in this context with appropriate outcomes in most cases.

DTC does occur in solid organ transplant and LT recipients. The frequency of DTC is consistently reported at 3–6 cases per 10 000 transplants. The frequency in LT is similar. Most DTCs are occult cancers that had not been identified in the donor before transplantation. However, it is likely that there are many unpublished cases of DTC and that some may relate to human errors during donor workup before, during, or even after organ recovery.

According to the recent systematic review, most DTCs in LT are lymphomas, melanomas, and neuroendocrine tumors.[30] Different types of DTCs (eg, colorectal, lung) were identified in the review displayed in Table 2. DTCs are usually diagnosed during the first 2 y after transplantation.[30] The outcome of LT recipients with DTC is often fatal, with an overall survival probability of 55.7% and 51.8% at 1 and 2 y after diagnosis.[30] The probability of death is greatest for DTCs that have already metastasized at the time of diagnosis.[30]

The information described in this section on DTCs is flawed by the limited evidence available. To enable a realistic risk estimation for DTCs and better understand the risks of malignancy transmission, it will be essential to include detailed donor cancer data in national registries, establish accurate national biovigilance programs to properly manage, and compile information on malignancies identified in the donor and on suspected cases of DTCs, as well as to define a basic data set and link international data while respecting the sensitivity of the reported information.

HOW TO MINIMIZE THE OCCURRENCE OF DONOR-TRANSMITTED CANCER IN LIVER TRANSPLANT RECIPIENTS?

Minimizing the risk of DTC requires proper characterization of the organ donor. Donor characterization is a dynamic process that extends from the initial evaluation of the potential donor until after the transplantation of organs, because information from the donor may become available at any time point. Characterization is a multidisciplinary process that entails the collaborative participation of professionals caring for the potential donor, donor coordinators or staff of the organ procurement organization, procurement surgeons, and transplant teams.

Table 3 highlights critical elements of donor characterization.[6,31] Of note, the universal determination of tumor markers may lead to false-positive results and to the unnecessary loss of potential liver donors.[6] Where a donor with a previous malignancy had positive tumor markers, a new determination can help to assess the current situation. In women of childbearing age with a history of menstrual irregularities, miscarriages, or intracranial hemorrhage of unknown origin, beta-human chorionic gonadotropin levels may be determined to exclude choriocarcinoma.[32]

Routine computed tomography (CT) in potential donors is performed in certain jurisdictions. Although a CT may help to identify occult cancers in potential donors,[33] its real benefit is not well proven, and it increases the complexity of the donation procedure. On some occasions, CT may be necessary for more detailed evaluation of donors with risk factors or suspected active cancer, or in whom it is anticipated that adequate intraoperative examination of the thoracic/abdominal cavity will not be possible.[34]

Where a history of cancer is identified during donor characterization, detailed information should be obtained from existing clinical and histopathological reports. All information described should be properly documented. Information to be obtained includes date of diagnosis; detailed histological report, grade, and stage; treatment (type of surgery, radiotherapy, chemotherapy, others) and dates of treatment; follow-up (clinics, imaging tests, tumor markers) and dates; tumor recurrence and date; disease-free interval. The American Joint Committee on Cancer/Union for International Cancer Control TNM staging system was updated in 2018[5] and the WHO classification of CNS neoplasia was updated in 2016.[35] Therefore, the stage and grade of cancers diagnosed before 2017 might differ from current staging and classification systems.

Assessing the Risk of DTC

When a donor is diagnosed with an active or previous history of malignancy, the risk of DTC should be stratified to guide decision making and adequately inform potential recipients and their legal representatives. Knowing the theoretical risk of DTC helps to make a more approximate risk–benefit assessment, taking into consideration the clinical situation of recipients.

Several classifications of the risk of DTC have been proposed (Table 4).[6,36-38] The most recent, suggested by the Council of Europe, consciously omits any numerical estimation of the risk of DTC because of the limited evidence available.[6] Grading of risk, according to the Council of Europe classification but adapted to the LT setting, is

TABLE 2.

Summary of findings of donor-transmitted cancer in recipients of solid organs and of liver transplants based on registry studies

	All solid organs				Liver transplants		
Authors, y (period analyzed), country	**Donors with malignancy/ total donors**	**Reported transmissions/ resulting in death**	**Tumor transmission rate (transmissions/all recipients)**	**Transmitted tumors**	**Reported transmissions/ resulting in death**	**Tumor transmission rate (transmissions/ all recipients)**	**Transmitted tumors**
Chui et al, 1999 (1989–1996), only CNS neoplasia, Australia and New Zealand[11]	46/1781 Includes 28 high-risk tumors	0	0		0	0	
Kauffman et al, 2000 (1994–1996) United States[22]	257/14 795	0	0		0	0	
Kauffman et al, 2000 (1992–1999), only CNS neoplasia, United States[27]	397/42 340 Includes 19 high-risk tumors	0	0		0	0	
Pokorna and Vítko, 2001 (1986–1998) only CNS neoplasia, Czech Republic[12]	42/2048	0	0		0	0	
Birkeland and Storm, 2002 (1969–1996) Denmark[13]	13/626	1/1		Melanoma	0	0	
Kauffman et al, 2002 (1994–2001) United States[24]	13/34 933	15/6 All undetected in donor	0.01%	Adenocarcinoma, breast, lung, melanoma, neuroendocrine, oncocytoma, pancreas, papillary, prostate, small cell, undiff squamous	5/2		Adenocarcinoma, melanoma, neuroendocrine, pancreas, undiff squamous
Kauffman et al, 2007 (2000–2005) United States[25]	1069/39 455 Includes several high-risk tumors	4/4 Known in donor history	0.004%	Glioblastoma, melanoma	1/1		Glioblastoma
Garrido and Matesanz, 2008 (1990–2006), Spain[18]	117/20 016	10/7 All undetected in donor	0.06%	Germinal cell cancer, renal, sarcoma, undiff carcinoma	3/3	0.02%[a]	NA
Zucchini et al, 2008 (2002–2005), Italy[15]	114/4459 Includes 14 high-risk donors with malignancies identified after transplantation	0	0		0	0	
Watson et al, 2010 (1985–2001) only CNS neoplasia, United Kingdom[19]	177/11 799 Includes 33 high-grade tumors	0	0		0	0	
Desai et al, 2012 (2001–2010), United Kingdom[20]	NA/14 986	15/3 All undetected in donor	0.05%	Colon, lung, lymphoma, neuroendocrine, renal	2/1	0.03%	Colon, neuroendocrine

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TABLE 2. (Continued)

Summary of findings of donor-transmitted cancer in recipients of solid organs and of liver transplants based on registry studies

	All solid organs				Liver transplants		
Authors, y (period analyzed), country	Donors with malignancy/ total donors	Reported transmissions/ resulting in death	Tumor transmission rate (transmissions/all recipients)	Transmitted tumors	Reported transmissions/ resulting in death	Tumor transmission rate (transmissions/ all recipients)	Transmitted tumors
Moench et al, 2012 (2006–2011), Germany[14]	248/7483 Includes high-risk and unacceptable risk donors	13/7 All undetected in donor	0.05%	Breast, colorectal, neuroendocrine, renal	4/4	0.06%	Breast, colorectal, neuroendocrine
Desai et al, 2014 (1990–2008), England[21]	202/17 639 Includes 61 high-risk and unacceptable risk donors	0	0			0	
Eccher et al, 2019 (2006–2015), Italy[16]	415/11 271	10/9 All undetected in donor	0.03%	Intestinal, leukemia, lymphoma, undiff	4/4	0.04%[a]	Intestinal, leukemia, lymphoma, undiff
Hynes et al, 2017 (1994–2014), only CNS neoplasia and recipients of thoracic organs, United States[28]	NA/NA Histology available from 89 donors, including 5 glioblastomas and 1 gliomatosis cerebri	0	0				
Lee et al, 2020 (2005–2014), only CNS neoplasia, South Korea[17]	28/2804	0	0		0	0	
Kaul et al, 2020 (2008–2017), DTAC United States[29]	NA/NA	47/18	0.026%	Adenocarcinoma (unknown origin), hematological, Kaposi's sarcoma, liver, lung, melanoma, neuroendocrine, renal, urothelial, other	18/NA	0.026%[a]	Adenocarcinoma (unknown origin), hematological, Kaposi's sarcoma, liver, lung, melanoma, neuroendocrine, renal, other
ONT, 2020 (2013–2018), Spain (Organización Nacional de Trasplantes, unpublished data, 2020)	339/11 631 Includes 35 high-risk and unacceptable risk donors	16/9 All undetected in donor	0.06%	Cholangiocarcinoma, duodenal, lung, prostate, renal, undiff	6/3	0.09%	Cholangiocarcinoma, lung, prostate, undiff
Total		131/64 (49%)			43/18 (42%)		

[a]Denominators have been extracted from the Global Observatory on Donation and Transplantation (http://www.transplant-observatory.org).
CNS, central nervous system; DTAC, Disease Transmission Advisory Committee; NA, not available; ONT, Organización Nacional de Trasplantes; Undiff, undifferentiated.

TABLE 3.

Recommendations for the assessment and characterization of organ and liver donors with regard to malignancy

Assessment during donor evaluation	
Review of donor's clinical history	• Lifestyle habits (smoking behavior and harmful alcohol consumption). • Symptoms or signs that may suggest a malignancy (ie, involuntary weight loss or menstrual irregularities after pregnancy or miscarriages in women of childbearing age, which may be a sign of choriocarcinoma).
Documentation of any previous diagnosis of malignancy	• Date of diagnosis. • Detailed histological report, grade, and stage. • Treatment (type of surgery, radiotherapy, chemotherapy, others) and dates of treatment. • Follow-up (clinics, imaging tests, tumor markers) and dates. • Tumor recurrence and date; disease-free interval.
Complete and careful physical examination	• Detailed exploration of the skin (current lesions and scars of previous surgical procedures). • Excision and histopathological examination of any suspicious lesion. • Careful examination of donor scars that may provide insight into prior treated malignancies and alert professionals about further investigation.
Conventional laboratory tests	• May raise suspicion about an active malignancy.
Tumor markers	• In case of a known malignancy in the donor's history and previous information available on tumor markers, new determination to assess the current situation. • β-HCG levels in women of childbearing age with a history of menstrual irregularities, miscarriages, or intracranial hemorrhage of unknown origin.
Image tests	• Review radiological exams performed during the admission of the potential donor to the hospital. • Chest X-ray and abdominal ultrasound (particularly in donors with a previous history of hepatitis B or C infection even without cirrhosis, alcoholic or nonalcoholic liver steatosis, genetic hemochromatosis, and in those with cirrhosis, to exclude a hepatocarcinoma) are recommended, if possible. • CT in selected cases.
Assessment during organ recovery	
• Full exploration of the thoracic and abdominal cavities. • In the thoracic cavity, bimanual palpation of the lungs and esophagus, visual inspection of both the pericardium and mediastinal lymph nodes. • Inspection of the abdominal cavity, including the liver, stomach, colon, small bowel, and pelvis. • In women, inspection of the ovaries and uterus. • Special attention should be put on renal examination.	
Histopathological analysis	
• Analysis of any suspicious lesions or lymphadenopathy through frozen sections: - Ideally, by an expert pathologist. - Preferably refer the entire lesion with safety margins (eg, resection with curative intent in case of space-occupying lesions in the kidney). - Agree with the pathologist on the medium in which the sample should be sent (based on the estimated time of transport). - Immediately alert all transplant centers when a suspicious lesion is identified in the donor during or after organ recovery. - If the grafts have already been transplanted and histology reveals a malignancy other than small renal cell carcinoma, a complete autopsy of the donor should be requested whenever possible to obtain detailed information on the origin of the tumor and the degree of spread. • Full histology of intracranial space-occupying lesions before transplantation, whenever possible. Though neuroradiological diagnosis may be possible for some lesions, it is advisable to perform a histopathological assessment. If it is not possible, a risk–benefit evaluation must also be performed considering the likelihood and nature of malignancy vs the clinical condition of the patient on the WL. • Whenever a preliminary histopathological result is available and final results are pending or when an autopsy of the donor is performed, the final histopathological diagnosis and relevant findings should be promptly communicated to all transplant teams involved.	

CT, computed tomography; HCG, human chorionic gonadotropin; WL, waiting list; β-HCG, beta-human chorionic gonadotropin.

provided in Table 5 for a range of cancer types, either when identified in the donor history or when discovered during the donor workup.

According to the risk of DTC, LT may be considered subject to the clinical condition of patients on the WL:

- Minimal risk: livers from these donors can be allocated to any patient on the LT WL.
- Low to intermediate risk: allocation may be justified by the condition of the recipient, based on a risk–benefit analysis. This includes patients with hepatocellular carcinoma not responding to locoregional treatment,[39,40] recipients with model for end-stage liver disease (MELD) score ≥30,[41,42] and those who are estimated to have a high probability of death or drop-out from the WL in the following weeks.
- High risk: acceptance may be discussed in exceptional cases and for some life-saving LT procedures in the absence of any other therapeutic options on a case-by-case basis, after careful and reasonable risk–benefit assessment and with the informed consent of the patient. This includes patients with acute liver failure, particularly if no other organ is expected within 48 h,[43] MELD ≥40,[41,42] acute-on-chronic liver failure grade 3 regardless of MELD,[44] and those who are estimated to have a high probability of death or drop-out from the WL in the following days or weeks.

TABLE 4.

International recommendations for the assessment of transmission risk of donor malignancies

DTAC/United States 2011[36]	SaBTO/United Kingdom 2020[37]	CNT/Italy 2015[38]	Council of Europe[6]
No significant risk		Standard risk	
Minimal risk (<0.1%)	Minimal risk (<0.1)	Nonstandard-negligible risk	Minimal risk: donor acceptable for all organs and all recipients
Low risk (0.1%–1%)	Low risk (0.1%–2%)	Nonstandard acceptable risk	Low to intermediate risk: donor acceptable, justified by the specific health situation of the recipient or the severity of their clinical condition, based on a risk–benefit analysis
Intermediate risk (1%–10%)	Intermediate risk (2%–10%)		
High risk (>10%)	High risk (>10%)		High risk: acceptance may be discussed in exceptional cases and for some life-saving transplantation procedures in the absence of any other therapeutic options on a case-by-case basis, after careful and reasonable risk–benefit assessment, and with the informed consent of the patient
	Absolute contraindication	Nonstandard unacceptable risk	Unacceptable risk: absolute contraindication because of active malignancy or metastatic disease
Unknown risk (not equivalent to absolute contraindication)			

CNT, Centro Nazionale Trapianti; DTAC, Disease Transmission Advisory Committee; SaBTO, Advisory Committee on the Safety of Blood, Tissues, and Organs.

TABLE 5.

Summary of findings of donor-transmitted cancer in recipients of solid organs and of liver transplants based on registry studies

Cancer diagnosed during donor procurement or recently diagnosed

Minimal	Low to intermediate	High	Unacceptable
• Basal and squamous cell carcinoma of the skin • In situ carcinomas (cervix, low-grade breast, vocal cord, PanIn) • Nonmuscle-invasive urinary bladder cancers, in situ urothelial (pTis) and intraepithelial papillary, urothelial carcinoma (pTa/G1–2) • Prostate cancer small intraprostatic, low-grade (Gleason score ≤6) • RCC <1 cm (stage T1a) and Fuhrman grade I/II • Thyroid solitary papillary carcinoma <0.5 cm and minimally invasive follicular carcinoma <1 cm • CNS neoplasia WHO grades 1/2	• In situ high-grade breast, colon, lung, melanoma/lentigo maligna • Small (<2 cm) GIST of the stomach or duodenum and <5 and mitotic count • Prostate cancer intraprostatic Gleason score 7 • RCC 1–4 cm (stage T1a) and Fuhrman grade I/II—low risk • RCC >4–7 cm (stage T1b) and Fuhrman grade I/II—intermediate risk • Thyroid solitary papillary carcinoma 0.5–2 cm and minimally invasive follicular carcinoma 1–2 cm—intermediate risk • CNS neoplasia WHO grade 3—intermediate risk–low risk (risk increases with VP or VA shuts, previous resection, or chemo/radiotherapy) • CNS neoplasia WHO grade 4—intermediate risk (risk increases with VP or VA shunts, previous resection, or chemo/radiotherapy)	• Colorectal cancer pT1 • GIST from other primary sites than stomach or duodenum, of size >2 cm or high mitotic count • Prostate cancer intraprostatic, Gleason score >7 • RCC >7 cm (stage T2) and Furhman grade I/II • RCC Fuhrman grade III/IV	• Choriocarcinoma • Colorectal cancer beyond pT1 • Newly diagnosed invasive breast cancer • Any newly diagnosed lung cancer independent of histology • Kaposi's sarcoma, Merkel cell carcinoma, and skin sarcoma • Melanoma • Esophageal, gastric, pancreatic, liver, and biliary cancers • Oropharyngeal cancer • Ovarian cancer • Prostate cancer with extraprostatic extension • Neuroendocrine carcinomas • RCC with extension beyond the kidney (stages T3/T4) • Sarcoma • Thyroid medullary and anaplastic cancers • Leukemia, lymphoma, and plasmocytoma • Primary cerebral lymphoma • Any metastasized tumor

(*Continued next page*)

TABLE 5. (Continued)

Summary of findings of donor-transmitted cancer in recipients of solid organs and of liver transplants based on registry studies

Cancer in donor history

Minimal	Low to intermediate	High	Unacceptable
• Basal and squamous cell carcinoma of the skin • In situ carcinomas (cervix, low-grade breast, vocal cord, PanIn) • Non–muscle-invasive urinary bladder cancers, in situ urothelial (pTis) and intraepithelial papillary, urothelial carcinoma (pTa/G1–2) • Prostate cancer ≤pT2 (confined to prostate) and Gleason 3+3, and very small prostate cancers and Gleason 3+3 under active surveillance and nonsuspicious follow-up. • Prostate cancer ≤pT2 (confined to the prostate) and Gleason grade = 7 after curative treatment and cancer-free period >5 y • RCC <1 cm (stage T1a) and Fuhrman grade I/II[a] • Thyroid solitary papillary carcinoma <0.5 cm and minimally invasive follicular carcinoma <1 cm • CNS neoplasia WHO grades 1–2	• In situ high-grade breast, colon, lung, melanoma/lentigo maligna • Colorectal cancer pT1/pT2 tumors without lymph node or distant metastases after adequate treatment and disease-free survival >5 y. Risk increases with stage, and probability of presumed cure has to be taken into account. • Breast cancer stage 1A (AJCC, 8th edition) with curative surgery and cancer-free period >5 y • Small (<2 cm) GIST of the stomach or duodenum and mitotic count <5% (minimal risk depending on therapy, follow-up time, and recurrence-free survival) • RCC 1–4 cm (stage T1a) and Fuhrman grade I/II—low risk[a] • RCC >4–7 cm (stage T1b) and Fuhrman grade I/II—intermediate risk[a] • Thyroid solitary papillary carcinoma 0.5–2 cm and minimally invasive follicular carcinoma 1–2 cm—intermediate risk • CNS neoplasia WHO grade 3—intermediate risk–low risk (risk increases with VP or VA shuts, previous resection, or chemo/radiotherapy) • CNS neoplasia WHO grade 4—intermediate risk (risk increases with VP or VA shuts, previous resection, or chemo/radiotherapy)	• Invasive breast cancer after full treatment, complete remission, and stringent follow-up for >5 y • GIST from other primary sites than stomach or duodenum, of size >2 cm or high mitotic count • Lung cancer treated (risk may decrease after curative therapy, with recurrence-free time and with increasing probability of cure) • Melanoma treated (if precise donor data about staging, therapy, follow-up, and recurrence-free survival are available, and evaluation by the dermato-oncologist concludes there is a low probability of recurrence and metastases) • Esophageal, gastric, pancreatic, liver, and biliary cancers (risk may decrease for early stages after curative therapy, with recurrence-free time >5 y and with increasing probability of cure, especially in cases of long-term survivors) • Oropharyngeal cancer treated (risk may decrease for early stages after curative therapy, with recurrence-free time >5 y and with increasing probability of cure, especially in cases of long-term survivors) • Ovarian cancer treated (risk may decrease for early stages after curative therapy, with recurrence-free time >5 y and with increasing probability of cure, especially in cases of long-term survivors) • Neuroendocrine neoplasms treated • Prostate cancer with a history of extraprostatic extension • RCC >7 cm (stage T2) and Fuhrman I/II and RCC Fuhrman III/IV[a]	• Choriocarcinoma (high or unacceptable depending on the recurrence-free period) • Kaposi's sarcoma, Merkel cell carcinoma, and skin sarcoma • RCC with extension beyond the kidney (stages T3/T4)[a] • Sarcoma (risk may be considered high after curative treatment and a recurrence-free survival of >5 y) • Thyroid medullary and anaplastic cancers (may be considered with the highest caution for treated cases and after a long-term recurrence-free follow-up) • Leukemia, lymphoma, and plasmocytoma (risk may decrease in treated cases of acute leukemia and lymphoma after a definite disease-free interval >10 y) • Primary cerebral lymphoma • Any tumor with distant metastases

[a]Same risk than during procurement in the first 5 y after initial diagnosis. After this time, the risk of advanced stages may decrease.

AJCC, American Joint Committee on Cancer; CNS, central nervous system; GIST, gastrointestinal stromal tumor; PanIn, intraepithelial pancreatic neoplasia; RCC, renal cell carcinoma; VA, ventriculoatrial; VP, ventriculoperitoneal; WHO, World Health Organization.

SPECIAL CONSIDERATIONS FOR THE LIVING LIVER DONOR

The risk of DTCs in living donor liver transplantation (LDLT) has rarely been discussed. Uchiyama et al[45] reported a 59-y-old male donor who had undergone distal gastrectomy for early gastric cancer 17 y before live donation of left lobe including caudate. Dense adhesions around the hepatoduodenal ligament caused by lymph node dissection at the time of cancer surgery created technical difficulties during donor surgery. Fujiwara et al[46] described a 42-y-old female donor who was incidentally diagnosed with early gastric cancer during preoperative cancer screening.[46] She underwent simultaneous distal gastrectomy with lymph

node dissection and left lateral sectionectomy. The risks of liver metastases and circulating cancer cell migration to the liver graft were not null and the ethical issue of combining gastrectomy and hepatectomy in the donor was also taken into consideration.[47] Both donors were carefully selected on the basis of the assumption that there was a minimal risk of transmission to the recipient.

Donor evaluation in LDLT with regard to DTC should be based on the same principles as those in the deceased liver donation, with some advantages. First, information on any past history of cancer is obtained in first person (presumably more accurate than the third-person perspective in deceased donation). Second, donor candidates can undergo complete cancer screening and specific diagnostic tests if needed in the absence of time constraints, except for urgent cases of LDLT. Finally, any malignancy diagnosed during the follow-up of living donors and their recipients can be immediately checked, increasing the chance of early detection and treatment of cancer.

In alignment with clinical practice guidelines for living kidney donors,[48] a living liver donor candidate with a history of cancer should be avoided. If the potential recipient has no alternative donor, particularly in regions where deceased donor LT is not well developed, an individual risk–benefit assessment should be undertaken. The potential harms to the donor undergoing cancer screening and additional tests/procedures for cancer diagnosis and physical and psychosocial stress undergoing simultaneous (or sequential) treatment for cancer and liver donation, need to be carefully balanced with the prognosis of the recipient without LDLT under the double equipoise concept.[49,50]

Assessment of the risk of malignancy transmission for individual tumor types should be based on the same principles applied to deceased donation. Although livers from donors classified as minimal risk of malignancy transmission could be considered for any patient in need of a transplant, livers from donors classified as low to high risk can be considered suitable for specific recipients based on a careful risk–benefit analysis. It is important to keep in mind that the malignant potential of each tumor type may vary across countries, and therefore the classification in Table 5 needs to be applied flexibly. For example, colorectal cancer (CRC) and gastric cancer rank second and third of the most common cancers in some Asian countries, and their guidelines clearly document that early-stage CRC and gastric cancer that fulfill the criteria for endoscopic resection are considered curable diseases, and no additional treatment is indicated.[51,52]

THE RISK OF DONOR-TRANSMITTED CANCER IN LIVER TRANSPLANTATION FOR DIFFERENT CANCER TYPES

This section reviews the risk of DTC through LT for some selected cancer types. An overview of such risks for a broad range of cancers is provided in Table 5.

In Situ Carcinomas

No clear case of transmission of an in situ carcinoma has been reported in solid organ transplantation and LT, despite the use of organs from donors with this diagnosis has been described in the literature.[13]

Most in situ carcinomas, including in situ carcinoma of the cervix or cervical intraepithelial neoplasia III, vocal cord carcinoma, superficial papillary carcinoma of the bladder, and nonmelanoma skin carcinoma, are associated with a minimal risk of transmission.[6,36] Certain in situ carcinomas may be associated with a higher risk of transmission through LT, such as in situ breast, colorectal, and lung cancer and melanoma; therefore, proceeding with LT in the presence of a history of one of these in situ carcinomas requires careful balance of the low transmission risk with the condition of the potential recipient.[53,54]

In situ urothelial carcinomas and intraepithelial pancreatic neoplasms are associated with minimal risk to an LT recipient.[6,36]

Breast Cancer

Breast cancer is the most frequent cancer in females and is associated with the highest mortality.[55] Screening programs facilitate its early detection, and treatment has improved, so an increasing number of potential donors with a history of breast cancer will be encountered. Breast cancer has high potential for late and aggressive recurrence and metastases.

Registry studies have described the transplantation of organs from donors with a past history of breast cancer, with no DTC reported (Organización Nacional de Trasplantes, unpublished data, 2020).[13,14,21-23,25] It is likely that transplants from these donors were highly selected on the basis of careful assessment and long disease-free intervals.

Cases of donor-transmitted breast cancer have been described, usually concerning donors in whom breast cancer was unknown at the time of transplantation.[14,24,56] Matser et al[56] described the transmission of occult breast cancer by a single donor to 4 transplant recipients, including an LT recipient. This patient was diagnosed with a DTC limited to the liver graft 4 y after LT.

Dormancy in breast cancer is well known. Tumor cells can be inactive and occult for years, and metastases can appear metachronously. Therefore, in the case of potential donors with a history of breast cancer, liver donation should only be considered after appropriate treatment and follow-up and long disease-free intervals.[6] Histological information may help us to discriminate between tumors with favorable prognosis (eg, expression of estrogen/progesterone and human epidermal growth factor receptor 2/neu$^+$ receptor).[57,58] Stage 1 breast cancer[5] with curative resection and disease-free survival >5 y seems to be associated with a low to intermediate risk of transmission.[6] Imaging of potential donors with a history of breast cancer (eg, CT) looking for evidence of metastatic spread may be indicated before proceeding.

Colorectal Cancer

CRC is common in the population and a common cause of mortality.[55] The liver is the most frequent site of metastasis.[59] The transplantation of organs from donors with a known history of CRC has been reported with no evidence of transmission (Organización Nacional de Trasplantes, unpublished data, 2020).[13,14,20,60]

Occult CRCs have been transmitted through LT with differing results. There are 2 reports of retransplantation following the diagnosis of DTCs, with no evidence

of recurrence, albeit 1 recipient died soon after from an unrelated cause.[61,62] In contrast, 2 other LT recipients diagnosed with a donor-transmitted CRC were not retransplanted because of their poor clinical condition, both of whom died.[63,64] Transmission of CRC through the transplantation of solid organs including LT has also been reported in different registry studies.[14,16,20,29]

The Council of Europe stresses caution for the acceptance of donors with a recently diagnosed pT1 CRC because submucosal infiltration depth (sm1–3), lymphovascular invasion (L0–1), tumor budding, and microsatellite instability may influence the risk of lymph node and distant metastases.[6] All other stages of newly diagnosed CRCs and those identified during organ recovery are considered of unacceptable risk (and high risk by the American guidelines).[36] Donors with a history of CRC are considered high risk in both guidelines, with the exception of pT1 CRC after long periods of remission.

CNS Neoplasia

Primary CNS tumors rarely spread outside the brain and are present in 1%–2% of deceased organ donors. Nevertheless, spread does occasionally occur and there have been several reports of transmission to solid organ transplant including LT recipients. Decision making may be further confounded by the fact that many tumors in the brain represent secondary spread from outside the CNS, and many donors with CNS tumors have not had a biopsy performed at the time of death, but rather the diagnosis was based on radiological appearance alone.

The 2016 WHO classification of CNS tumors divides tumors according to their cell of origin (eg, astrocytes, oligodendrocytes) and grades tumors into 4 levels of aggressiveness (grade 1 being the least and grade 4 the most aggressive). By definition, all grade 4 tumors have vascular invasion and thus have breached the blood–brain barrier (Table 6).[35] Many lower-grade tumors may progress over time becoming higher grade (eg, an anaplastic astrocytoma [grade 3] becoming a glioblastoma). Tumors are now also classified according to molecular phenotype, although for the purposes of decision making in transplantation, it is sufficient to consider them in the broader category.

Estimation of risk of DTC from donors with CNS malignancy comes from analysis of the incidence of spread in nontransplant patients and transmission of tumors to transplant patients. CNS tumors do not exhibit dormancy, unlike melanoma for example, so it is likely that spread in a nontransplant patient equates to the risk of disease transmission.

Metastatic spread of CNS tumors is uncommon and is most likely with high-grade tumors such as medulloblastoma and glioblastoma.[65,66] All CNS tumors have a risk of extracranial spread following resection, but that risk remains low. Where spread does occur, it is typically at the craniotomy site in the scalp and its draining lymph nodes or along the track of a ventricular shunt.[65] In addition, the duration of the tumor has also been associated with increased likelihood of metastases, the suggestion being that rapidly progressing CNS tumors probably kill early and before they have time to spread.

Early reports based on data from the Israel Penn International Transplant Tumor Registry suggested a high transmission risk,[9] and some early reports used incorrect tumor grading nomenclature or assumed grades without histological confirmation.[9,67-69] Subsequent reports, where both numerator and denominator were known and WHO grading adopted, have suggested that the risk of transmission is much lower (Organización Nacional de Trasplantes, unpublished data, 2020).[11,12,17,19,25,27] A review of recent registry data is displayed in Table 7. Of >77 donors with grade 4 CNS tumors donating to >338 recipients (>34 liver recipients), there was only 1 that transmitted cancer, with 3 recipients affected.[25,26] It is likely that donors were highly selected; this cannot be determined from the reports. Similarly, the interval from tumor diagnosis to donation is unknown, nor is the use of shunts in most cases. Despite these favorable registry reports, there have been cases of CNS tumor transmission,[70-72] including 6 in LT recipients.[9,26,73-76]

Published guidance on the use of organs from donor with CNS tumors varies. Although the DTAC quoted transmission risk of >10%,[36] the Council of Europe considers grade 3 CNS cancer of high risk and of unacceptable risk in the presence of any additional risk factor.[6] Grade 4

TABLE 6.

World Health Organization grading of common neoplasia of the central nervous system

	Grade 1	Grade 2	Grade 3	Grade 4
Astrocytes and oligodendrocytes	Pilocytic astrocytoma	Diffuse astrocytoma, IDH mutant Oligodendroglioma, IDH mutant, and 1p19q co-deleted	Anaplastic astrocytoma, IDH mutant Anaplastic oligodendroglioma (IDH mutant and 1p19q co-deleted)	Glioblastoma (IDH mutant and wild type)
Ependymal tumors	Subependymoma	Ependymoma	Anaplastic ependymoma Ependymoma RELA fusion positive (grade 2 or 3)	
Embryonal tumors				Medulloblastoma Medulloepithelioma
Pineal tumors	Pineocytoma	Papillary tumor of pineal region		Pineoblastoma
Meningeal tumors	Meningioma	Atypical meningioma	Anaplastic meningioma	
Tumors of the sellar region	Craniopharyngioma Pituicytoma Granular cell tumor			
Mesenchymal tumors	Hemangioblastoma			

IDH, isocitrate dehydrogenase.

TABLE 7.

Registry data on donor-transmitted cancer in recipients of solid organs obtained from donors diagnosed with grade 4 neoplasia of the central nervous system

Authors, y (period analyzed), country	All CNS tumors and grade 4 tumors	Donor cancers	Outcome
Chui et al, 1999 (1989–1996) Australia & New Zealand[11]	Total number of CNS tumors	28 donors	96 recipients; no transmission
	Grade 4 tumors	4 glioblastoma 5 medulloblastoma	Number of recipients unknown
Pokorna and Vítko, 2001 (1986–1998) Czech Republic[12]	Total number of CNS tumors	41 donors	89 recipients; no transmission
	Grade 4 tumors	9 glioblastoma 2 medulloblastoma	27 organs transplanted, including 3 liver recipients; no transmission
Kauffman et al, 2000 (1992–1999), United States[27]	Total number of CNS tumors	397 donors	1220 recipients, including 293 liver recipients; no transmission
	Grade 4 tumors	17 glioblastoma 2 medulloblastoma	56 organs transplanted, including 15 liver recipients; no transmission
Kauffman et al, 2007 (2000–2005), United States[25]	Total number of CNS tumors	Number of donors not stated	642 recipients, including 179 liver recipients
	Grade 4 tumors	Number of donors with grade 4 tumors not stated	175 recipients; 1 transmission, to lung, liver, and 1 kidney recipient (nodal spread present at organ retrieval)
Watson et al, 2010 (1985–2001), United Kingdom[19]	Total number of CNS tumors	177 donors	448 recipients, including 73 liver recipients; no transmission
	Grade 4 tumors	24 glioblastoma 9 medulloblastoma 1 pineoblastoma	68 recipients, including 11 liver recipients; no transmission
Lee et al, 2020 (2005–2014), South Korea[17]	Total number of CNS tumors	17 donors	60 recipients, including 17 liver recipients; no transmission
	Grade 4 tumors	1 glioblastoma 1 medulloblastoma 1 mixed germ cell tumor	10 recipients, including 3 liver recipients; no transmission
ONT, 2020	Total number of CNS tumors	104 donors	279 recipients
(2013–2018), Spain (Organización Nacional de Trasplantes, unpublished data, 2020)	Grade 4 tumors	1 glioblastoma	2 recipients, including 1 liver recipient; no transmission

CNS, central nervous system; ONT, Organización Nacional de Trasplantes.

CNS cancers are deemed of unacceptable risk. In contrast, United Kingdom guidance quotes a 2.2% risk of transmission of grade 4 neoplasia.[77] None of the published guidance reflects the accumulating literature in Table 7.

There are 3 caveats in the use of organs from donors with CNS cancer:

- It is important to establish that the intracranial tumor is a primary CNS tumor.[78] In the absence of a biopsy, an expert neuroradiological opinion of cross-sectional brain imaging may reduce uncertainty.
- It is difficult to be sure that a primary cerebral lymphoma is truly a primary tumor, and donors with this diagnosis should not be used.
- The risk of dissemination of primary brain tumors where a ventriculoperitoneal or ventriculoatrial shunt has been performed is unknown but has been anecdotally reported to be high although most CNS tumor metastases occur in the absence of 1.[71] It is essential that the shunt track is carefully inspected and any craniotomy wound also inspected. Abnormal tissue should undergo histological examination before any organs are transplanted.

Lung Cancer

Lung cancer is the most common cancer in males and fourth common in females; it has a high mortality in both.[55,79] The proportion of patients who die with confirmed lung cancer metastases varies between histological subtypes.[80] The liver is one of the most frequent metastatic sites. At the time of diagnosis, 35% of patients who die have metastatic disease.

Transmission of lung cancer to LT recipients has been reported with fatal consequences in 2 cases, including 1 undergoing urgent transplantation when the adenocarcinoma was found on donor autopsy.[81,82] There are also reports of transmission in a number of registry studies (Organización Nacional de Trasplantes, unpublished data, 2020).[20,29,83-86] In contrast, there are several reports of donor lung cancer not being transmitted to LT recipients (Organización Nacional de Trasplantes, unpublished data, 2020).[20,29,60]

The Council of Europe Guide to the quality and safety of organs for transplantation considers that active lung cancer poses an unacceptable risk for transplantation. In the case of treated lung cancer in the donor history, transplantation

of organs and liver may be considered but assumed to be associated with a high risk of transmission. This risk may decrease with curative treatment, recurrence-free time, and probability of cure.[6] The American Guidelines make a similar assessment of the risk of transmission of lung cancer through solid organ transplantation and LT.[36]

Prostate Adenocarcinoma

Prostate adenocarcinoma is a frequent cancer in men, and its incidence increases with age.[87] Usually, prostate cancer shows a slow progression and high survival rates. In advanced stages, metastases are found primarily in bones and lymph nodes and also in lungs and liver.[88]

Prostate adenocarcinoma is classified according to the Gleason score, associated with significant differences in prognosis (higher scores/groups result in poorer outcomes) (Table 8).[87] Prostate-specific antigen is not considered a good marker for donor prostate cancer detection and is only a long-term marker for prognosis.[87,89,90]

There is only 1 reported case of transmission of a well-differentiated prostate adenocarcinoma through LT, detected in the right hepatic lobe 2 mo after transplant.[91] One further case of transmission of prostate carcinoma through solid organ transplantation has been reported, involving a heart recipient.[92] That donor had a poorly differentiated, metastasized prostate adenocarcinoma discovered during organ recovery. No abdominal organs were used, but the heart transplant was too far advanced to stop; the recipient died of donor-transmitted metastatic prostate cancer.

Incidental prostate cancer has been described in 0.5% of donors aged <50 y, the incidence increasing to 23% in donors aged 50–59 y, 35% in donors aged 60–69 y, and 45% in those aged >70 y.[93] As advanced age is no longer a contraindication to liver donation, it is certain that organs obtained from male donors with undiagnosed prostate cancer are regularly transplanted.

In addition, many papers have reported single-center experiences or registries including cases or small series of LT using donors with Gleason score ≤6 or Gleason score 7 without transmission of cancer to the LT recipients involved (Organización Nacional de Trasplantes, unpublished data, 2020).[14,16,21,60,94-99] A review published in 2014 collected 76 reported cases of LT from donors with prostate cancer without any case of DTC.[100] More recently, an Italian group reported their experience with 5 LTs from deceased donors with Gleason scores 8 and 9, without DTC.[97]

Due to the rarity of prostate cancer transmission with transplantation, there is no clear evidence that a specific detection policy in potential donors might be useful to decrease this risk. Indeed, an active detection policy could lead to an unnecessary loss of donor organs.

Renal Cell Carcinoma

The true incidence of RCC in deceased organ donors is probably <1%.[101,102] In the nontransplanted population, RCC incidence increases with age and metastases are mainly found in lungs, bones, and lymph nodes, whereas liver metastases are rare.[103,104]

There is no reported case of transmission of RCC through LT. Most reported RCC transmissions occurred in kidney, but transmission has also rarely been described after heart or lung transplantation.[8,105-107] The United Network for Organ Sharing reported no RCC transmission in a series of 198 recipients of nonrenal organs obtained from 147 donors with known RCC.[101] This large series confirmed previous United Network for Organ Sharing data,[24,25,86] smaller registries from the United Kingdom,[21] Spain,[18] Italy,[108,109] and single-center series.[60,95,97,110] Precise RCC staging was lacking in most of these reports, but it is likely that nonrenal organs were accepted when RCCs were diagnosed at an early stage or transplants were already being performed when information about the donor RCC became available.

The Council of Europe Guide classifies RCC based on the estimated risk of transmission, according to TNM stage[103] and nucleolar Fuhrman grading.[6] Regarding donors with a past history of RCC, there are no strong published guidelines to help in decision making.

MANAGEMENT OF DONOR-TRANSMITTED CANCER EVENTS

All suspected DTCs or malignancies identified in the donor after transplantation must be reported to all stakeholders including transplant centers caring for other recipients from the same donor and the donor center to activate a coordinated investigation and management plan. This includes assessing the likelihood that a malignancy derives from the donor, informing recipients at risk, and anticipating corrective measures; coordination will ideally be the responsibility of an oversight agency.[111,112]

Investigation of a DTC Event

Evaluation of an LT recipient with regard to DTC events depends on the clinical scenario. If a donor malignancy is identified in the immediate posttransplant period, evaluation and management may be based on the type of tumor and risk of transmission. In case of a suspected DTC in LT recipient, further characterization with CT or magnetic resonance imaging is warranted. Depending on imaging characteristics, biopsy versus serial imaging versus no further analysis in the case of a definitely benign lesion may be indicated.

TABLE 8.

Classification of prostate adenocarcinoma according to Gleason score

			Risk of recurrence
Group 1	Gleason score ≤6	(3 + 3)	Low risk
Group 2	Gleason score 7	(3 + 4)	Intermediate risk
Group 3	Gleason score 7	(4 + 3)	
Group 4	Gleason score 8	(4 + 4, 3 + 5, 5 + 3)	High risk (strongest histological predictors of aggressiveness and local or distant extension)
Group 5	Gleason score ≥9	(4 + 5, 5 + 4, 5 + 5)	

In most cases, DTCs occur within the first 12 mo after transplantation, though some DTCs have been diagnosed up to 5 y after LT.[30] Nonetheless, tumors arising >1 y after LT raise the issue of whether the tumor is of donor origin or de novo malignancy in the recipient. When the origin of the tumor is ambiguous, recipients of other organs from the same donor should be identified and investigated. Early malignancy with multiple metastases within the first month after transplantation is strongly suggestive of DTCs. Biopsy can be needed to make a distinction. Fluorescence in situ hybridization with identification of XX and XY pairs of chromosomes is an option in case of gender mismatch between donor and recipient. Microsatellite allelic analysis allows distinguishing cells from different individuals based on genetic polymorphism of repetitive sequences of DNA. Comparative genomic hybridization is another option to compare the genome that can also be performed on the basis of paraffin-embedded biopsy.[6]

Management of a DTC Event

Once the tumor has been characterized in the donor, the recipient should be informed about a possible risk of DTCs in a balanced manner, according to the risk of transmission and the aggressiveness of the tumor.

When the risk of DTCs is considered as high, removal of the transplanted organ and cessation of immunosuppression are only possible in kidney and pancreas transplant recipients. In LT, retransplantation is an option that does not always prevent transmission because circulating tumor cells may have already spread in the recipient.[82] Retransplantation is associated with significant morbidity and mortality[113-115] and should be considered in the context of organ shortage.

No guidelines exist on retransplantation in DTC events. Decisions should be made on a case-by-case basis with a multidisciplinary approach and after discussion with the patient or relatives. Retransplantation may be reasonably considered when the tumor identified in the donor is deemed of intermediate or high risk of transmission; by contrast, retransplantation is questionable for tumors at minimal or low risk of transmission (Table 5).

Management of Immunosuppression

In LT recipients at risk of DTCs, minimization of immunosuppression, whenever possible, is strongly recommended. Immunosuppressive agents used in solid organ transplantation trigger tumor development and accelerate growth of malignancy.[116-118]

Immunosuppression should not be completely discontinued because of a high risk of rejection with the need to restart immunosuppressive agents at higher doses. The approach should be similar to that of patients with de novo malignancy. Weaning from immunosuppression should only be considered late after transplantation and a gradual decrease is recommended.[119] Maintenance immunosuppression with low target levels of CNIs is recommended.[120] There is no evidence of an increased risk of tumor progression with a combination of mycophenolate (MMF) and CNIs compared with CNIs alone.[28,121,122] However, discontinuation of MMF has been recommended following a diagnosis of posttransplant lymphoproliferative disorder, in part to protect the bone marrow before any necessary chemotherapy.[123] Whether MMF should be discontinued in LT recipients at risk of malignancy transmission is still a matter of debate and not supported by clear evidence.

The place of mechanistic target of rapamycin (mTOR) inhibitors is also a matter of debate. On theoretical grounds, mTOR inhibitors could be attractive in recipients at risk of DTC as these agents have both immunosuppressive and anticancer properties.[124] For instance, everolimus has been approved for the treatment of advanced RCC, advanced neuroendocrine pancreatic tumors, and human epidermal growth factor receptor 2–negative breast cancer.[124] However, contrasting results have been reported on mTOR inhibitors in solid organ transplantation.

Overall, the benefit from mTOR inhibitors to prevent de novo malignancy or recurrence of malignancy in solid organ transplantation seems less than expected, albeit mTOR inhibitors are a safe option for immunosuppression, with or without reduced dose of CNIs.[125-129]

Practically, there are 2 approaches for maintenance immunosuppression with mTOR inhibitors consisting of (1) discontinuation of CNIs and switching to mTOR inhibitors (with or without antimetabolites) and (2) combination of mTOR inhibitors plus reduced-dose CNIs. Intuitively, mTOR inhibitors without CNIs may be the preferred option in patients at high risk of DTCs. The pros and cons for the use of mTOR inhibitors in recipients at risk of DTCs are summarized in Table 9. It is important to note that recommended doses of everolimus are markedly different for the treatment of malignancies than for immunosuppression in transplantation. Doses of 5–10 mg daily are recommended for the treatment of neuroendocrine tumors or RCCs compared with 0.75–1.25 mg twice daily

TABLE 9.

Switching from calcineurin inhibitors to mTOR inhibitors in liver transplant recipients at risk of donor-transmitted cancers: pros and cons

Pro	Con
Anticancer properties in vitro and in vivo	No clear evidence of lower rates of cancers other than nonmelanoma skin cancer after transplantation
Approved for the treatment of several malignancies	Contrasting results concerning the efficacy of mTOR inhibitors to prevent recurrence of HCC
Effective to prevent rejection in liver transplantation with reduced-dose CNIs or antimetabolites	No demonstrated efficacy to prevent donor-transmitted malignancy
Reduces the rate of recurrence of nonmelanoma skin cancer in solid organ transplant recipients	Substantial proportion of discontinuation of mTOR inhibitors after switching because of adverse events
	Higher rate of rejection with mTOR inhibitors alone
	Doses of mTOR inhibitors used in oncology markedly higher than those recommended in transplantation

CNI, calcineurin inhibitor; HCC, hepatocellular carcinoma; mTOR, mechanistic target of rapamycin.

in liver and kidney transplant recipients.[118] In addition, lifelong administration of mTOR inhibitors is needed for immunosuppression in transplantation, whereas the use of mTOR inhibitors to treat malignancies is sequential. There are no data on which protocol is best in LT recipients at risk of DTCs.

Surveillance of Recipients at Risk of DTCs

Most DTCs manifest during the first year after transplantation and during this period, screening should be considered in recipients at risk of DTCs. No guidelines exist on how and at which time intervals screening should be performed. The approach will need to be decided on a case-by-case basis, depending on the recipient's health, the donor's cancer type, its predicted aggressiveness, and therapeutic options.[130]

Total body CT seems the most effective tool for screening as (1) in the immunosuppressed recipient, DTCs can virtually involve any organ and (2) the accuracy of CT to detect small lesions is superior to that of magnetic resonance imaging. There is no evidence that positron emission tomography adds to CT in this context. In line with the timing of occurrence of DTCs, CT at 1, 2, 6, 9, and 12 mo after transplantation is suggested as an example.

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