Review

Oncological Complications of Liver Transplant: A Narrative Re-View on *De Novo* and Donor-Transmitted Cancers

Tancredi Vincenzo Li Cavoli , Armando Curto , Erica Nicola Lynch * , Andrea Galli

Posted Date: 17 February 2025

doi: 10.20944/preprints202502.1237.v1

Keywords: liver; transplantation; immunosuppression; tumour; malignancy

 doi:10.20944/preprints202502.1237.v1

Review

Oncological Complications of Liver Transplant: A Narrative Review on *de novo* and Donor-Transmitted Cancers

Tancredi Vincenzo Li Cavoli [1], Armando Curto [1], Erica Nicola Lynch [1,2,*] and Andrea Galli [1]

[1] Gastroenterology Research Unit, Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, 50134, Italy
[2] Department of Medical Biotechnologies, University of Siena, Siena, 53100, Italy
* Correspondence: ericanicola.lynch@unifi.it

Abstract: Liver transplantation (LT) has deeply transformed the treatment of end-stage liver disease and hepatocellular carcinoma, offering the most effective therapy for many liver conditions. However, LT carries inherent risks, including the development of cancers, which can arise from the transmission of neoplastic cells from the donor, the recurrence of pre-existing cancers, or as a long-term effect of the transplant originating from the recipient's own cells. The development of cancer in LT recipients is influenced by a variety of factors, such as age, gender, race, the underlying cause of liver disease, lifestyle factors (like alcohol use and smoking), and the use of immunosuppressive therapy. These combined factors increase the susceptibility of LT recipients to several types of cancer, including skin cancers, gastrointestinal malignancies, and lymphoproliferative disorders. While long-term survival after LT has significantly improved, there has been a notable increase in the incidence of *de novo* malignancies, which underscores the importance of diligent cancer screening and monitoring in transplant recipients, especially as they age. To manage this increased risk, various screening programs are recommended, including annual skin exams, colonoscopies for patients with primary sclerosing cholangitis (PSC) or inflammatory bowel disease (IBD), and lung cancer screening with low-dose CT for former smokers. When cancer is detected in LT recipients, reducing immunosuppression is a crucial strategy. Decreasing calcineurin inhibitors (CNIs) and integrating mTOR inhibitors (mTORi) provide promising avenues for balancing immunological control with oncological risk. Understanding these risk factors and adjusting immunosuppression appropriately is vital for improving cancer outcomes in LT recipients. Although evidence from LT-specific studies remains limited, insights from other solid organ transplant (SOT) settings, especially kidney transplants, offer valuable guidance in managing cancer risks in LT recipients. This narrative review focuses on prevention and management of *de novo* and donor-transmitted malignancies.

Keywords: liver; transplantation; immunosuppression; tumour; malignancy

1. Introduction

Liver transplantation (LT) has significantly transformed the treatment of end-stage liver disease and hepatocellular carcinoma, becoming the most effective therapy for various acute and chronic liver conditions. In 2019, a total of 35,784 liver transplants were performed across 70 countries, leading to significant improvements in patients' lifespan and quality of life [1], with one-year survival rates exceeding 93% and five-year rates over 60%. This success is due to advancements in donor and recipient selection, waiting list management, surgical techniques, and post-transplant care [1,2].

However, LT carries inherent risks. Despite screening procedures, unexpected transmission of diseases from donors, including cancers, can affect LT recipients. In addition, LT recipients face an elevated risk of developing *de novo* cancers, particularly those transplanted due to alcohol-related liver disease or hepatitis C. In particular, they are at increased risk of lymphoproliferative diseases

 doi:10.20944/preprints202502.1237.v1

and skin cancer, while the risk of other tumours such as breast cancer remains unchanged. Recipients are advised to avoid risky behaviours and undergo appropriate monitoring [3–6].

For donors with a known history of cancer, the risks of disease transmission with organ donation depend on the type of cancer, treatments received, and the time interval between diagnosis and donation [10]. It is crucial to balance the risk of cancer transmission with the risk of mortality for patients awaiting a graft, as strict adherence to guidelines may increase overall patient deaths [6].

Types of Cancer

In liver transplant recipients, cancers can be classified into four types [9]:

1. **Donor Transmitted Cancer (DTC)**: Present in the allograft at the time of transplantation.
2. **Donor Derived Cancer (DDC)**: Develops from the donor's cells after transplantation.
3. **De Novo Malignancy (DNM)** : Arises from the recipient's cells as a long-term effect of the transplant.
4. **Recurrent Cancer**: Recurrence of cancer treated before transplantation.

While these definitions are helpful, classifying cancers in clinical practice can be challenging. Distinguishing between DTC and DDC may be difficult if the donor has no known cancer, or if cancer appears long after the transplant. Additionally, when a recipient has multiple tumours of the same type, it can be hard to tell a new primary cancer from a recurrence, especially with cancers like melanoma or non-melanoma skin cancer, which can develop in multiple locations over time.

This review focuses on cancer in liver allograft recipients, addressing both donor-transmitted and *de novo* cancers, but excluding DDC, which are numerically less relevant, and recurrent cancers, as this topic includes the recurrence of hepatocellular carcinoma after LT which deserves a specific in-depth analysis.

2. Donor Transmitted Cancer (DTC)

DTCs are present in the graft at the time of transplantation, whereas DDCs develop from transplanted donor cells after the transplant. This differentiation is important because DTCs pose a shared risk for all recipients from the same donor, while DDCs do not. Although the occurrence of DTCs is generally low, their frequency may increase as the donor population ages. Therefore, expanding the donor pool necessitates a better understanding of DTC risks and avoiding unnecessary loss of viable organs when donor cancers are identified.

The management of patients at risk for or diagnosed with DTCs requires coordinated efforts among various stakeholders to ensure timely intervention. Certain donor cancers may carry minimal transmission risks and be acceptable for most recipients, while high-risk cancers may only be suitable for patients facing imminent death or those who do not meet standard suitability criteria.

2.1. Epidemiology

Cancer transmission from donors was first recognised in kidney transplantation, with early cases linked to donors who died from active cancer. This led to a cautious approach, significantly reducing the incidence of DTC. However, cases have still been reported from both donors with a known history of cancer and those without any known malignancies.

The frequency of DTC in solid organ transplantation, particularly LT, requires comprehensive registry data for accurate assessment. The Israel Penn International Transplant Tumour Registry aims to report cases of malignancies post-transplantation, including DTC, but its voluntary nature may lead to an overestimation of DTC risk. Mandatory registries provide more reliable data, although they may lack detailed insights into specific DTC cases [2].

A systematic literature review found 92 LT recipients diagnosed with DTC across 67 studies. Transplants from donors with a history of neoplasia occur in 2%-4% of deceased donors, primarily with low transmission risk due to the type of cancer or disease-free intervals. Nonetheless, some high-

 doi:10.20944/preprints202502.1237.v1

risk tumours, such as high-grade central nervous system cancers, have been transplanted, resulting in low DTC occurrences. [1]

The reported frequency of DTC is about 3-6 cases per 10,000 transplants, similar for LT, with most cases being occult cancers not detected prior to transplantation. The systematic review identified lymphomas, melanomas, and neuroendocrine tumours as common DTCs, typically diagnosed within the first two years post-transplant [50]. The overall survival probability for LT recipients with DTC is low, with a significantly worse prognosis for those with metastases at diagnosis.

A recent UK survey identified 15 cases of DTC among 30,765 organ transplant recipients over a decade, including two cases in 6,645 liver recipients. Notably, none of these cases involved donors known to have active or past cancer, highlighting the rarity and the ongoing challenge of completely eliminating this risk [3].

To improve risk estimation for DTCs and understand malignancy transmission better, it is crucial to include detailed donor cancer information in national registries and establish robust biovigilance programs to track malignancies in donors and suspected DTC cases, while ensuring the sensitivity of the data is respected.

LT can transmit a variety of cancers, including known primary central nervous system tumours, tumours diagnosed post-donation at autopsy, and those identified upon examination of stored donor tissue after DTC is found in the recipient.

The transmission of cancer, in the context of transplantation, can be derived from the following situations:

- **Donor with a history of cancer**: Transmission of cancer from donors with a history of cancer to organ recipients is rare. A major study from the UNOS/OPTN registry analysed 39,455 deceased donors between 2000 and 2005, finding that out of 1,069 donors with cancer, only two cancers (glioblastoma and melanoma) were transmitted to four recipients. The glioblastoma was active at donation, while the melanoma had been treated 32 years earlier with no signs of recurrence. However, the study did not account for the number of potential donors with previous cancer whose organs were rejected [7]. The low incidence of DTC among transplant recipients is largely due to the exclusion of high-risk donors as suggested by the latest guidelines from the Council of Europe (CoE) [4]. Given the low transmission rates, the cautious selection process may lead to organ wastage and potential loss of life for recipients in need.
- **Donors without a history of cancer**: The risk of cancer transmission from donors without a history of cancer is very low but not entirely absent, affecting both deceased and living donors. There have been instances where donors, initially assessed as cancer-free, transmitted cancer, with some cases identified only upon post-mortem examination. Therefore, a thorough examination of the donor's thoracic and abdominal cavities is recommended, though this can be challenging, especially in rapid retrieval situations after circulatory death. A survey in the UK identified 15 instances of cancer transmission from 13 donors, none of whom were known to have cancer at the time of donation. One case involved a lymphoma detected post-mortem, leading to subsequent identification in a recipient [3]. This underscores the difficulty of eliminating cancer transmission risks, making informed consent vital for all recipients. Those facing increased risks, such as recipients from donors with recent cancer histories, should receive specific counselling, although these discussions can be challenging. While there have been no reported cancer transmissions from living liver donors, living kidney donations have resulted in cases where cancers were transmitted from donors with no prior evidence of the disease [8]. Therefore, living donors should be monitored for at least one-year post-donation.

Cerebral haemorrhage, which coulb be caused by bleeding from undetectable metastases, is a common cause of death in brain-dead organ donors. Reported cases of cancer transmission in these situations include colon, pancreas, melanoma, and choriocarcinoma. To mitigate this risk, donors with cerebral haemorrhage should undergo thorough assessments that go beyond standard evaluations, including additional tests such as cross-sectional imaging of the brain, thorax, abdomen,

 doi:10.20944/preprints202502.1237.v1

and pelvis, as well as tumour marker tests. While some tumours may be identified during organ retrieval, the urgency of the process often prevents comprehensive examinations. Therefore, conducting a full post-mortem examination after organ procurement can be beneficial, as it allows for the early identification of donor cancers, which can significantly impact the management of organ recipients.

2.2. Different Cancer Types in the Context of DTCs

- **In Situ Carcinomas:** Transmission of in situ carcinomas during solid organ transplantation has not been clearly documented, even when organs from such donors have been used. Most in situ carcinomas, like cervical intraepithelial neoplasia III, vocal cord carcinoma, superficial papillary bladder carcinoma, and nonmelanoma skin carcinoma, carry a minimal risk of transmission [10]. However, some in situ carcinomas, such as those of the breast, colorectal, and lung, as well as melanoma, may pose a higher risk. Thus, proceeding with LT in these cases requires a careful assessment of the low transmission risk against the recipient's condition [11,12]. In situ urothelial carcinomas and intraepithelial pancreatic neoplasms are generally considered to have minimal risk for LT recipients [10].
- **Breast cancers:** Breast cancer is the most common cancer among females and is linked to high mortality rates [13]. With improved screening and treatment, more potential organ donors with a history of breast cancer are emerging. Although registry studies report no documented DTC from selected donors with past breast cancer, cases have occurred, typically involving undiagnosed cancer at the time of donation. For example, Matser et al. described one case where a donor transmitted occult breast cancer to four recipients, with DTC detected in the liver graft four years post-transplant [14]. Given the potential for late recurrence and metastasis in breast cancer, careful consideration is essential for liver donation from these donors. It is recommended that such donors undergo appropriate treatment and monitoring, ensuring a long disease-free interval before donation. Histological assessments can help identify tumours with a favourable prognosis, while stage 1 breast cancer with a curative resection and over five years of disease-free survival may pose a low to intermediate transmission risk [15]. Additionally, imaging, such as CT scans, may be necessary to check for metastatic spread before proceeding with organ donation.
- **Colorectal cancers (CRC):** CRC is prevalent and a significant cause of mortality, often metastasising to the liver [13]. Reports indicate that organs from donors with known CRC histories have been transplanted without evidence of cancer transmission, although cases of occult CRC transmission through LT have been documented [3,16]. There are two reports of re-transplantation after diagnosing donor-transmitted cancers, where one recipient died from unrelated causes [17,18], while two other recipients, who were diagnosed with donor-transmitted CRC, did not undergo re-transplantation due to poor clinical conditions and subsequently died [19,20].

Registry studies have noted instances of CRC transmission via organ transplantation, prompting caution in accepting donors with recently diagnosed pT1 CRC, as factors like submucosal infiltration and lymphovascular invasion may heighten the risk of metastasis [15]. Generally, newly diagnosed CRCs beyond pT1 and those found during organ recovery are deemed high risk, according to both European and American guidelines [10]. Donors with a history of CRC are classified as high risk, except in cases of pT1 CRC after extended periods of remission.

- **Central Nervous System (CNS) cancers:** Primary CNS tumours rarely spread outside the brain and are found in only 1%–2% of deceased organ donors. However, there are reports of tumour transmission in organ transplants, particularly in LT recipients. Factors influencing the risk of CNS tumour transmission through transplantation include tumour histological grade and interventions that breach the blood-brain barrier, such as cerebrospinal fluid shunts and craniotomy. Decision-making is complicated by the fact that many brain tumours are secondary and often diagnosed based solely on imaging, without biopsy. The 2016 WHO classification

 doi:10.20944/preprints202502.1237.v1

categorises CNS tumours by cell origin and grades them from 1 (least aggressive) to 4 (most aggressive), with all grade 4 tumours exhibiting vascular invasion [21]. While lower-grade tumours can progress to higher grades, the risk of disease transmission in organ transplants primarily correlates with the tumour grade and duration. Metastatic spread from CNS tumours is rare, especially for lower-grade tumours, but high-grade tumours like glioblastoma carry a higher risk [22,23]. The actual risk of tumour transmission from donors has been reassessed and appears lower than previously thought, with recent data indicating only one transmission event from over 77 donors with grade 4 tumors[7,24]. Guidance on using organs from donors with CNS tumours varies significantly. Some sources cite a transmission risk exceeding 10% [60], while others suggest only a 2.2% risk for grade 4 tumours [25]. However, some studies, as the one by Watson et al., found no transmission cases among 448 transplant recipients from donors with primary CNS cancer, including high-grade tumours [6]. It is essential to perform a careful risk-benefit assessment when considering organs from high-risk donors, balancing the potential harm from cancer transmission against the risk of death for recipients waiting for transplants.

- **Lung cancer:** Around 35% of patients who die from lung cancer have metastatic disease at diagnosis, with the liver being a common site for metastasis. There have been reports of lung cancer transmission to LT recipients, including fatal cases, notably one where adenocarcinoma was discovered during a donor autopsy. However, some studies have also shown cases where lung cancer did not transmit to LT recipients [26,27]. The Council of Europe considers active lung cancer in donors as posing an unacceptable risk for transplantation. For donors with a history of treated lung cancer, organ transplantation may be possible but is generally associated with a high risk of transmission, which may decrease with successful treatment and a recurrence-free period. American guidelines align with this assessment regarding the risk of lung cancer transmission through solid organ transplantation.
- **Prostate adenocarcinoma:** Prostate adenocarcinoma is a common cancer in men, particularly among older individuals, with a generally slow progression and high survival rates [28]. Metastases typically occur in bones, lymph nodes, lungs, and liver, and the disease is classified using the Gleason score, which correlates with prognosis—higher scores indicate poorer outcomes [29]. There has been one reported case of transmission of well-differentiated prostate adenocarcinoma through LT, detected in the recipient shortly after the transplant [30]. Another case involved a heart transplant recipient who died from donor-transmitted metastatic prostate cancer from a poorly differentiated tumour discovered during organ recovery [31]. Incidental prostate cancer is found in a small percentage of donors under 50 years old (0.5%), rising to 45% in those over 70 [32]. As age is no longer a contraindication for liver donation, organs from older male donors with undiagnosed prostate cancer are frequently transplanted. Many studies have documented cases of LT from donors with lower Gleason scores (≤6 or 7) without cancer transmission to recipients [33]. A 2014 review found no cases of disease transmission in 76 reported instances of liver transplants from prostate cancer donors, and recent reports also support this finding for donors with higher Gleason scores (8 and 9) [34]. Exclusion of donors with localised prostate cancer (PCa) may be unnecessary, as the risk of transmitting this type of cancer is minimal, and such exclusions could reduce organ donation rates [167]
- **Renal cell carcinoma (RCC):** The incidence of renal cell carcinoma (RCC) in deceased organ donors is likely less than 1% [35]. In the general population, RCC incidence increases with age, and while metastases typically occur in the lungs, bones, and lymph nodes, liver metastases are rare [36]. There have been no reported cases of RCC transmission through LT, with most documented transmissions occurring in kidney transplants. Rare instances of RCC transmission have also been noted following heart and lung transplants. A report from the United Network for Organ Sharing found no RCC transmission among 198 recipients of non-renal organs from 147 donors with known RCC [35]. This finding aligns with other registries from the UK [37], Spain [38], and Italy [39,40], although many lacked precise staging information. It is likely that non-renal organs were accepted from donors diagnosed with early-stage RCC or when

 doi:10.20944/preprints202502.1237.v1

transplants were underway before RCC information was available. The Council of Europe Guide categorises RCC based on the risk of transmission, determined by TNM stage and nucleolar Fuhrman grading. However, there are no strong published guidelines regarding decision-making for donors with a history of RCC.

2.3. Assessment of the Risk of DTC Before Tranplantation

Minimising the risk of disease transmission through transplantation DTC relies on thorough donor characterisation, which is an ongoing, multidisciplinary process involving various healthcare professionals, donor coordinators, procurement surgeons, and transplant teams. This characterisation begins with the initial evaluation of the donor and continues through to after organ transplantation, as new information about the donor may emerge at any time. Key elements of donor characterisation include assessing tumour markers, which can sometimes yield false positives and lead to unnecessary exclusion of potential donors. For example, if a donor with a history of cancer has elevated tumour markers, re-testing may provide a clearer assessment. In women of childbearing age with relevant health histories, measuring beta-human chorionic gonadotropin levels can help rule out choriocarcinoma. Routine CT scans may be performed in some regions to detect occult cancers in potential donors, although their effectiveness is not conclusively proven, and they can complicate the donation process. CT may be warranted for donors with known risk factors or suspected active cancer when adequate intraoperative evaluation is not feasible. If cancer is identified during donor characterisation, detailed information must be gathered, including the date of diagnosis, histological reports, grade and stage, treatment history, follow-up care, tumour recurrence, and disease-free intervals. This information should be thoroughly documented. It is important to note that cancer staging and classification systems, such as the TNM system and World Health Organisation (WHO) classifications, have been updated in recent years, which may affect how cancers diagnosed before these updates are categorised.

When a donor is diagnosed with active or previous malignancy, assessing the risk of disease transmission through transplantation DTC is crucial for clinical decision-making and to properly inform potential recipients and their representatives. Understanding the theoretical risk aids in conducting a thorough risk-benefit analysis based on the clinical circumstances of the recipients.

Several classifications for DTC risk have been proposed, with the Council of Europe opting not to provide specific numerical risk estimates due to limited evidence. Their grading system, adapted for LT, categorises risk as follows:

-**Minimal risk:** Livers from these donors can be allocated to any patient on the LT waiting list.

-**Low to intermediate risk**: Allocation may be justified based on the recipient's condition and includes patients with hepatocellular carcinoma not responding to treatment, those with a MELD score ≥30, and patients likely to experience significant deterioration or death on the waiting list in the coming weeks.

-**High risk:** Acceptance of organs may be considered in exceptional cases, particularly for life-saving LT procedures, after a careful risk-benefit assessment and with informed patient consent. This applies to patients with acute liver failure, MELD ≥40, or acute-on-chronic liver failure grade 3, particularly if they are at imminent risk of death or dropping off the waiting list.

These classifications help guide allocation decisions and ensure that recipients are adequately informed about potential risks.

2.4. Management of DTC Events

All suspected cases of disease transmission through transplantation DTC or malignancies identified in the donor after transplantation must be reported to all relevant stakeholders, including transplant centres caring for other recipients from the same donor and the donor centre. This initiates a coordinated investigation and management plan, focusing on determining the likelihood that the malignancy originated from the donor, informing at-risk recipients, and planning corrective actions, ideally coordinated by an oversight agency [41,42].

 doi:10.20944/preprints202502.1237.v1

Evaluating a LT recipient for potential DTC events depends on the clinical context. If a donor's malignancy is discovered shortly after transplantation, management will be guided by the type of tumour and its risk of transmission. In cases of suspected DTC in the recipient, further imaging with CT or MRI is recommended. Depending on the imaging results, options may include biopsy, serial imaging, or no further action if the lesion is definitively benign. Most DTCs manifest within the first year after transplantation, but some cases can arise up to five years later. Tumours detected more than a year post-transplant raise questions about their origin—whether they are donor-derived or new malignancies in the recipient.

When the origin of a tumour is unclear, it is crucial to identify and evaluate other recipients who received organs from the same donor. Early detection of malignancy with multiple metastases within the first month after transplantation is a strong indicator of DTC. Biopsy may be necessary to clarify the diagnosis. Techniques such as fluorescence in situ hybridisation can help determine donor origin in cases of gender mismatch between donor and recipient, while microsatellite allelic analysis can distinguish cells from different individuals based on genetic differences. Comparative genomic hybridisation can also be used for genetic comparison, using paraffin-embedded biopsy samples.

- **Retransplantation for a DTC Event:** When a tumour has been characterised in the donor, recipients should be informed about the potential risk of DTCs in a balanced manner, considering the risk of transmission and the tumour aggressiveness. For recipients at high risk of DTCs, removal of the transplanted organ and cessation of immunosuppression are feasible only for kidney and pancreas transplant recipients [43]. In LT, retransplantation is possible but may not prevent transmission, as tumor cells could have already disseminated within the recipient. Retransplantation carries significant morbidity and mortality risks and should be weighed against the ongoing organ shortage [44]. Currently, there are no established guidelines for retransplantation in DTC events. Each case should be assessed individually through a multidisciplinary approach, with thorough discussions involving the patient or their family. Retransplantation may be considered reasonable when the tumour in the donor is classified as having an intermediate or high risk of transmission; however, it is less justifiable for tumours assessed as minimal or low risk.
- **Management of immunosuppression**: For LT recipients at risk of disease transmission through transplantation DTCs, minimising immunosuppression is strongly advised. Immunosuppressive agents can promote tumour development and accelerate cancer growth [45–47]. However, complete discontinuation of immunosuppression is not recommended due to the high risk of organ rejection, which may necessitate restarting immunosuppressive therapy at higher doses.

The strategy for managing immunosuppression should resemble that for patients with de novo malignancies. A gradual reduction in immunosuppression should be considered only after the early post-transplant period [48]. Maintenance therapy should involve low target levels of calcineurin inhibitors (CNIs) [49].

There is no evidence indicating increased tumour progression risk when combining mycophenolate mofetil (MMF) with CNIs, but MMF may be discontinued following a diagnosis of posttransplant lymphoproliferative disorder to protect bone marrow before potential chemotherapy [50–52]. The necessity of stopping MMF for LT recipients at risk of malignancy transmission remains debated.

The role of mechanistic target of rapamycin inhibitors (mTORi) is also under discussion. These agents possess both immunosuppressive and potential anticancer properties, making them theoretically attractive for DTC-risk patients. For example, everolimus is approved for treating various advanced cancers [53]. However, the effectiveness of mTORi preventing new or recurring malignancies in transplant settings has not met expectations [54–58].

Two primary approaches for maintenance immunosuppression with mTORi exist: (1) switching from CNIs to mTORi (with or without antimetabolites) and (2) combining mTORi with reduced-dose CNIs. The first approach may be preferred for patients at high risk of DTCs.

 doi:10.20944/preprints202502.1237.v1

It's important to note that the dosing of everolimus for treating malignancies (5–10 mg daily) differs significantly from that for immunosuppression in transplantation. Additionally, while lifelong use of mTORi is necessary for transplant immunosuppression, cancer treatment typically involves sequential administration. Currently, there is no consensus on the optimal protocol for LT recipients at risk of DTCs.

3. De Novo Malignancy (DNM)

Advancements in LT techniques, postoperative management, and the development of immunosuppressive agents have significantly improved long-term survival rates. However, long-term transplant recipients who undergo prolonged immunosuppression face an increased risk of DNM due to the oncogenic effects of these immunosuppressive drugs and heightened susceptibility to viral infections. However, the occurrence and type of DNM also depend on factors like patient demographics, underlying liver disease, and lifestyle choices (e.g., smoking and alcohol use).

3.1. Epidemiology of DNM

The risk of cancer in LT recipients is 2-3 times higher than in the general population, with certain cancers like Kaposi's sarcoma, non-melanoma skin cancers, and lymphoma being particularly prevalent. However, the risks for breast, prostate, and multiple myeloma cancers are not significantly increased. Studies show that young transplant recipients are more likely to develop malignancies than the general population, and the incidence rises sharply after the age of 45. [59]

LT recipients have a higher incidence of oral/pharyngeal/laryngeal (OPL) cancers compared to recipients of other solid organs, such as kidney transplant recipients. In contrast, they tend to have a lower incidence of genitourinary malignancies (e.g., bladder and renal cancers) [164].

Research on DNM after LT highlights significant regional differences in cancer types between Western and Asian populations, with variations in the standardised incidence rates (SIR) compared to the general population.

In Western countries, including the United States, Canada, and Italy, the most common DNMs are post-transplant lymphoproliferative disorder (PTLD), skin cancer, and head and neck cancers, with prostate and breast cancers being less frequent. The SIR for solid organ cancers in these regions is typically about twice that of the general population, while for haematological malignancies, the SIR is about 30 times higher [60–63]. Racial differences are also evident, with Hispanic patients being more prone to PTLD, gastrointestinal, and urinary cancers, while Black patients have higher incidences of lung and reproductive organ cancers. Caucasian patients, on the other hand, show a higher prevalence of PTLD, lung cancer, and skin cancer [64].

In contrast, studies from Asia, such as those by Kim et al. [65], Park et al. [66] and Masuda et al. [164] reveal a different pattern. While PTLD remains common, stomach and CRC are notably more frequent among LT recipients, reflecting trends observed in the general Asian population. Additionally, prostate and breast cancers—relatively less common in the West—show higher rates in Asian transplant recipients.

These regional differences underscore the need for tailored cancer surveillance strategies based on geographic and ethnic factors.

3.2. Different Cancer Types in the Context of DNM

The risk of developing de novo malignancies after LT varies across different tumour types, as indicated by cancer registry studies (Table 1). These cancers are generally categorised into three main groups: PTLD, skin cancers and solid organ cancers.

- **PTLD**: PTLD occurs in 1% to 5.5% of LT patients, with a higher risk when the recipient is EBV-seronegative and receives an organ from an EBV-seropositive donor [94]. PTLD can develop as early as one month after LT and may continue to occur for decades. The risk of PTLD is increased

 doi:10.20944/preprints202502.1237.v1

in patients with strong immunosuppression or those on immunosuppressive agents such as azathioprine, CNIs, or anti-thymocyte agents.

Although PTLD remains a major complication in both Western and Eastern transplant populations, its incidence has decreased due to improvements in treatment strategies. The majority of PTLD cases are caused by EBV, and while there is no well-established cutoff for EBV-DNA levels, early detection of the virus can help identify PTLDs at an earlier stage [95,96]. Despite high mortality rates—up to 85% at 1 year and 69% at 5 years—survival rates have improved with better management approaches [97,98].

Notably, patients on tacrolimus-based regimens have a significantly better survival rate compared to those treated with cyclosporine (81.2% vs 50% after 5 years post-PTLD diagnosis) [97]. LT for conditions such as hepatitis C and alcohol-related liver disease (ALD) has also been linked to a higher risk of PTLD, although the reasons for this association remain unclear. Multidisciplinary approaches, including immunosuppressant weaning, interferon therapy, surgery, radiotherapy, and chemotherapy, are being used to reduce the incidence and recurrence of PTLD [99,100].

- **skin cancers**: The most represented malignancies in adult LT recipients are skin cancers particularly the category of nonmelanoma skin cancers (NMSC), that involved squamous cell carcinomas and basal cell carcinomas, with a significantly higher risk compared to the general population [101–103]. NMSC is often a late complication of transplantation, typically developing about 50 months post-transplant [104]. Risk factors for NMSC include sun exposure, lighter skin color, intensity of post-transplant immunosuppression, older age at transplantation, male gender, and a history of excessive alcohol consumption [105,106]. In a recent Danish study, NMSC accounted for 60% of de novo cancers in liver transplant recipients, with a median time to diagnosis of 3.8 years post-transplant, highlighting its prevalence and early onset compared to other malignancies [16].

In addition, human papillomavirus (HPV) infections, a history of actinic keratosis, fair skin, blue or hazel eyes, and CD4 lymphocytopenia also increase the risk of skin tumours after OLT [107,108].

While cyclosporine (CsA) is strongly associated with a higher risk of skin cancer—patients treated with CsA tend to develop skin malignancies more quickly than those treated with tacrolimus—recent reports have shown a decline in skin cancer incidence among OLT recipients [105]. This trend may be due to improved sun protection measures, avoidance of UV radiation, and changes in immunosuppressive protocols. Liver transplantation for conditions such as hepatitis C and ALD has also been linked to an increased risk of NMSC, although the underlying reasons for this association remain unclear [109].

In addition to NMSC, KS, a rare, angioproliferative tumour linked to human herpesvirus-8, is another malignancy that occurs more frequently in OLT recipients. KS affects liver transplant patients about 500 times more than the general population, but its incidence has been declining in recent years [110,111]. Immunosuppressive therapies, especially CsA and tacrolimus, are strongly linked to the development of KS. However, switching immunosuppression to mTORi has shown promise in reducing the growth of KS [112,114]. Therefore, a tailored approach to immunosuppressive therapy, along with careful monitoring and management, is crucial in minimising the risk of both NMSC and KS in liver transplant recipients.

- **Upper GI and Respiratory System Cancers**: Airway cancers, which include cancers of the oral cavity, pharynx, larynx, and lung, are common malignancies observed in LT recipients. These cancers are strongly associated with smoking and alcohol use, and they arise from the tissues of the aerodigestive tract, which includes the respiratory tract and upper digestive tract (such as the lips, mouth, tongue, nose, throat, vocal cords, and parts of the oesophagus and windpipe). In the LT population, head and neck cancers and lung cancer are particularly common, with a significantly higher risk compared to the general population.

A meta-analysis on head and neck cancer after LT found a SIR of 3.8 (95% CI: 2.7–4.9), with cancers typically developing between 34 and 61 months after transplant [115,116]. Liver transplant recipients with a history of tobacco use or ALD are at a particularly high risk for head and neck

 doi:10.20944/preprints202502.1237.v1

cancers, with some studies showing that these cancers only develop in patients with a history of ALD. Tobacco use is linked to the development of pharyngeal and tongue cancers, while alcohol plays a predominant role in the onset of oropharyngeal and upper aerodigestive squamous tumours [117,118].

A systematic review and meta-analysis also identified an elevated risk of esophageal cancer in LT recipients. The study reported a significantly higher risk compared to the general population, with a SIR of 6.75 (95% CI: 4.35–10.46). Risk factors for esophageal cancer in LT recipients include the use of immunosuppressants, tobacco and alcohol, along with genetic variants influencing alcohol metabolism. Moreover, rapid progression of Barrett's esophagus to cancer is commonly observed in post-transplant patients, likely due to the effects of immunosuppressants. Notably, patients transplanted for ALD exhibit an SIR over ten times higher than the general population, with risk progressively increasing after the first five years post-transplant and slowing after 15 years. [164]

Similarly, lung cancer after LT has a SIR of 1.95 (95% CI: 1.74–2.19), with lung cancers typically developing 42 to 50 months post-transplant [98]. Smoking is the main risk factor for lung cancer in LT recipients, but those transplanted for ALD are also at higher risk compared to those transplanted for other causes (4.3% vs. 0.7%, $P < 0.001$), though tobacco use may confound these findings [119].

Some treatments, like mTORi, may help reduce malignancy risk, but their use must be balanced with the risk of transplant rejection. Currently, no standardised early detection protocols exist for LT patients, but the study recommends using low-dose computed tomography (LDCT) for smokers after LT to catch lung cancer at an early stage. [169]

While there is a well-established link between tobacco and alcohol use and the development of these cancers, it remains unclear how long the elevated cancer risk persists after cessation of smoking and alcohol consumption. Given the significant risks, it is crucial to follow a regular screening for smokers and former alcohol users after LT, particularly for those with a history of ALD.

- **Colon-rectal cancer**: Colon cancer is the most common gastrointestinal malignancy among solid organ transolantation (SOT) recipients, with LT recipients at particular risk [82]. The SIR for colon cancer in LT recipients varies widely, ranging from 1.4 to as high as 27.3 in subsets of high-risk patients, particularly those with PSC [120,121]. PSC, especially when combined with inflammatory bowel disease (IBD), significantly increases the risk of CRC. While PSC alone may not be a strong risk factor for gastrointestinal malignancies, as shown in a study by Watt et al. (HR = 1.9, P = 0.12), the combination of PSC and IBD, particularly with intact colons, results in a much higher risk (HR = 3.51, 95% CI: 1.48-8.36, P = 0.005) [84].

Patients with PSC-IBD have a particularly high risk of colon cancer after LT, with the risk rising even more for those with ulcerative colitis (UC). The SIR for colon cancer is significantly higher in LT recipients with UC (SIR = 27.3) compared to those without (SIR = 3.5), and the risk is even more pronounced in older patients, particularly those over 40 (SIR = 4.8 vs 1 in younger patients) [83]. A longer duration of IBD and more extensive colonic involvement further elevate the risk for CRC in LT recipients with PSC [122]. Notably, CRC develops at a younger age in LT recipients compared to the general population and is often associated with a poorer prognosis [123–125].

In addition to colon cancer, studies have shown that LT recipients, especially those with PSC-IBD, are also at heightened risk for other cancers. A South Korean study, for example, reported a relatively high incidence of both colon and stomach cancers, although East Asian studies generally report lower rates of de novo malignancies (2.2%-2.3%) [126,127]. Despite the increased risk of CRC in these patients, survival outcomes can be favourable if the cancer is diagnosed early. For instance, a study analysing CRC outcomes in LT recipients found that patients with stage 1 CRC had overall survival rates comparable to the general population, and even those with stage 2-3 cancer did not have extremely poor survival, underscoring the value of early detection and treatment [126].

These findings highlight the importance of vigilant surveillance, particularly in LT recipients with PSC and IBD, to ensure early diagnosis and improve survival outcomes. Specialized monitoring is crucial, as the use of immunosuppressive therapies post-transplant can compromise immune surveillance and complicate the management of CRC. [128,129]

 doi:10.20944/preprints202502.1237.v1

- **Genitourinary tract cancers**: OLT recipients do not have an overall increased risk of prostate cancer compared to the general population. However, non-prostate genitourinary cancers are often more aggressive and tend to develop earlier in these patients [130,131]. Renal malignancies have a SIR of 3.3, and annual ultrasound screenings are recommended after OLT [132,133]. Registry studies show an increased SIR for certain genitourinary cancers, such as cervical, vulvar, bladder, and kidney cancers, but not for all gender-specific cancers like prostate, uterine, or ovarian cancers. Specifically, cervical cancer has a notably higher SIR (30.7) [134], and other HPV-related cancers (vulvar, vaginal, anal, penile) also show elevated SIR values ranging from 2.4 to 7.6 [135]. Bladder cancer risk is increased in transplant recipients, with SIR values ranging from 1.5 to 2.4, and typically develops late (around 10 years) after LT [136,137].

Table 1. Incidence of cancer in Western country divided into general population and in liver transplant recipients.

Incidence of cancers in Western-countries	In general population [13,156,171]	Incidence in Liver Transplant Recipients [133,157–159]
Non Melanoma Skin Cancer	0.02-0.03 cases per 1,000 inhabitants.	2-4 cases per 1,000 transplant patients.
Non-Hodgkin Lymphoma (NHL):	0.005-0.02 cases per 1,000 inhabitants.	0.2-0.4 cases per 1,000 transplant patients.
Melanoma	0.02-0.05 cases per 1,000 inhabitants	3-6 cases per 1,000 liver transplant patients
Colorectal cancers	0.1-0.2 cases per 1,000 inhabitants.	0.1-0.2 cases per 1,000 transplant patients.
Bladder Cancer	0.03 cases per 1,000 inhabitants	0.5-0.8 cases per 1,000 liver transplant patients
Lung Cancer	0.1-0.2 cases per 1,000 inhabitants	0.6-1.2 cases per 1,000 liver transplant patients
Female breast cancer	0.2 cases per 1,000 inhabitants	0.4 cases per 1,000 liver transplant patients
Prostate cancer	0.07 cases per 1,000 inhabitants	0.25 cases per 1,000 liver transplant patients

3.3. Survival After DNM

SOT recipients are at a higher risk for being diagnosed with advanced-stage cancers (AJCC stage >2) and face worse cancer-specific survival compared to the general population [138]. A comparison between SOT patients and the general population revealed a relative risk of cancer-related mortality at 2.9 times higher for transplant recipients (95% CI: 1.59-5.11) [139]. In one large study, de novo malignancies (excluding NMSC) were a leading cause of mortality (14.2%), along with infections (15%), disease recurrence (13%), and cardiovascular complications (9%) [140]. Survival rates for transplant recipients diagnosed with de novo malignancy were significantly lower: at 1.3 and 5 years post-diagnosis, survival rates were 55% and 36%, compared to 100% and 67% for patients with only NMSC (P = 0.001) [141]. Similarly, de novo malignancies, excluding NMSC, were associated with a nearly five-fold increased risk of mortality (HR = 4.9, 95% CI: 1.67-14.2, P = 0.003).

Patients with PTLD exhibit considerable variability in survival, with some studies reporting median survival as low as 2 months (95% CI: 0.3-3.5 months), especially in high-risk PTLD cases [74]. However, other LT series have reported longer survival, with median survival intervals ranging from 27 to 35 months, and 1-year and 5-year survival rates of 56% and 46%, respectively [99].

Survival rates for specific cancers in transplant recipients vary: oropharyngeal cancer has 1-year and 5-year survival rates of 43%-78% and 56%, respectively; lung cancer has 1-year and 5-year

 doi:10.20944/preprints202502.1237.v1

survival rates of 41%-43% and 16%, respectively; gastrointestinal cancers have 1-year and 5-year survival rates of 67%-80% and 52%, respectively; and genitourinary cancers show 1-year and 5-year survival rates of 79%-100% and 71%, respectively [137,141]. These figures highlight the challenges in managing cancer in transplant recipients and the need for enhanced monitoring and early intervention.

3.4. Prevention of DNM

DNM pose a significant challenge for liver transplant recipients, highlighting the need for effective surveillance strategies. Current guidelines, such as the ILTS-SETH Consensus Conference Guidelines produced in 2022 [142], offer detailed recommendations for cancer screening, including annual skin exams, colonoscopies for those with PSC or IBD, and lung cancer screening with low-dose CT for ex-smokers. These protocols are designed to identify cancers early, improve treatment outcomes, and reduce mortality. Recommendations on DNM prevention are summarised in Table 2.

However, liver transplant recipients in Korea present a different pattern of DNM occurrence, with gastric and CRCs (unrelated to PSC or UC) being more common, deviating from trends seen in Western countries. This necessitates modifications to the ILTS guidelines for Korea, where a national cancer screening programme already targets prevalent cancers like stomach, liver, colorectal, breast, and cervical cancers, offering financial support for screening. Using this national cancer screening programme for DNM screening could be an efficient strategy, while adjusting endoscopy intervals based on age and prior screening history is recommended. Despite limited evidence for specific screening protocols, the general principle of personalised surveillance, especially for high-risk groups, remains crucial [143].

The importance of minimising immunosuppression, counselling against smoking and alcohol, and providing education on cancer risks, early symptoms, and screening remains vital. Liver transplant recipients should also be advised on factors like EBV status, sun exposure, and vaccination (e.g., for hepatitis B).

The overall approach to managing post-liver transplant cancers should focus on minimising risk factors and tailoring surveillance strategies based on regional cancer patterns and individual needs. Early detection through these methods has shown to improve survival and outcomes, making cancer prevention and screening essential components of post-transplant care.

Table 2. Main recommendations for surveillance against DNM:.

- **Skin Cancer**: Annual full-body skin exams.
- **CRC**: Annual colonoscopies for IBD or PSC patients. Five years colonoscopies for (NASH and HCC patients who are over age 50.
- **Lung Cancer**: Advised annual low-dose chest CT scans for ex-smokers.
- **Head and Neck Cancers**: Annual ENT exams for those with a history of oropharyngeal or head and neck cancers.
- **Cervical/Vulvar/Vaginal Cancer**: Annual pelvic exams, Papanicolaou (PAP) tests, and HPV testing for female patients.
- **Breast Cancer**: Recommended every 1-2 years mammograms for females.
- **Prostate Cancer**: Follow general population guidelines for PSA screening for males.
- **Renal Cancer**: Annual CT scan for patients with a history of renal cell cancer, polycystic kidney disease, or Von Hippel-Lindau disease
- **PTLD**: Monitoring EBV DNA levels is recommended for high-risk recipients (EBV seronegative and receive a graft from an EBV-seropositive)

Table 2 Abbreviations: DNM: De Novo Malignancy; CRC: Colon Rectal Cancer; IBD: Inflammatory bowel disease; PSC: primary sclerosing cholangitis; NASH: non-alcoholic

 doi:10.20944/preprints202502.1237.v1

steatohepatitis; HCC: hepatocellular carcinoma; CT: computed Tomography; ENT: ear, nose, and throat; HPV: Human Papilloma Virus; PSA: prostate-specific antigen; PTLD: post-transplant lymphoproliferative disorders; EBV: Epstein Barr Virus

3.5. Management of DNM After LT

When DNM is detected in liver transplant recipients, treatment strategies generally focus on two main approaches:

1. **Immunosuppressant Reduction**: Reducing the use of CNIs like tacrolimus and cyclosporine is crucial, as these drugs can suppress antiviral immunity, induce DNA damage, and promote tumour growth. Alternatives such as mTORis or MMF are recommended, as they do not increase the risk of DNM and can reduce reliance on CNIs.
2. **Aggressive Local Treatment**: Early detection of DNM should prompt aggressive local treatment. For gastric cancer, interventions like endoscopic submucosal dissection or surgery are advised. Similarly, for CRC, early treatment can improve the prognosis.

The management of immunosuppressive therapy in LT recipients who develop DNM is a critical aspect of post-transplant care. These malignancies arise after transplantation, and while immunosuppressive medications are essential to prevent graft rejection, they can also contribute to an increased risk of cancer due to their impact on immune surveillance. Therefore, adjusting immunosuppression after the diagnosis of a malignancy requires a careful balancing act to reduce the risk of cancer progression while maintaining adequate immune suppression to protect the transplanted liver.

CNIs, including tacrolimus and cyclosporine, play a crucial role in immunosuppressive therapy following LT. They block T-cell activation causing a reduction of the body's immune response to the transplanted organ. However, while they prevent organ rejection, they also interfere with immune surveillance and promote tumour growth. CNIs upregulate factors such as vascular endothelial growth factor (VEGF) and transforming growth factor beta 1 (TGF-β1), which can promote angiogenesis and tumour development. Retrospective studies have shown that long-term exposure to CNIs increases the risk of de novo malignancies in liver transplant recipients, and higher tacrolimus trough levels have been specifically linked to both de novo malignancies and the recurrence of previously treated cancers [144,145]. Moreover, one study showed that lowering cyclosporine doses in kidney transplant patients resulted in a reduced cancer risk, with a decrease from 32% to 19% at five years [146]. Given these risks, a common approach in managing DNM after LT is to consider reducing the doses of CNIs or switching to other immunosuppressive regimens, such as mTOR inhibitors (sirolimus or everolimus).

Azathioprine, a purine analogue that was once commonly used in liver transplant recipients, has been associated with an increased risk of skin cancers, particularly cutaneous squamous cell carcinoma (cSCC). Azathioprine inhibits purine synthesis, which affects DNA replication and repair, causing DNA damage and impaired DNA repair, thus increasing the risk of skin cancers [147]. As a result, most liver transplant centres have replaced azathioprine with MMF , a medication that does not have the same pro-oncogenic effects and may even reduce the overall risk of de novo malignancies. Unlike azathioprine, MMF does not contribute to DNA damage and is considered a safer alternative, especially in terms of reducing cancer risks [148–150].

The role of **mTORis** (sirolimus and everolimus) in the management of immunosuppression after de novo malignancies is of significant interest. These drugs work by inhibiting the mTOR pathway, which is involved in neoangiogenesis, cell growth and proliferation and is often deregulated in cancers. Sirolimus has shown a 40% reduction in malignancy risk in kidney transplant recipients, but its use is not without drawbacks. It is associated with a paradoxical increase in mortality, probably due to its effects on wound healing and overall immune function [151]. Moreover, his controversial role, can be underlined by his protective effects against specific malignancies (such as skin cancers and lymphomas) but also carry the risk of promoting other types of cancers, particularly solid tumours (renal cell carcinoma, gastrointestinal cancers, and other solid tumours) [160]. Everolimus,

 doi:10.20944/preprints202502.1237.v1

a similar drug, has a better safety profile, but its effectiveness in reducing cancer risk in liver transplant recipients remains unproven [161]. Nevertheless, due to its potential anti-cancer properties, sirolimus is often considered in cases where de novo malignancies are diagnosed, but its use should be closely monitored for any potential adverse effects, such as wound healing complications and infections. Everolimus, while potentially safer, may still be considered as an alternative if the risks of sirolimus outweigh its benefits. These drugs may slow tumour progression but carry risks, including increased mortality [168]

Induction agents are also part of the immunosuppressive regimen, especially in the early post-transplant period. Anti-thymocyte globulin (ATG) is a potent T-cell depleting agent used in liver transplant recipients, but it has been associated with an increased risk of PTLD and melanoma. The risk of these malignancies is particularly pronounced in patients who are also infected with EBV [152–154]. Therefore, ATG should be used cautiously in high-risk patients, and recipients receiving this induction therapy should be closely monitored for signs of PTLD and melanoma. On the other hand, anti-IL-2 receptor antibodies (such as basiliximab) is generally associated with a lower risk of skin cancers and PTLD compared to other immunosuppressive therapies, but the risk of hepatocellular carcinoma and other solid tumours remains a concern due to the overall immunosuppressive burden in liver transplant patients [162].

In summary, the management of immunosuppression after the diagnosis of DNM in liver transplant recipients requires individualised adjustments to reduce cancer risk while preventing organ rejection. Reducing the doses of CNIs or switching to mTORi like sirolimus or everolimus can help achieve this balance (Table 3). Additionally, replacing azathioprine with MMF can lower the risk of skin cancers, and careful monitoring is needed when using induction agents like ATG due to their association with post-transplant malignancies. The goal is to reduce the burden of cancer while maintaining graft survival, and this requires ongoing collaboration between hepatologists, transplant surgeons, and oncologists.

Table 3. Recommendations for Immunosuppression Management in LT Recipients with Cancer:.

1. **CNI Reduction**: CNIs should be reduced to the lowest possible dose to decrease the risk of DNM
2. **Balance Immunosuppression**: Modification of immunosuppression should be balanced with the risk of rejection and interactions with cancer treatments
3. **Use of mTORi and MMF**: Both mTOR inhibitors and mycophenolate mofetil do not increase cancer risk and should be considered as part of CNI-sparing strategies [169]
4. **Induction Agents**: Minimize lymphocyte-depleting induction agents and prefer IL-2 receptor antagonists when feasible.
5. **NMSC Management**: For LT recipients with NMSC, consider reducing CNIs and adding or switching to mTORi to reduce recurrence, particularly for squamous cell carcinoma.
6. **Kaposi Sarcoma Treatment**: In LT patients with Kaposi sarcoma, immunosuppression should be tapered to the lowest possible level, with mycophenolate elimination and conversion to mTOR-based immunosuppression.

Table 3 Abbreviations: CNI: Calcineurin inhibitors; DNM: De Novo Malignancy; mTORi: rapamycin inhibitors; MMF mycophenolate mofetile; NMSC: Non Melanoma Skin Cancers

4. Conclusion

The development of de novo malignancies in LT recipients represents a multifaceted challenge driven by the interplay of immunosuppressive therapy, demographic factors, and underlying liver

 doi:10.20944/preprints202502.1237.v1

disease. While advancements in surgical techniques, immunosuppression protocols, and post-transplant care have significantly improved long-term survival, the increased incidence of cancer underscores the need for tailored strategies to mitigate this risk. These malignancies, which include skin cancers, lymphoproliferative disorders, and various solid tumours, highlight the long-term vulnerability of LT recipients to oncogenic processes.

Effective cancer prevention in this population requires a comprehensive approach. Optimising immunosuppression is critical; the reduction of CNIs and the integration of mTORi present promising avenues for balancing immunological control with oncological risk. However, further liver-specific studies are essential to establish definitive guidelines for managing immunosuppression in the context of de novo malignancies. In addition, the role of MMF as a safer alternative to azathioprine warrants closer examination in terms of long-term cancer outcomes.

Beyond immunosuppression, a proactive focus on cancer surveillance is imperative. Regular skin examinations, LDCT for lung cancer in high-risk populations, and colonoscopies for recipients with PSC or IBD should be integrated into routine care. These measures not only enable early detection but also improve treatment outcomes and survival. The incorporation of patient education regarding lifestyle modifications, such as smoking cessation, alcohol reduction, and sun protection, remains an essential component of long-term cancer prevention strategies.

Collaboration across disciplines—encompassing hepatology, oncology, transplant surgery, and primary care—is vital to addressing the unique challenges posed by de novo malignancies. Personalised care pathways that consider individual risk factors, regional cancer patterns, and patient-specific needs can significantly enhance outcomes. As the field of transplantation evolves, it is crucial to continue refining strategies that balance the benefits of long-term graft survival with the prevention and management of malignancies. Ultimately, these efforts will contribute to improved quality of life and longevity for liver transplant recipients.

5. Future Directions

Adequate monitoring of DTC should be performed as whith the aging of donors, DTC could become more prevalent, though the transmission risk currently remains low. It is also essential to implement protective strategies to minimise the risk of DNM – such as reducing tacrolimus use, promoting anti-smoking and alcohol initiatives, and limiting UV exposure – and to develop screening programmes that are specifically tailored to each patient's individual risk.

Author Contributions: T. V. L. wrote the first version of the manuscript. A. C., E. N. L., and A. G. critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The authors did not receive support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript. No funding was received for conducting this study. No funds, grants, or other support was received.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LT	Liver transplantation
DTC	Donor Transmitted Cancer:
DDC	Donor Derived Cancer
DNM	De Novo Malignancy

 doi:10.20944/preprints202502.1237.v1

SIR	standardized incidence rates
CRC	Colorectal cancers
CNS	Central Nervous System
RCC	Renal cell carcinoma
IBD	Inflammatory bowel disease
UC	Ulcerative Colitis
PSC	Primary sclerosing cholangitis;
NASH	Non-alcoholic steatohepatitis
HCC	Nepatocellular carcinoma
CT	Computed Tomography
LDCT	Low Dose Computed Tomography
ALD	Alcoholic liver disease
ENT	Ear, nose, and throat
HPV	Human Papilloma Virus
PSA	Prostate-specific antigen
NMSC	Non Melanoma Skin Cancers
PTLD	Post- transplant lymphoproliferative disorders
EBV	Epstein Barr Virus
KS	Kaposi Sarcoma
CsA	cyclosporine
CNI	Calcineurin inhibitors
mTORi:	rapamycin inhibitors
MMF	mycophenolate mofetile
ATG	anti-thymocyte globulin

References

1. Eccher A, Girolami I, Marletta S, et al. Donor-transmitted cancers in transplanted livers: analysis of clinical outcomes. Liver Transpl. 2021;27:55–66
2. Murray JE, Gleason r, bartholomay a. third report of the human kidney transplant registry. Transplantation 1965; 3: 294-302 [PMID: 14265505 DOI: 10.1097/00007890-196503000-00039]
3. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors-unavoidable but low risk. Transplantation 2012; 94: 1200-1207
4. Council of Europe: Guide to the Safety and Quality Assurance for the Transplantation of Organs, Tissues and Cells: Council of Europe; 2010 (cited 2013 16 September). Available from: http://www.edqm.eu/en/blood-organ-guides-1131.html.
5. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114: 97-109 [PMID: 17618441 DOI: 10.1007/s00401-007-0243-4]
6. Watson CJ, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, Counter C, Collett D, Bradley JA. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK Registry data. Am J Transplant 2010; 10: 1437-1444 [PMID: 20486904 DOI: 10.1111/j.1600-6143.2010.03130.x]
7. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. Transplantation 2007; 84: 272-274 [PMID: 17667822 DOI: 10.1097/01.tp.0000267919.93425.fb]
8. Neipp M, Schwarz A, Pertschy S, Klempnauer J, Becker T. Accidental transplantation of a kidney with a cystic renal cell carcinoma following living donation: management and 1 yr follow-up. Clin Transplant 2006; 20: 147-150 [PMID: 16640518 DOI: 10.1111/j.1399-0012.2005.00455.x]
9. Desai R, Neuberger J. Donor transmitted and de novo cancer after liver transplantation. World J Gastroenterol. 2014 May 28;20(20):6170-9. doi: 10.3748/wjg.v20.i20.6170. PMID: 24876738; PMCID: PMC4033455.

 doi:10.20944/preprints202502.1237.v1

10. Nalesnik MA, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, Covington S, Taranto S, Gockerman JP, Shapiro R, Sharma V, Swinnen LJ, Yoshida A, Ison MG. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant 2011; 11: 1140-1147 [PMID:21645251 DOI: 10.1111/j.1600-6143.2011.03565.x]
11. Nalesnik MA. Tumors and solid organ transplantation: intersections at multiple levels. Medscape. 2003. Available at http://cme.medscape. com/viewarticle/449388. Accessed August 20, 2017.
12. Feng S, Buell JF, Chari RS, et al. Tumors and transplantation: the 2003 Third Annual ASTS State-of-the-Art Winter Symposium. Am J Transplant. 2003;3:1481–1487
13. Ferlay J, Ervik M, Lam F, et al. eds, Global Cancer Observatory: Cancer Today (Version 1.0). International Agency for Research on Cancer; 2024. Accessed February 1, 2024. https://gco.iarc.who.int/today
14. Matser YAH, Terpstra ML, Nadalin S, et al. Transmission of breast cancer by a single multiorgan donor to 4 transplant recipients. Am J Transplant. 2018;18:1810–1814.
15. European Committee on Organ Transplantation. European Directorate for the Quality of Medicines & HealthCare. Guide to the Quality and Safety of Organs for Transplantation. 7th ed. European Committee on Organ Transplantation. European Directorate for the Quality of Medicines & HealthCare; 2018
16. Benkö T, Hoyer DP, Saner FH, et al. Liver transplantation from donors with a history of malignancy: a single-center experience. Transplant Direct. 2017;3:e224.
17. Loosen SH, Schmeding M, Roderburg C, et al. A liver nodule in a patient transplanted for primary sclerosing cholangitis: an interdisciplinary diagnostic approach. Z Gastroenterol. 2017;55:56–62.
18. Snape K, Izatt L, Ross P, et al. Donor-transmitted malignancy confirmed by quantitative fluorescence polymerase chain reaction genotype analysis: a rare indication for liver retransplantation. Liver Transpl. 2008;14:155–158
19. Zelinkova Z, Geurts-Giele I, Verheij J, et al. Donor-transmitted metastasis of colorectal carcinoma in a transplanted liver. Transpl Int. 2012;25:e10–e15.
20. Kim B, Woreta T, Chen PH, et al. Donor-transmitted malignancy in a liver transplant recipient: a case report and review of literature. Dig Dis Sci. 2013;58:1185–1190.
21. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131:803–820.
22. Cavaliere R, Schiff D. Donor transmission of primary brain tumors:a neurooncologic perspective. Transplant Rev (Philadelphia). 2004;18:204–213.
23. Awan M, Liu S, Sahgal A, et al. Extra-CNS metastasis from glioblastoma: a rare clinical entity. Expert Rev Anticancer Ther. 2015;15:545–552.
24. Armanios MY, Grossman SA, Yang SC, et al. Transmission of glioblastoma multiforme following bilateral lung transplantation from an affected donor: case study and review of the literature. Neuro Oncol. 2004;6:259–263.
25. Warrens AN, Birch R, Collett D, et al.; Advisory Committee on the Safety of Blood, Tissues and Organs, UK. Advising potential recipients on the use of organs from donors with primary central nervous system tumors. Transplantation. 2012;93:3
26. Sonbol MB, Halling KC, Douglas DD, et al. A case of donor-transmitted non-small cell lung cancer after liver transplantation: an unwell come guest. Oncologist. 2019;24:e391–e393.
27. Lipshutz GS, Baxter-Lowe LA, Nguyen T, et al. Death from donor-transmitted malignancy despite emergency liver retransplantation. Liver Transpl. 2003;9:1102–1107.
28. Mottet N, Bastian P, Bellmunt J, et al. EAU–EANM–ESTRO–ESUR–SIOG: Guidelines on Prostate Cancer. European Association of Urology; 2020.
29. Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol. 2016;34:1652–165
30. Sánchez-Montes C, Aguilera V, Prieto M, et al. Periesophageal lymph node metastasis of prostate adenocarcinoma from liver transplant donor. Am J Gastroenterol. 2019;114:378
31. Loh E, Couch FJ, Hendricksen C, et al. Development of donor-derived prostate cancer in a recipient following orthotopic heart transplantation. JAMA. 1997;277:133–137.

 doi:10.20944/preprints202502.1237.v1

32. Yin M, Bastacky S, Chandran U, et al. Prevalence of incidental prostate cancer in the general population: a study of healthy organ donors. J Urol. 2008;179:892–895
33. Doerfler A, Tillou X, le Gal S, et al. Prostate cancer in deceased organ donors: a review. Transplant Rev. 2014;28:1–5.
34. Pezzati D, Ghinolfi D, Lai Q, et al. Use of donors with genitourinary malignancies for liver transplantation: a calculated risk? Transpl Int. 2017;30:737–739.
35. Pavlakis M, Michaels MG, Tlusty S, et al. Renal cell carcinoma suspected at time of organ donation 2008–2016: a report of the OPTN ad hoc Disease Transmission Advisory Committee Registry. Clin Transplant. 2019;33:e13597
36. Carver BS, Zibari GB, McBride V, et al. The incidence and implications of renal cell carcinoma in cadaveric renal transplants at the time of organ recovery. Transplantation. 1999;67:1438–1440
37. Desai R, Collett D, Watson CJ, et al. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. Br J Surg. 2014;101:768–774.
38. Garrido G, Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. Transplantation. 2008;85:S61–S63
39. Taioli E, Mattucci DA, Palmieri S, et al. A population-based study of cancer incidence in solid organ transplants from donors at various risk of neoplasia. Transplantation. 2007;83:13–16.
40. Pretagostini R, Peritore D, Fiaschetti P, et al. Incidence of neoplastic donors in Organizzazione Centro Sud Trapianti area during the 2003–2005 period. Transplant Proc. 2007;39:1746–1748.
41. Organ Procurement and Transplantation Network. OPTN Policies. Available at https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed June 2021
42. European Parliament, Council of the European Union. Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. Available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32010L0053. Accessed June 2021.
43. Lipshutz GS, Baxter-Lowe LA, Nguyen T, et al. Death from donor-transmitted malignancy despite emergency liver retransplantation. Liver Transpl. 2003;9:1102–1107
44. Lui SK, Garcia CR, Mei X, et al. Re-transplantation for hepatic artery thrombosis: a national perspective. World J Surg. 2018;42:3357–3363.
45. Allaire M, Sérée O, Coilly A, et al. De novo primary liver cancer after liver transplantation: a French National Study on 15803 patients. Exp Clin Transplant. 2018;16:779–780.
46. Dantal J, Soulillou JP. Immunosuppressive drugs and the risk of cancer after organ transplantation. N Engl J Med. 2005;352:1371–1373.
47. Krisl JC, Doan VP. Chemotherapy and transplantation: the role of immunosuppression in malignancy and a review of antineoplastic agents in solid organ transplant recipients. Am J Transplant. 2017;17:1974–1991
48. Shaked A, DesMarais MR, Kopetskie H, et al. Outcomes of immunosuppression minimization and withdrawal early after liver transplantation. Am J Transplant. 2019;19:1397–1409.
49. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998;351:623–628.
50. Robson R, Cecka JM, Opelz G, et al. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Transplant. 2005;5:2954–2960.
51. Coghill AE, Johnson LG, Berg D, et al. Immunosuppressive medications and squamous cell skin carcinoma: nested case-control study within the Skin Cancer after Organ Transplant (SCOT) cohort. Am J Transplant. 2016;16:565–573.
52. Dierickx D, Tousseyn T, De Wolf-Peeters C, et al. Management of posttransplant lymphoproliferative disorders following solid organ transplant: an update. Leuk Lymphoma. 2011;52:950–9
53. de Fijter JW. Cancer and mTOR inhibitors in transplant recipients. Transplantation. 2017;101:45–55.

 doi:10.20944/preprints202502.1237.v1

54. Fischer L, Saliba F, Kaiser GM, et al.; H2304 Study Group. Three-year outcomes in de novo liver transplant patients receiving everolimus with reduced tacrolimus: follow-up results from a randomized, multicenter study. Transplantation. 2015;99:1455–1462.
55. Saliba F, Duvoux C, Gugenheim J, et al. Efficacy and safety of everolimus and mycophenolic acid with early tacrolimus withdrawal after liver transplantation: a multicenter randomized trial. Am J Transplant. 2017;17:1843–1852.
56. Saliba F, Duvoux C, Dharancy S, et al. Early switch from tacrolimus to everolimus after liver transplantation: outcomes at 2 years. Liver Transpl. 2019;25:1822–1832.
57. Cillo U, Saracino L, Vitale A, et al. Very early introduction of everolimus in de novo liver transplantation: results of a multicenter, prospective, randomized trial. Liver Transpl. 2019;25:242-251.
58. Asrani SK, Wiesner RH, Trotter JF, et al. De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000–2003 phase II prospective randomized trial. Am J Transplant. 2014;14:356–366.
59. Taborelli M, Piselli P, Ettorre GM, et al.; Italian Transplant and Cancer Cohort Study. Survival after the diagnosis of de novo malignancy in liver transplant recipients. Int J Cancer. 2019;144:232–239.
60. Jiang Y, Villeneuve PJ, Fenton SS, et al. Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. Liver Transpl. 2008;14:1588–1597.
61. Sérée O, Altieri M, Guillaume E, et al. Longterm risk of solid organ de novo malignancies after liver transplantation: a French national study on 11,226 patients. Liver Transpl. 2018;24:1425–1436.
62. Zhou J, Hu Z, Zhang Q, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the Scientific Registry of Transplant Recipients Database. PLoS One. 2016;11:e0155179.
63. Piselli P, Verdirosi D, Cimaglia C, et al. Epidemiology of de novo malignancies after solid-organ transplantation: immunosuppression, infection and other risk factors. Best Pract Res Clin Obstet Gynaecol. 2014;28:1251–1265.
64. Haider M, Bapatla A, Ismail R, Chaudhary AJ, Iqbal S, Haider SM. The spectrum of malignant neoplasms among liver transplant recipients: sociodemographic factors, mortality, and hospital burden. Int J Med Sci 2022;19:299-309.
65. Kim S, Rovgaliyev B, Lee JM, Lee KW, Hong SK, Cho JH, et al. Clinical significance of de novo malignancy after liver transplant: a single-center study. Transplant Proc 2021;53:200-206
66. Park HW, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, et al. De novo malignancies after liver transplantation: incidence comparison with the Korean cancer registry. Transplant Proc 2012;44:802-805.
67. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004; 21: 137-148 [PMID: 15308095 DOI: 0.1016/j.immuni.2004.07.017]
68. Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. Am J Transplant 2008; 8: 2212-2218 [PMID: 18785960 DOI: 10.1111/j.1600-6143.2008.02391.x]
69. Vivarelli M, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. Transplantation 2010; 89: 227-231 [PMID: 20098287 DOI: 10.1097/TP.0b013e3181c3c540]
70. Chinnakotla S, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E, Onaca N, Goldstein R, Levy M, Klintmalm GB. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. Liver Transpl 2009; 15: 1834-1842 [PMID:19938137 DOI: 10.1002/lt.21953]
71. Bilbao I, Sapisochin G, Dopazo C, Lazaro JL, Pou L, Castells L, Caralt M, Blanco L, Gantxegi A, Margarit C, Charco R. Indications and management of everolimus after liver transplantation. Transplant Proc 2009; 41: 2172-2176 [PMID: 19715864 DOI:10.1016/j.transproceed.2009.06.087]
72. Jiménez-Romero C, Manrique A, Marqués E, Calvo J, Sesma AG, Cambra F, Abradelo M, Sterup RM, Olivares S, Justo I, Colina F, Moreno E. Switching to sirolimus monotherapy for de novo tumors after liver transplantation. A preliminary experience. Hepatogastroenterology 2011; 58: 115-121 [PMID: 21510297]
73. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation 2005; 80: 883-889 [PMID: 16249734 DOI: 10.1097/01.TP.0000184006.43152.8D]

 doi:10.20944/preprints202502.1237.v1

74. Benlloch S, Berenguer M, Prieto M, Moreno R, San Juan F, Rayón M, Mir J, Segura A, Berenguer J. De novo internal neoplasms after liver transplantation: increased risk and aggressive behavior in recent years? Am J Transplant 2004; 4: 596-604 [PMID: 15023152 DOI: 10.1111/j.1600-6143.2004.00380.x]
75. Tressler RJ, Garvin LJ, Slate DL. Anti-tumor activity of mycophenolate mofetil against human and mouse tumors in vivo. Int J Cancer 1994; 57: 568-573 [PMID: 8181860 DOI: 10.1002/ijc.2910570421]
76. Robson R, Cecka JM, Opelz G, Budde M, Sacks S. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Transplant 2005; 5: 2954-2960 [PMID: 16303010 DOI: 10.1111/j.1600-6143.2005.01125.x]
77. Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF, Engels EA. Risk of Colorectal Cancer After Solid Organ Transplantation in the United States. Am J Transplant 2016; 16: 960-967[PMID: 26731613 DOI: 10.1111/ajt.13549]
78. Aberg F, Pukkala E, Höckerstedt K, Sankila R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population-based study. Liver Transpl 2008; 14: 1428-1436 [PMID: 18825704DOI: 10.1002/lt.21475]
79. Jonas S, Rayes N, Neumann U, Neuhaus R, Bechstein WO, Guckelberger O, Tullius SG, Serke S, Neuhaus P. De novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. Cancer 1997; 80: 1141-1150 [PMID: 9305716 DOI: 10.1002/(SICI)1097-0142(19970915)80]
80. Yao FY, Gautam M, Palese C, Rebres R, Terrault N, Roberts JP, Peters MG. De novo malignancies following liver transplantation: a case-control study with long-term follow-up. Clin Transplant 2006; 20: 617-623 [PMID: 16968488 DOI: 10.1111/j.1399-0012.2006.00527.x]
81. Herrero JI, Lucena JF, Quiroga J, Sangro B, Pardo F, Rotellar F, Alvárez-Cienfuegos J, Prieto J. Liver transplant recipients older than 60 years have lower survival and higher incidence of malignancy. Am J Transplant 2003; 3: 1407-1412 [PMID: 14525602]
82. Engels EA, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306: 1891-1901 [PMID: 22045767 DOI: 10.1001/jama.2011.1592]
83. Oo YH, Gunson BK, Lancashire RJ, Cheng KK, Neuberger JM. Incidence of cancers following orthotopic liver transplantation in a single center: comparison with national cancer incidence rates for England and Wales. Transplantation 2005; 80: 759-764 [PMID: 16210962 DOI: 10.1097/01.TP.0000173775.16579.18]
84. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo Mukthinuthalapati PK et al. . Cancers occurring after LT 541 April 28, 2016|Volume 8|Issue 12|WJH|www.wjgnet.com malignancy after liver transplantation. Gastroenterology 2009; 137:2010-2017 [PMID: 19766646 DOI: 10.1053/j.gastro.2009.08.070
85. Maggi U, Consonni D, Manini MA, Gatti S, Cuccaro F, Donato F, Conte G, Bertazzi PA, Rossi G. Early and late de novo tumors after liver transplantation in adults: the late onset of bladder tumors in men. PLoS One 2013; 8: e65238 [PMID: 23785414 DOI: 10.1371/ journal.pone.0065238]
86. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81: 353-373 [PMID: 16529140 DOI: 10.4065/81.3.353]
87. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993; 72: 1369-1375n[PMID: 8339227 DOI: 10.1002/1097-0142(19930815)72]
88. Leithead JA, Ferguson JW, Hayes PC. Smoking-related morbidity and mortality following liver transplantation. Liver Transpl 2008; 14: 1159-1164 [PMID: 18668649 DOI: 10.1002/lt.21471]
89. Castelli E, Hrelia P, Maffei F, Fimognari C, Foschi FG, Caputo F, Cantelli-Forti G, Stefanini GF, Gasbarrini G. Indicators of genetic damage in alcoholics: reversibility after alcohol abstinence. Hepato gastroenterology 1999; 46: 1664-1668 [PMID: 10430317]

 doi:10.20944/preprints202502.1237.v1

90. Castellsagué X, Muñoz N, De Stefani E, Victora CG, Quintana MJ, Castelletto R, Rolón PA. Smoking and drinking cessation and risk of esophageal cancer (Spain). Cancer Causes Control 2000;11: 813-818 [PMID: 11075870 DOI: 10.1023/A:1008984922453]
91. Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, Slooff MJ, Jansen PL. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001; 34: 84-91 [PMID: 11211912 DOI: 10.1016/S0168-8278(00) 00077-5
92. Kelly DM, Emre S, Guy SR, Miller CM, Schwartz ME, Sheiner PA. Liver transplant recipients are not at increased risk for nonlymphoid solid organ tumors. Cancer 1998; 83: 1237-1243 [DOI: 10.1002/(SICI)1097-0142(19980915)83:6<1237::AID-CNCR25>3.0.CO;2-5]
93. Castelli E, Hrelia P, Maffei F, Fimognari C, Foschi FG, Caputo F, Cantelli-Forti G, Stefanini GF, Gasbarrini G. Indicators of genetic damage in alcoholics: reversibility after alcohol abstinence. Hepato gastroenterology 1999; 46: 1664-1668 [PMID: 10430317]
94. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Engl J Med 2018;378:549-562.
95. Bakker NA, van Imhoff GW, Verschuuren EA, van Son WJ. Presentation and early detection of post-transplant lymphoproliferative disorder after solid organ transplantation. Transpl Int 2007; 20: 207-218 [PMID: 17291214 DOI: 10.1111/j.1432-2277.2006.00416.x]
96. Dierickx D, Tousseyn T, De Wolf-Peeters C, Pirenne J, Verhoef G. Management of posttransplant lymphoproliferative disorders following solid organ transplant: An update. Leuk Lymphoma 2011; 52: 950-961 [PMID: 21338285 DOI: 10.3109/10428194.2011.557453]
97. Mizuno S, Hayasaki A, Ito T, Fujii T, Iizawa Y, Kato H, Murata Y, Tanemura A, Kuriyama N, Azumi Y, Kishiwada M, Usui M, Sakurai H, Isaji S. De Novo Malignancy Following Adult-to-Adult Living Donor Liver Transplantation Focusing on Posttransplantation Lymphoproliferative Disorder. Transplant Proc 2018; 50: 2699-2704 [PMID: 30401380 DOI: 10.1016/j.transproceed.2018.03.059]
98. Jain A, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, Eghtesad B, Marsh W, Cacciarelli T, Fontes P, Abu-Elmagd K, Sindhi R, Demetris J, Fung J. Posttransplant lymphoproliferative disorders in liver transplantation: A 20-year experience. Ann Surg 2002; 236: 429-36; discussion 436-7 [PMID:12368671 DOI: 10.1097/00000658-200210000-00005]
99. Kremers WK, Devarbhavi HC, Wiesner RH, Krom RA, Macon WR, Habermann TM. Post-transplant lymphoproliferative disorders following liver transplantation: Incidence, risk factors and survival. Am J Transplant 2006; 6: 1017-1024 [PMID: 16611339 DOI: 10.1111/j.1600-6143.2006.01294.x
100. Newell KA, Alonso EM, Whitington PF, Bruce DS, Millis JM, Piper JB, Woodle ES, Kelly SM, Koeppen H, Hart J, Rubin CM, Thistlethwaite JR. Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. Transplantation 1996; 62: 370-375 [PMID: 8779685 DOI: 10.1097/00007890-199608150-00012]
101. Ducroux E, Boillot O, Ocampo MA, Decullier E, Roux A, Dumortier J, Kanitakis J, Jullien D, Euvrard S. Skin cancers after liver transplantation: Retrospective single-center study on 371 recipients. Transplantation 2014; 98: 335-340 [PMID: 24621534 DOI:10.1097/TP.0000000000000051]
102. Krynitz B, Edgren G, Lindelöf B, Baecklund E, Brattström C, Wilczek H, Smedby KE. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—a Swedish population-based study. Int J Cancer 2013; 132: 1429-1438 [PMID: 22886725 DOI: 10.1002/ijc.27765]
103. Tran M, Sander M, Ravani P, Mydlarski PR. Incidence of melanoma in organ transplant recipients in Alberta, Canada. Clin Transplant 2016; 30: 1271-1275 [PMID: 27448204 DOI: 10.1111/ctr.12818]
104. Saigal S, Norris S, Muiesan P, Rela M, Heaton N, O'Grady J. Evidence of differential risk for posttransplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. Liver Transpl 2002; 8: 482-487 [PMID: 12004349 DOI: 10.1053/jlts.2002.32977]
105. Mithoefer AB, Supran S, Freeman RB. Risk factors associated with the development of skin cancer after liver transplantation. Liver Transpl 2002; 8: 939-944 [PMID: 12360438 DOI: 10.1053/jlts.2002.35551]
106. Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, Torbenson M, Starzl TE, Fung JJ, Demetris AJ. Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. Transplantation 2001; 72: 619-626 [PMID: 11544420 DOI: 10.1097/00007890-200108270-00010]

 doi:10.20944/preprints202502.1237.v1

107. D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002; 47: 1-17; quiz 18-20 [PMID: 12077575 DOI:10.1067/mjd.2002.125579]
108. Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: A prospective study in Queensland, Australia. Am J Kidney Dis 2003; 41: 676-683 [PMID: 12612993 DOI: 10.1053/ajkd.2003.50130]
109. Otley CC, Cherikh WS, Salasche SJ, McBride MA, Christenson LJ, Kauffman HM. Skin cancer in organ transplant recipients: Effect of pretransplant end-organ disease. J Am Acad Dermatol 2005; 53: 783-790 [PMID: 16243126 DOI: 10.1016/j.jaad.2005.07.061]
110. Piselli P, Taborelli M, Cimaglia C, Serraino D; Italian Transplant & Cancer Cohort Study. Decreased incidence of Kaposi sarcoma after kidney transplant in Italy and role of mTOR-inhibitors: 1997-2016. Int J Cancer 2019; 145: 597-598 [PMID: 30613958 DOI: 10.1002/ijc.32098]
111. Berber I, Altaca G, Aydin C, Dural A, Kara VM, Yigit B, Turkmen A, Titiz MI. Kaposi's sarcoma in renal transplant patients: Predisposing factors and prognosis. Transplant Proc 2005; 37: 967-968 [PMID:15848593 DOI: 10.1016/j.transproceed.2004.12.034]
112. Euvrard S, Kanitakis J. Skin cancers after liver transplantation: What to do? J Hepatol 2006; 44: 27-32 [PMID: 16290909 DOI: 10.1016/j.jhep.2005.10.010]
113. Schneider JW, Dittmer DP. Diagnosis and Treatment of Kaposi Sarcoma. Am J Clin Dermatol 2017; 18:529-539 [PMID: 28324233 DOI: 10.1007/s40257-017-0270-4]
114. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP, Grandaliano G. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005; 352:1317-1323 [PMID: 15800227 DOI: 10.1056/NEJMoa042831]
115. Liu Q, Yan L, Xu C, Gu A, Zhao P, Jiang ZY. Increased incidence of head and neck cancer in liver transplant recipients: a meta-analysis. BMC Cancer 2014; 14: 776 [PMID: 25338638 DOI:
116. Chak E, Saab S. Risk factors and incidence of de novo malignancy in liver transplant recipients: a systematic review. Liver Int 2010; 30: 1247-1258 [PMID: 20602682 DOI: 10.1111/j.1478-3231.20]
117. Herrero JI, Pardo F, D'Avola D, Alegre F, Rotellar F, Iñarrairaegui M, Martí P, Sangro B, Quiroga J. Risk factors of lung, head and neck, esophageal, and kidney and urinary tract carcinomas after liver transplantation: the effect of smoking withdrawal. Liver Transpl 2011; 17: 402-408 [PMID: 21445923 DOI: 10.1002/lt.22247]
118. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 2005; 56: 87-99 [PMID: 15979889 DOI: 10.1016/j.critrevonc.2004.12.011]
119. Jiménez C, Rodríguez D, Marqués E, Loinaz C, Alonso O, Hernández-Vallejo G, Marín L, Rodríguez F, García I, Moreno E. De novo tumors after orthotopic liver transplantation. Transplant Proc 2002; 34: 297-298 [PMID: 11959293 DOI: 10.1016/S0041-1345(01)02770-1]
120. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant 2010; 10: 1889-1896 [PMID: 20659094 DOI: 10.1111/j.1600-6143.20]
121. Baccarani U, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P. Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. Dig Liver Dis 2010; 42: 55-60 [PMID: 19497797 DOI: 10.1016/j.dld.2009.04.017]
122. Bleday R, Lee E, Jessurun J, Heine J, Wong WD. Increased risk of early colorectal neoplasms after hepatic transplant in patients with inflammatory bowel disease. Dis Colon Rectum 1993; 36: 908-912 [PMID: 8404380 DOI: 10.1007/BF02050624]
123. Fabia R, Levy MF, Testa G, Obiekwe S, Goldstein RM, Husberg BS, Gonwa TA, Klintmalm GB. Colon carcinoma in patients undergoing liver transplantation. Am J Surg 1998; 176: 265-269 [PMID: 9776156 DOI: 10.1016/S0002-9610(98)00141-X]
124. Vera A, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, Mayer A, Buckels JA, McMaster P, Neuberger J, Mirza

125. DF. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation 2003; 75: 1983-1988 [PMID: 12829898 DOI: 10.1097/01.tp.0000058744.34965.38]
126. Buell JF, Papaconstantinou HT, Skalow B, Hanaway MJ, Alloway RR, Woodle ES. De novo colorectal cancer: five-year survival is markedly lower in transplant recipients compared with the general population. Transplant Proc 2005; 37: 960-961 [PMID: 15848590 DOI: 10.1016/j.transproceed.2004.12.122]
127. Johnson EE, Leverson GE, Pirsch JD, Heise CP. A 30-year analysis of colorectal adenocarcinoma in transplant recipients and proposal for altered screening. J Gastrointest Surg 2007; 11: 272-279 [PMID: 17458597 DOI: 10.1007/s11605-007-0084-4]
128. Vera A, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, Mayer A, Buckels JA, McMaster P, Neuberger J, Mirza DF. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation 2003; 75: 1983-1988 [PMID: 12829898 DOI: 10.1097/01.tp.0000058744.34965.38]
129. Park HW, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, Song GW, Jung DH, Park GC, Namgoong JM, Yoon SY, Park CS, Park YH, Lee HJ, Lee SG. De novo malignancies after liver transplantation: incidence comparison with the Korean cancer registry. Transplant Proc 2012; 44: 802-805 [PMID: 22483500 DOI: 10.1016/j.transproceed.2012.01.027]
130. Yu S, Gao F, Yu J, Yan S, Wu J, Zhang M, Wang W, Zheng S. De novo cancers following liver transplantation: a single center experience in China. PLoS One 2014; 9: e85651 [PMID: 24475047 DOI: 10.1371/journal.pone.0085651]
131. Kim M, Kim CW, Hwang S, Kim YH, Lee JL, Yoon YS, et al. Characteristics and prognosis of colorectal cancer after liver or kidney transplantation. World J Surg 2021;45:3206-3213.
132. Carenco C, Faure S, Herrero A, Assenat E, Duny Y, Danan G, Bismuth M, Chanques G, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Incidence of solid organ cancers after liver transplantation: Comparison with regional cancer incidence rates and risk factors. Liver Int 2015; 35: 1748-1755 [PMID: 25488375 DOI: 10.1111/liv.12758]
133. Nordin A, Åberg F, Pukkala E, Pedersen CR, Storm HH, Rasmussen A, Bennet W, Olausson M, Wilczek H, Ericzon BG, Tretli S, Line PD, Karlsen TH, Boberg KM, Isoniemi H. Decreasing incidence of cancer after liver transplantation-A Nordic population-based study over 3 decades. Am J Transplant 2018; 18: 952-963 [PMID: 28925583 DOI: 10.1111/ajt.14507
134. Burra P, Rodriguez-Castro KI. Neoplastic disease after liver transplantation: Focus on de novo neoplasms. World J Gastroenterol 2015; 21: 8753-8768 [PMID: 26269665 DOI: 10.3748/wjg.v21.i29.8753]
135. Burra P, Shalaby S, Zanetto A. Long-term care of transplant recipients: De novo neoplasms after liver transplantation. Curr Opin Organ Transplant 2018; 23: 187-195 [PMID: 29324517 DOI: 10.1097/MOT.0000000000000499
136. Baccarani U, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P. Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. Dig Liver Dis 2010; 42: 55-60 [PMID: 19497797 DOI: 10.1016/j.dld.2009.04.017]
137. Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, Ekbom A, Adami HO, Granath F. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003; 89: 1221-1227 [PMID: 14520450 DOI: 10.1038/sj.bjc.6601219]
138. Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, Woodle ES. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation 2009; 87: 1347-1359 [PMID: 19424035 DOI: 10.1097/TP.0b013e3181a238f6]
139. Herrero JI, Lorenzo M, Quiroga J, Sangro B, Pardo F, Rotellar F, Alvarez-Cienfuegos J, Prieto J. De Novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. Liver Transpl 2005; 11: 89-97 [PMID: 15690541 DOI: 10.1002/lt.20319]
140. Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, Zak M, Rakela J, Irish W, Fung JJ. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using

 doi:10.20944/preprints202502.1237.v1

surveillance epidemiologic end result data. Trans plantation 1998; 66: 1193-1200 [PMID: 9825817 DOI: 10.1097/00007890-199811150-00014]

141. Chatrath H, Berman K, Vuppalanchi R, Slaven J, Kwo P, Tector AJ, Chalasani N, Ghabril M. De novo malignancy post-liver transplantation: a single center, population controlled study. Clin Transplant 2013; 27: 582-590 [PMID: 23808800 DOI: 10.1111/ctr.12171]
142. Colmenero, Jordi MD, PhD1; Tabrizian, Parissa MD, MSc2; Bhangui, Prashant MBBS, MS3; Pinato, David James MD, PhD4; Rodríguez-Perálvarez, Manuel L. MD, PhD5; Sapisochin, Gonzalo MD PhD, MD6; Bhoori, Sherrie MD7; Pascual, Sonia MD8; Senzolo, Marco MD, PhD9; Al-Adra, David MD, PhD10; Herrero, J. Ignacio MD11; Petrowsky, Henrik MD, FACS12; Dawson, Laura A. MD13; Hosni, Ali MBBCh, MSc, PhD13; Kutzke, Jade L. PharmD14; Gastaca, Mikel MD15; Watt, Kymberly D. MD16. De Novo Malignancy After Liver Transplantation: Risk Assessment, Prevention, and Management—Guidelines From the ILTS-SETH Consensus Conference. Transplantation 106(1):p e30-e45, January 2022. | DOI: 10.1097/TP.0000000000003998
143. Jung DH, Hwang S, Song GW, Ahn CS, Moon DB, Ha TY, et al. Survival benefit of early cancer detection through regular endoscopic screening for de novo gastric and colorectal cancers in Korean liver transplant recipients. Transplant Proc 2016;48:145-151.
144. Tjon AS, Sint Nicolaas J, Kwekkeboom J, et al. Increased incidence of early de novo cancer in liver graft recipients treated with cyclosporine: an association with C2 monitoring and recipient age. Liver Transpl. 2010;16:837–846.
145. Wimmer CD, Angele MK, Schwarz B, et al. Impact of cyclosporine versus tacrolimus on the incidence of de novo malignancy following liver transplantation: a single center experience with 609 patients. Transpl Int. 2013;26:999–1006.
146. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998;351:623–628
147. Jiyad Z, Olsen CM, Burke MT, et al. Azathioprine and risk of skin cancer in organ transplant recipients: systematic review and meta analysis. Am J Transplant. 2016;16:3490–3503.
148. O'Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplanta- tion: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:1186–1191.
149. Robson R, Cecka JM, Opelz G, et al. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Transplant. 2005;5:2954–2960.
150. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005;80:1233–1243.
151. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ. 2014;349:g6679.
152. Rodríguez-Perálvarez M, Guerrero-Misas M, Thorburn D, et al. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. Cochrane Database Syst Rev. 2017;3:CD011639 .
153. Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4:222–230.
154. Hall EC, Engels EA, Pfeiffer RM, et al. Association of antibody induction immunosuppression with cancer after kidney transplantation. Transplantation. 2015;99:1051–1057.
155. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.
156. Choudhary NS, Saigal S, Saraf N, Soin AS. Extrahepatic Malignancies and Liver Transplantation: Current Status. J Clin Exp Hepatol. 2021 Jul-Aug;11(4):494-500. doi: 10.1016/j.jceh.2020.10.008. Epub 2020 Oct 24. PMID: 34276155; PMCID: PMC8267344.

157. Reyes, A.; Mohanty, A.; Pharaon, R.; Massarelli, E. Association between Immunosuppressive Therapy Utilized in the Treatment of Autoimmune Disease or Transplant and Cancer Progression. Biomedicines 2023, 11, 99. https://doi.org/10.3390/biomedicines11010099
158. Burra, Patrizia; Shalaby, Sarah; Zanetto, Alberto. Long-term care of transplant recipients: de novo neoplasms after liver transplantation. Current Opinion in Organ Transplantation 23(2):p 187-195, April 2018. | DOI: 10.1097/MOT.0000000000000499
159. Liu Y, Azizian NG, Sullivan DK, Li Y. mTOR inhibition attenuates chemosensitivity through the induction of chemotherapy resistant persisters. Nat Commun. 2022 Nov 17;13(1):7047. doi: 10.1038/s41467-022-34890-6. PMID: 36396656; PMCID: PMC9671908.
160. Blagosklonny MV. Cancer prevention with rapamycin. Oncotarget. 2023 Apr 14;14:342-350. doi: 10.18632/oncotarget.28410. PMID: 37057884; PMCID: PMC10103596.
161. Wang K, Xu X, Fan M. Induction therapy of basiliximab versus antithymocyte globulin in renal allograft: a systematic review and meta-analysis. Clin Exp Nephrol. 2018 Jun;22(3):684-693. doi: 10.1007/s10157-017-1480-z. Epub 2017 Oct 6. PMID: 28986715.Riis TH, Møller DL, Høgh J, Knudsen AD, Rostved AA, Akdag D, Kirkby N, Lassen U, Rasmussen A, Hillingsø JG, Pommergaard HC. Characteristics of de novo cancer in liver transplant recipients. APMIS. 2023 Apr;131(4):135-141. doi: 10.1111/apm.13296. Epub 2023 Feb 14. PMID: 36680559.
162. Li S, Zhang S, Sun X. Risk of de novo esophageal cancer in liver transplant recipients: systematic review and meta-analysis. J Gastrointest Oncol. 2024 Jun 30;15(3):851-861. doi: 10.21037/jgo-24-66. Epub 2024 Jun 27. PMID: 38989401; PMCID: PMC11231872.
163. Kim A, Waldron O, Daoud D, Huang Y, Patel J, Hong J, Butler T, Jain A. Comparative Review of Standardized Incidence Ratio of Nonlymphoid, De Novo Malignancies After Liver Transplant Versus After Kidney Transplant. Exp Clin Transplant. 2024 Aug;22(8):600-606. doi: 10.6002/ect.2024.0136. PMID: 39254071.
164. Masuda Y, Mita A, Ohno Y, Kubota K, Notake T, Shimizu A, Soejima Y. De Novo Malignancy After Adult-to-Adult Living Donor Liver Transplantation: A Single-Center Long-Term Experience. Transplant Proc. 2023 May;55(4):952-955. doi: 10.1016/j.transproceed.2023.03.044. Epub 2023 Apr 21. PMID: 37088616.
165. Sesa V, Silovski H, Basic-Jukic N, Kosuta I, Sremac M, Mrzljak A. Genitourinary tumors and liver transplantation: A comprehensive review. World J Transplant. 2024 Sep 18;14(3):95987. doi: 10.5500/wjt.v14.i3.95987. PMID: 39295969; PMCID: PMC11317849.
166. Waldron O, Kim A, Daoud D, Zhu J, Patel J, Butler T, Zhou S, Jain A. A Comparative Review of Standardized Incidence Ratios of De Novo Malignancies Post Liver Transplantation in Males Versus Females. Transplant Proc. 2024 Jul-Aug;56(6):1365-1373. doi: 10.1016/j.transproceed.2024.01.065. Epub 2024 Jul 14. PMID: 39003208.
167. Kobayashi T, Miura K, Ishikawa H, Sakata J, Takizawa K, Hirose Y, Toge K, Saito S, Abe S, Kawachi Y, Ichikawa H, Shimada Y, Takahashi Y, Wakai T, Kinoshita Y. Malignancy After Living Donor Liver Transplantation. Transplant Proc. 2024 Apr;56(3):660-666. doi: 10.1016/j.transproceed.2024.02.015. Epub 2024 Mar 21. PMID: 38519268.
168. Fu C, Li X, Chen Y, Long X, Liu K. Lung cancer incidences after liver transplantation: A systematic review and meta-analysis. Cancer Med. 2023 Aug;12(15):16119-16128. doi: 10.1002/cam4.6265. Epub 2023 Jun 23. PMID: 37351559; PMCID: PMC10469810.
169. Vanlerberghe BTK, van Malenstein H, Sainz-Barriga M, Jochmans I, Cassiman D, Monbaliu D, van der Merwe S, Pirenne J, Nevens F, Verbeek J. Tacrolimus Drug Exposure Level and Smoking Are Modifiable Risk Factors for Early De Novo Malignancy After Liver Transplantation for Alcohol-Related Liver Disease. Transpl Int. 2024 Feb 19;37:12055. doi: 10.3389/ti.2024.12055. PMID: 38440132; PMCID: PMC10909820.
170. Liu D, Youssef MM, Grace JA, Sinclair M. Relative carcinogenicity of tacrolimus vs mycophenolate after solid organ transplantation and its implications for liver transplant care. World J Hepatol. 2024 Apr 27;16(4):650-660. doi: 10.4254/wjh.v16.i4.650. PMID: 38689747; PMCID: PMC11056899.
171. European Commission, Joint Research Centre. European Cancer Information System (ECIS). https://ecis.jrc.ec.europa.eu/.

 doi:10.20944/preprints202502.1237.v1