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MINIREVIEWS

Genitourinary tumors and liver transplantation: A comprehensive review

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Abstract

Liver transplantation is as a crucial therapeutic option for patients with end-stage liver disease, but the persistent organ shortage emphasizes a need to explore unconventional donor sources, including individuals with a history of malignancies. This review investigates the viability of liver donation from individuals with current or past genitourinary malignancies, focusing on renal, prostate and urinary bladder cancers. The rising incidence of urogenital malignancies among potential donors is thought to result from increasing donor age. Analysis of transmission risks reveals low rates of donor-derived cancer transmission, particularly for early-stage renal and prostate cancers. Recipients with a history of genitourinary malignancy pose complex challenges regarding post-transplant immunosuppression and cancer recurrence. Nonetheless, the evidence suggests acceptable outcomes can be achieved with careful patient selection and tailored management strategies. Recommendations for pre-transplant evaluation and post-transplant surveillance are discussed, highlighting the need for individualized approaches in this patient population. Further prospective studies are warranted to refine guidelines and optimize outcomes in liver transplantation for patients with genitourinary malignancies.

Key Words: Liver transplantation; Genitourinary malignancies; Donor-transmitted cancer; Malignancy recurrence; Immunosuppression

Core Tip: While concerns of cancer transmission and recurrence exist, the evidence suggests that carefully selected donors and recipients may benefit from transplantation. Despite the heightened risk of post-transplant malignancy due to immunosuppression, early-stage urogenital tumors may not preclude transplantation, offering a life-saving option for eligible patients.

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INTRODUCTION

Liver transplantation (LT) is a life-saving intervention for patients with end-stage liver disease. Over the years, advances in surgical techniques and immunosuppressive therapies have significantly enhanced the survival rates of transplant recipients. However, a persisting disparity between organ supply and demand has resulted in significant mortality of patients on the waiting list. According to the Eurotransplant annual report of 2022, 1806 patients were delisted because of mortality or unsuitability for transplantation, underscoring the urgency of addressing the disparity[1]. This has prompted exploration of the viability of expanding the number of donors to include individuals with a current or history of malignant disease. Analysis of data from the Organ Procurement and Transplantation Network/United Network of Organ Sharing found four deaths from donor-transmitted malignancy between 2000 and 2005 compared to almost 40000 waitlist deaths[2]. A systematic review of the literature by Greenhall *et al*[3] of donor-transmitted cancer (DTC) in solid organ transplant recipients included 73 documented cases of DTC, with 51 occurring in liver recipients. Furthermore, the donor age has been increasing in the previous years. In the United States, 33% of donors are 50 years of age or older, as are more than 50% in some European countries[4]. Consequently, an increase in the prevalence of past or current occult malignancy in the donor population is to be expected[5]. On the other hand, current or recent malignancy in potential recipients was historically considered a contraindication for LT. Chronic immunosuppressive therapy following solid organ transplantation, especially the use of calcineurin inhibitors, is associated with an increased risk of initial or recurrent malignancy. Moreover, it is expected that malignant diseases will become the leading cause of death in this group of patients[6,7]. However, a meta-analysis by Acuna *et al*[8] showed that the risk of cancer recurrence in recipients with pre-transplant malignancy was considerably lower than it as in historical reports, with a pooled recurrence rate of 1.6 (95% confidence interval [CI]: 1.0-2.6) per 100 person-years for all studies. They also showed that the recurrence rate for liver recipients was lower (1.0 per 100 person-years, 95%CI: 0.4-2.6) than for kidney (2.4 per 100 person-years, 95%CI: 1.0-5.6) and cardiothoracic recipients (1.3 per 100 person-years, 95%CI: 0.6-2.7). The first studies in kidney transplant patients included in the Israel Penn International Transplant Tumor Registry led to recommendations to postpone transplantation for 2-5 years after curative malignancy treatment considering high rates of malignancy recurrence[9]. However, adherence to this recommendation may inadvertently exclude a subset of patients who urgently require LT. Unlike candidates for kidney transplantation who can remain on hemodialysis while awaiting transplantation, individuals with end-stage liver disease frequently face serious clinical deterioration that makes a delay in transplantation unfeasible. American and European Transplant Societies have suggested different waiting times depending on the type of malignant disease[10]. In the context of LT and malignant disease, it is imperative to address four distinct entities: (1) DTC, indicating malignancy existing within the allograft at the time of transplantation; (2) Donor-derived cancer, signifying malignancy originating from donor cells subsequent to transplantation; (3) *De-novo* cancer developing from recipient cells; and (4) Recurrent cancer, representing recurrence of a malignant disease for which the recipient was treated before transplantation. In this review, the emphasis is on urogenital malignancies within the framework of LT, particularly renal, prostate, and urinary bladder cancer. This includes consideration of potential recipients as well as donors with a present urogenital malignancy or a history of urogenital malignancy.

LIVER DONORS WITH GENITOURINARY MALIGNANCY

It has been projected that approximately 81610 kidney, 299010 prostate, and 83190 urinary bladder cancer cases will be newly diagnosed in the United States in 2024[11]. Considering this trend along with the aging demographic of donors, a concomitant rise in urogenital tumor incidence among potential liver donors is anticipated. According to Yin *et al*[12], incidental prostatic carcinoma has been reported in up to 20% of donors more than 50 years of age. In their retrospective

analysis, Skalski *et al*[13] identified 19 cases of prostate cancer (PCa) in a cohort of 72 men who were evaluated as potential liver donors. On the other hand, the incidence of renal cell carcinoma (RCC) in donors is expected to be much lower, probably < 1%[14]. Organ transplantation from donors with a prior or ongoing history of malignancy comprises 2%-4% of deceased donors[15]. A systematic review by Eccher *et al*[16] identified 67 publications documenting 92 cases of DTC in transplanted livers, with lymphoma, melanoma, and neuroendocrine tumors as the most commonly transmitted malignancies. In the context of RCC, an investigation by the United Network for Organ Sharing revealed an absence of RCC transmission within a cohort of 198 recipients of nonrenal organs obtained from 147 donors with known RCC[14]. Montalti *et al*[17] reported on 6 patients who underwent LT and received organs from donors with genitourinary cancer, 2 with renal and 4 with prostate carcinoma (Fuhrman grade up to 2, Gleason score 4-7). Four of the 6 died, but none from neoplastic disease. The mean follow-up was 12 ±8.1 mo, during which no evidence of transmission of donor malignancy was detected. A separate study by Benkö *et al*[18], described 24 cases of LT from donors with histories of genitourinary malignancy. Sixteen of the donors had a tumor-free interval of less than 5 years. None of the recipients developed donor-transmitted malignancy during a median follow-up of 19.9 mo. Similarly, Serralta *et al*[19] documented 6 cases of LT from donors with malignant genitourinary tumors, including 4 RCCs (T1-T2) and 2 PCas (Gleason 5). No evidence of tumor transmission was observed in any of the recipients over an average follow-up of 51 ± 20 mo. Hellström *et al*[20] identified 11 patients with urinary tract malignancies and 4 with RCC in a group of kidney transplant recipients from 1969 to 2014. Polymerase chain reaction of human leukocyte antigen genotypes and fluorescence *in-situ* hybridization determined that 3 of 10 urinary tract cancers and 3 of 4 RCCs in kidney transplant recipients were donor-derived. Literature on the transmission of urothelial carcinoma is far more scarce and is usually based on case reports or case series. Mitsuhata *et al* [21] described 3 cases of successful renal transplantation from living-related donors with lower ureteral cancer. All tumors had been excised prior to transplantation, had free margins, and were of low grade. All recipients survived without signs of DTC over a follow-up period of 109 mo. Mannami *et al*[22] described 8 kidney donors with ureteral cancers that were surgically removed prior to transplantation. There was only one transmission of ureteral cancer in the transplanted kidney 15 mo after surgery. Regarding PCa, a review published in 2014 by Doerfler *et al*[23] compiled 76 reported cases of LT from donors with PCa, yet none of these cases resulted in DTC. There is only one reported case of transmission of a well-differentiated prostate adenocarcinoma associated with LT, detected 2 mo after transplantation [24]. Moreover, although PCa with a Gleason score up to 7 is typically categorized as having a low to intermediate risk of recurrence, an Italian group reported their experience with five liver transplants from deceased donors with PCa and Gleason scores of 8 and 9. Despite the elevated Gleason scores, no cases of DTC were observed, with a median post-transplant patient and graft survivals of 5.6 years and 5.5 years, respectively[25]. A summary of recommendations regarding possible LT donors with history of or current genitourinary malignancy is shown in Table 1.

LIVER RECEPIENTS WITH CURRENT OR A HISTORY OF GENITOURINARY MALIGNANCY

Chronic immunosuppression following solid organ transplantation is linked to an elevated risk of malignancy development post-transplantation, with an incidence up to 20 times greater than that observed in the general population. These malignancies may manifest either as a *de-novo* occurrence or as the recurrence of a pretransplant malignancy[26]. The prognosis of many of these patients is compromised by the complex interaction of chemotherapeutic treatment and immunosuppression. Balancing the imperative to treat malignant disease with the potential risk of organ rejection poses a significant clinical challenge[27]. Active extrahepatic malignancy and a history of malignancy within 5 years of recurrence-free survival was considered as a contraindication for LT, with the exception of certain tumor subtypes such as basal cell carcinoma or early cervical carcinoma cured by surgical resection. According to the European Association for the Study of the Liver guidelines, LT may be considered acceptable if the risk of recurrence of the malignant disease is expected to be less than 10%. In line with this, a 5-year recurrence-free survival period is often cited as the optimal period before considering LT. However, it is important that they noted there are no definitive guidelines on this matter given the heterogeneous nature of the patient population. Consequently, decisions regarding LT in individuals with a history of malignancy must be made on a case-by-case basis[28]. In line with this are recommendations from American and European Transplant Societies for the waiting time until transplantation, which differ depending on the stage and type of malignancy[10,29]. During the pretransplant evaluation process, occult neoplasms of parenchymal organs, such as renal, prostate and urinary bladder are frequently detected. This raises the important question of whether candidates with these findings are appropriate for LT. The majority of incidental renal masses detected in potential LT recipients are typically ≤ 4 cm in size and predominantly consist of low-grade renal-cell carcinoma with minimal risk of extrarenal spread[30]. While the conventional approach for treating such tumors involves surgical resection, namely nephrectomy, experience with patients suffering from end-stage renal disease have demonstrated elevated perioperative morbidity and mortality rates if the procedure is done before transplantation. As a result, it has been recommended that nephrectomy be delayed for 3-6 mo after transplantation[31]. Similar considerations can be extended to patients with end-stage liver disease and portal hypertension, knowing that this patient group also has increased perioperative morbidity and mortality[32]. Lassailly *et al*[33] detailed 3 cases in which patients with incidental RCC underwent LT owing to rapid deterioration of liver function. Subsequently, they underwent either partial or radical nephrectomy. Pathohistological examination of the tumors revealed RCCs measuring 2-4 cm, Fuhrman grade II, and pT1a according to TNM classification in all 3 patients. During post-LT follow-up periods ranging from 5–19 years, no recurrence of malignant disease was observed in any of the patients. Similarly, Kosai-Fujimoto *et al*[34] reported a case of a patient with stage I RCC who underwent LT followed by partial nephrectomy 7 mo later. In a post-transplantation follow-up at 66 mo, no evidence of recurrent malignant kidney disease was detected in the patient. Given the advancing age of liver transplant recipients, it is conceivable that

Table 1 Possible proposal of acceptable liver donors with history of or current genitourinary malignancy (adapted from[15])

Minimal risk	Low to intermediate risk	High risk	Unacceptable risk
Current			
NMIBC – *in situ* and T1	Prostate cancer-Gleason score 7	Prostate cancer- Gleason score >7	Metastatic prostate cancer
Prostate cancer - Gleason score ≤ 6	RCC 1-4 cm and Fuhrman grade I/II	RCC > 7 cm and Fuhrman grade III/IV	RCC stages T3/T4
RCC < 1 cm and Fuhrman grade I/II	RCC 4-7 cm and Fuhrman grade I/II		MIBC – post chemoradiation
History			
Prostate cancer Gleason up to 6 Prostate cancer Gleason = 7 after curative treatment and cancer-free period > 5 yr	RCC 1-4 cm, FG I/II; RCC 4-7 cm, FG I/II	Prostate cancer with extraprostatic spread	Any metastatic genitourinary malignancy
RCC < 1 cm and FG I/II		RCC > 7 cm and FG III/IV	RCC stages T3/T4

RCC: Renal cell carcinoma; NMIBC: Nonmuscle-invasive bladder cancer; MIBC: Muscle-invasive bladder cancer; FG Fuhrman grade.

some may harbor previously undetected PCa. Currently, there are no established guidelines for screening this patient cohort either before or after LT. However, the existing literature suggests that immunosuppression does not notably influence the biology of PCa in these individuals, nor does that group have an elevated risk of accelerated progression or *de-novo* development of PCa. As a result, guidelines applicable to the general population are currently used for this patient demographic. Additionally, according to a review by Becher *et al*[35], following definitive treatment for Gleason grade group 1 to 3 PCa, there is no need for a waiting period before proceeding with organ transplantation. For individuals with high-risk disease, it is advised to wait at least 1 year, and if the prostate-specific antigen remains undetectable at that time, organ transplantation can be performed. In contrast, the American Transplant Society recommends proceeding with transplantation regardless of Gleason score, with the only contraindication being metastatic castration-resistant PCa or metastatic castration-sensitive PCa without 2 years of disease stability[29]. Concerning bladder cancer, recommendations regarding the waiting period until transplantation primarily depend on whether the cancer is nonmuscle-invasive or muscle-invasive. According to AST recommendations, patients with low and medium risk nonmuscle-invasive type should wait 6 mo prior to LT and those with high-risk or muscle-invasive bladder cancer after radical cystectomy should wait 2 years prior to LT. Patients with muscle-invasive type after chemoradiation should not be transplant candidates[29]. A summary of recommendations regarding liver transplant recipients with a history of genitourinary malignancies is shown in Table 2.

DISCUSSION

Malignant disease in the context of LT poses a complex challenge due to the absence of comprehensive prospective studies and guidelines. On one hand, there is concern of jeopardizing patients through the transmission of malignancy from a donor or the potential recurrence of underlying malignancies exacerbated by immunosuppression. On the other hand, there exists the prospect of denying life-saving treatment to a subset of patients. In this review, we aimed to consolidate existing research and guidelines regarding urogenital malignancies and LT. Our objective was to raise awareness among experts in this field that some donors and recipients with a history or current urogenital malignancy may still present an acceptable risk, yielding expected benefits from LT. Moreover, given the persistent disparity of organ demand and supply, consideration of donors with malignant conditions, including urogenital malignancies, is often unavoidable. Additionally, with the advancing age of donors, a rise in the incidence of incidental urogenital malignancies is anticipated. Therefore, it is imperative to approach the risk of malignancy transmission on an individual basis, taking into account the characteristics of both donor and recipient malignancy and many other factors (Figure 1). Given the indolent nature of early-stage urogenital malignancies with slow progression and low risk of metastasis, recipients with verified tumors during the pre-transplant assessment may still qualify for LT. Subsequent curative surgical interventions can be performed post-transplantation, thereby mitigating perioperative morbidity and mortality, as seen from data from patients with kidney transplantation[31]. Furthermore, considering the minimal risk of PCa transmission, stringent exclusion of local PCa donors may be unwarranted, potentially leading to an unnecessary reduction in organ donation rates. It is important to note that these observations refer only to urogenital tumors, as other malignancies exhibit different biological behaviors.

CONCLUSION

In conclusion, the evidence suggests acceptable outcomes in context of LT and genitourinary malignancies with careful

Table 2 Possible proposal of waiting time until liver transplantation for recipients with a history of genitourinary malignancy (adapted from[29])

Cancer	Tumor stage and/or grade	Time interval to transplant
Prostate	Up to T3 stage and regardless of Gleason score	No wait time
	Metastatic castration-sensitive prostatic cancer	Stable disease for 2 yr with prolonged estimated life expectancy – 2 yr
	Metastatic castration-resistant	Not a LT candidate
Renal cell carcinoma	T1a (≤ 4 cm) and T1b (4-7 cm) with N0, M0 and Fuhrman grade I/II	No wait time
	T1b, N0, M0 and FG III/IV and T2N0M0	2 yr
	T3 and T4 – both N0M0	Minimum 2 yr then reassess
	Any T, N+, M+	Not a LT candidate
Bladder	NMIBC (solitary tumor, low grade, absence of carcinoma *in situ* (CIS), high grade tumor < 3 cm)	6 mo
	NMIBC (any CIS, high-grade tumor > 3 cm, high grade T1 tumor, any recurrent high-grade Ta tumor, lymphovascular invasion)	2 yr
	MIBC, postradical cystectomy	2 yr
	MIBC, post chemoradiation	Not a LT candidate

FG: Fuhrman grade; LT: Liver transplantation; NMIBC: Nonmuscle-invasive bladder cancer; MIBC: Muscle-invasive bladder cancer.

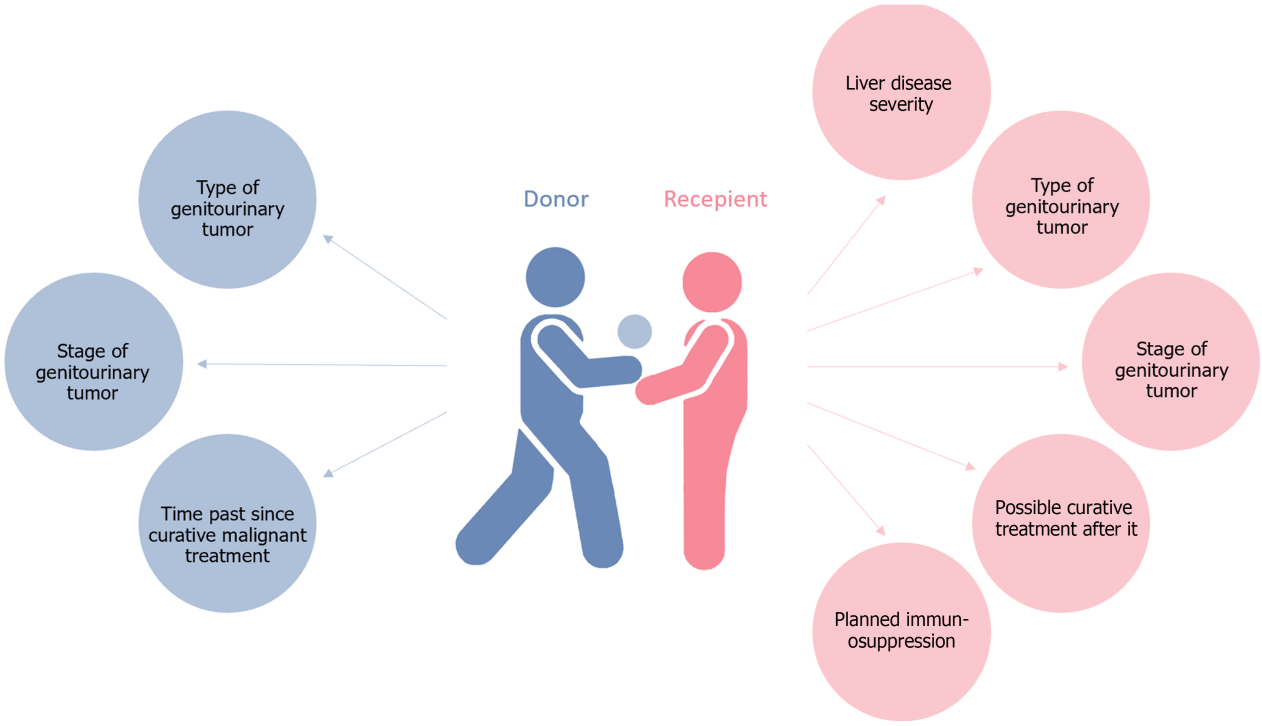

Figure 1 Key factors to consider regarding genitourinary tumors and liver transplantation. LT: Liver transplantation.

patient selection and tailored management strategies. Further prospective research is warranted to refine existing guidelines and optimize outcomes in LT for patients with genitourinary malignancies.

FOOTNOTES

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