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DE NOVO MALIGNANCIES AFTER LIVER TRANSPLANTATION: EPIDEMIOLOGY, RISK FACTORS, AND MANAGEMENT STRATEGIES

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Background. Liver transplantation (LT) significantly improves survival in patients with end-stage liver disease; however, it is associated with an increased risk of developing *de novo* malignancies. Long-term immunosuppression, viral infections, and unhealthy lifestyle choices increase the risk of post-transplant oncological complications. **Objective:** to summarize current evidence on the prevalence, risk factors, diagnostic, prevention, and treatment of *de novo* malignancies in liver transplant recipients. **Materials and methods.** This paper presents a literature review, including retrospective and prospective studies, meta-analyses, and clinical guidelines published over the past two decades. **Results.** The most common post-transplant malignancies include non-melanoma skin cancer, lymphoproliferative disorders, and solid organ tumors. Major risk factors are prolonged immunosuppression, viral infections, smoking, alcohol use, advanced recipient age, and the underlying liver disease. Current management strategies involve immunosuppression reduction, surgical resection, chemotherapy, and targeted therapy. In particular, mammalian target of rapamycin (mTOR) inhibitors have demonstrated antitumor efficacy in selected patients, particularly those with Kaposi's sarcoma and lymphoproliferative disorders. **Conclusion.** Given the high oncological risk, stratified screening programs and individualized patient management are necessary after LT. Immunosuppression reduction, lifestyle modification, and early detection of malignancies are key factors in improving long-term outcomes.

Keywords: liver transplantation, de novo malignancies, immunosuppression, lymphoproliferative disorders, Kaposi's sarcoma, skin cancer, mTOR inhibitors, cancer screening.

INTRODUCTION

LT is a definitive treatment for patients with decompensated end-stage liver disease, acute liver failure, and hepatocellular carcinoma. Advances in surgical techniques, perioperative management, and modern immunosuppressive therapies have significantly increased the number of LT procedures performed and improved long-term patient survival [1].

However, the requirement for lifelong immunosuppression is associated with an elevated risk of serious complications, including infections, cardiovascular events, renal dysfunction, and malignancies. Notably, retrospective studies indicate that up to 20–25% of deaths among patients who survive the early post-transplant period are attributable to the development of *de novo* malignancies [2, 3]. Compared with the general population, LT recipients exhibit approximately a twofold increased incidence of solid tumors and a markedly higher – up to 30-fold – risk of lymphoproliferative disorders [4–8].

Risk factors for the development of *de novo* malignancies following LT include chronic immunosuppression, prior alcohol and tobacco use, oncogenic viral infections, and the underlying liver disease. This review aims to summarize current evidence on the incidence, risk factors, screening strategies, and treatment approaches for *de novo* malignancies in LT recipients.

Non-melanoma skin cancers (NMSC) are the most common malignancies among Caucasian recipients of solid organ transplants. In LT recipients, NMSC incidence is more than 15-fold higher than in the general population [9, 10]. Among this population, squamous cell carcinoma (SCC) predominates, in contrast to the general population, where basal cell carcinoma (BCC) is more common. Additionally, cases of Merkel cell carcinoma following LT have been reported [11, 12].

NMSC typically develops as a late post-transplant complication, with a median interval of approximately 50 months from surgery to diagnosis [13, 14]. Although these malignancies generally have a limited impact on overall mortality, they can significantly impair quality of life and necessitate ongoing dermatological surveillance.

PREVALENCE AND TYPES OF *DE NOVO* MALIGNANT TUMORS FOLLOWING LIVER TRANSPLANTATION

Improved long-term survival after LT, coupled with the effects of chronic immunosuppression, has contributed to an increased incidence of tumor-related com-

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plications. Evidence from large cohort studies indicates that the risk of developing malignant neoplasms in LT recipients significantly exceeds that of the general population. Moreover, the spectrum of malignancies varies depending on the time elapsed since transplantation, recipient age, the intensity and type of immunosuppressive therapy, and the underlying liver disease [4–8]. The most common malignancies include skin cancers, post-transplant lymphoproliferative disorders (PTLD), and a range of solid tumors affecting different organ systems. Fig. 1 presents the main risk factors for the development of malignant neoplasms after LT.

Table summarizes data from retrospective and prospective studies on the incidence and spectrum of *de novo* malignancies in patients following LT. The table presents key parameters, including the number of patients, duration of follow-up, time to tumor development, overall incidence of malignancies, and the most common tumor types. Standardized incidence ratios (SIRs) are also included, enabling comparison of cancer risk in transplant recipients with that of the general population.

The most reported malignancies include skin cancers, PTLD, lung cancer, gastrointestinal tumors, and head and neck cancers. Reported incidence rates vary widely – from approximately 2% to over 30% – depending on follow-up duration, baseline pathology, and population characteristics.

The following section provides a structured overview of the current literature on the incidence and patterns of *de novo* malignant neoplasms in this patient population.

Skin tumors

A retrospective study reported that the cumulative incidence of skin neoplasms was 14% at 5 years and 24% at 10 years post-transplantation, compared with 11% and 22%, respectively, for non-skin tumors [15]. In another study involving 151 LT recipients, the overall incidence of malignant skin tumors was 22.5%, with squamous cell carcinoma identified as the predominant subtype [16]. Similarly, a prospective cohort study of 161 adult patients demonstrated a progressive increase in the incidence of precancerous and malignant skin lesions over time: 5% at 2–3 years, 12% at 3–5 years, and 28% after more than 5 years of follow-up [17]. The incidence of malignant lesions specifically was 0% at 2–3 years, rising to 9% at 3–5 years and 12% beyond 5 years post-transplant. The main risk factors associated with the development of *de novo* skin tumors are summarized in Fig. 1.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a multifocal neoplastic disease affecting the skin and mucous membranes, strongly associated with human herpesvirus 8 (HHV-8). It accounts for approximately 4% of all malignancies in post-transplant patients [18, 19]. The disease primarily develops in individuals with severe immunodeficiency [20]. A higher prevalence of KS is observed among populations from regions with elevated HHV-8 seroprevalence, including Central and Southern Africa, the Mediterranean, the Caribbean, and the Middle East [21].

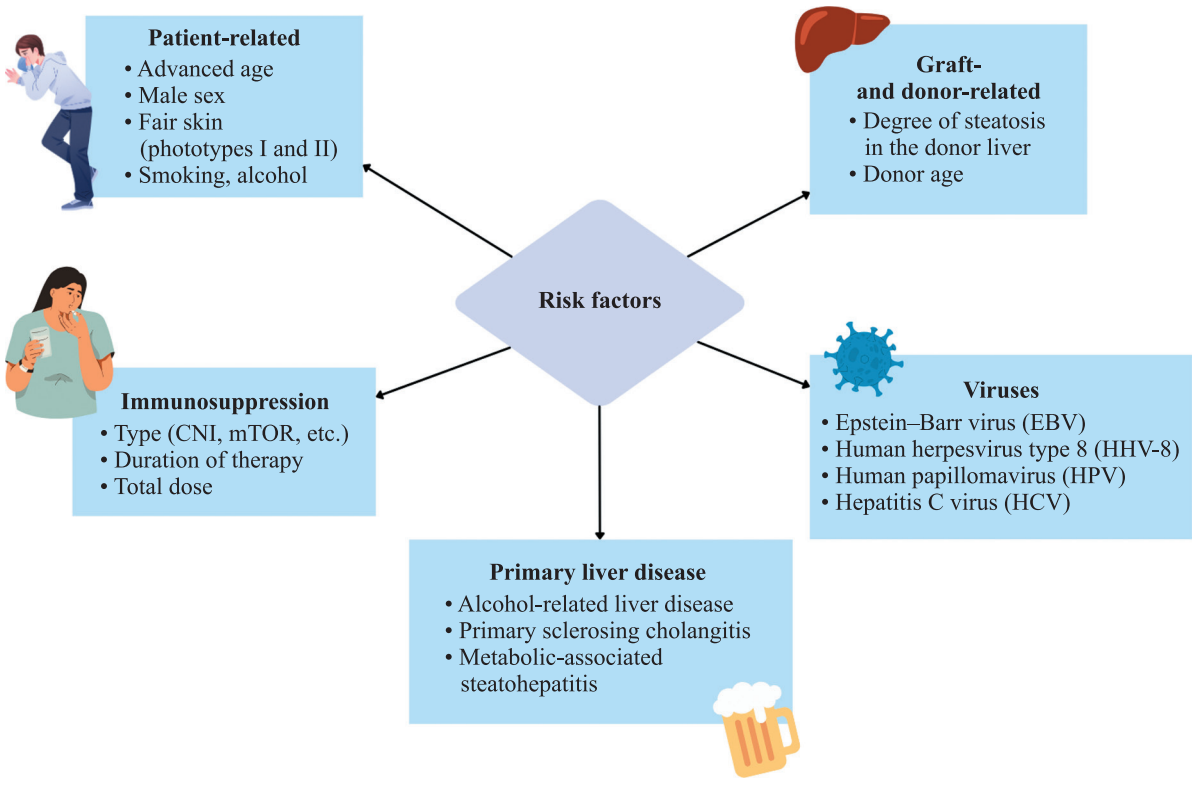

Fig. 1. Major risk factors for *de novo* malignancies after liver transplantation

Table

Prevalence and types of *de novo* malignancies after liver transplantation

Author	Country	Study period	Number of liver transplant recipients	Follow-up (years)	Time to development of *de novo* malignancies (years)	Overall incidence of *de novo* malignancies (n, %)	Most common tumors (%)	Overall standardized incidence ratio (SIR)
1	2	3	4	5	6	7	8	9
Frezza et al. [115]	USA	Until 1992	1657	–	–	64 (3.8%)	Basal cell carcinoma – 25%; squamous cell carcinoma (SCC) – 20.3%; melanoma – 6.2%.	–
Krynitz et al. [116]	Sweden	1970–2008	1221	20	–	27 (2.2%)	All malignancies – 3.4 (2.9–4.0); excluding SCC – 2.3 (1.9–2.8); all skin cancers – 16 (12–20); SCC – 32 (24–42)	–
Haagsma et al. [117]	Netherlands	1979–1996	174	5.9	5.1	23 (12%)	Skin and lip cancer – 52%	4.3
Oo et al. [118]	UK	1982–2004	1778	6.5	–	141 (7.9%)	Skin cancer (excluding melanoma) – 36.1%; lymphoma – 12.7%; colorectal cancer – 12.7%; lung cancer – 10%	2.1
Aberg et al. [5]	Finland	1982–2005	540	6.3	5.1	39 (7.2%)	Non-melanoma skin cancer – 25.6%; non-Hodgkin lymphoma – 20.5%	2.59
Finkenstedt et al. [51]	Austria	1982–2007	779	4.1	4.4	105 (12.3%)	Skin cancer – 17%; lung cancer – 16%; oropharyngeal carcinoma – 11%	1.9
Jiang et al. [119]	Canada	1983–1998	2034	3.5 ± 2.8	3.5 ± 2.8	113 (5.5%)	Non-Hodgkin lymphoma – 35.3%; colorectal cancer – 12.3%; lung cancer – 8.8%	2.5
Schrem et al. [120]	Germany	1983–2010	2000	7.3	6.8	120 (6%)	Post-transplant lymphoproliferative disorder (PTLD) – 19.1%; lung cancer – 11.6%; colorectal cancer – 10.8%; gynecological cancers – 8.0%; breast cancer – 6.6%; gastric/esophageal cancer – 5.8%	2
Galve et al. [121]	Spain	1984–1996	1827	–	2.5 ± 1.8	70 (3.83%)	–	–
Mouchli et al. [122]	USA	1984–2012	293	11.5	–	73 (25%)	PTLD – 30.1%; malignant tumors in solid organ transplantation (SOT) – 63%	–
Sanchez et al. [123]	USA	1985–1999	1421	5.5 ± 3.7	–	123 (88%)	Skin cancer – 32.8%; lymphoma – 25%; lung cancer – 8%; colon cancer – 5%	–
Wimmer et al. [124]	Germany	1985–2007	609	4.8	5.7 ± 3.7	87 (14.2%)	SCC – 15%; basal cell carcinoma (BCC) – 27.6%	–
Taborelli et al. [125]	Italy	1985–2014	2818	Not applicable	Not applicable	244 (8.6%)	–	–
Shalaby et al. [126]	Italy	1985–2014	2653	3.6 with HCC, 6.6 without HCC	2.7 with HCC, 4.5 without HCC	62 (6.6%) with HCC, 127 (7.4%) without HCC	–	–

Continuation Table

1	2	3	4	5	6	7	8	9
Jiménez et al. [127]	Spain	1986–2000	505	–	–	62 (12.3%)	Skin cancer and Kaposi's sarcoma – 25.8%; PTLD – 21.6%; head and neck cancer – 16%	–
Tjon et al. [128]	Denmark	1986–2007	385	–	–	66 (17.1%)	Non-melanoma skin cancer – 55%; PTLD – 21%	2.2
Engels et al. [7]	USA	1987–2008	37888	–	–	1563 (4.1%)	PTLD – 23.3%	–
Jonas et al. [129]	Germany	1988–1994	458	4.2	3.6	33 (7.2%)	Skin cancer – 24%; PTLD – 21%; gynecological cancer – 21%	–
Kelly et al. [130]	UK	1988–1996	888	–	2 ± 1.5	31 (3.4%)	Skin cancer and Kaposi's sarcoma – 25.8%; lung cancer – 3%	–
Saigal et al. [14]	UK	1988–1999	1140	–	3.8 ± 2.8	30 (2.6%)	Skin cancer – 43%; oropharyngeal cancer – 6%; bladder cancer – 6%; acute leukemia – 6%	–
Yao et al. [131]	USA	1988–2000	1043	6.7	–	53 (5%)	Skin cancer – 32%; gastrointestinal cancer – 21%; hematological tumors – 17%	–
Rademacher et al. [69]	Germany	1988–2006	1616	14	–	322 (19.9%)	Skin cancer – 25.7%; hematological – 15.2%; solid tumors – 60%	–
Watt et al. [37]	USA	1990–1994	798	10	–	271 (34%)	Skin cancer – 54.2%; hematological – 10.7%; solid tumors – 35%	–
Herrero et al. [15]	Spain	1990–2001	187	5.5	–	63 (33%)	Skin neoplasms – 55.5%, non-skin neoplasms – 44.4%	–
Ettorre et al. [132]	Italy	1990–2008	1675	5.2	3.2	98 (5.9%)	PTLD – 18.4%; head and neck cancer – 19.3%; lung cancer – 13.2%; colon cancer – 11.2%; Kaposi's sarcoma – 6.2%	–
Tajima et al. [133]	Japan	1990–2020	1781	~12	–	153 (8.6%)	PTLD – 53%; colon cancer – 9.1%; lung cancer – 7.8%; gastric cancer – 7.8%	1993–1995: 8.12; 1996–1998: 3.11; 2005–2007: 1.31; 2008–2010: 1.34; 2014–2016: 2.27; 2017–2019: 2.07
Benlloch et al. [71]	Spain	1991–2001	772	4.3	–	41 (5.3%)	Solid tumors – 75.6%; hematological – 24.3%	–
Baccarani et al. [8]	Italy	1991–2005	417	6.7	4.2	43 (10.3%)	Non-Hodgkin's lymphoma – 21%; head and neck cancer – 18.6%; Kaposi's sarcoma – 14%	–
Sanaei et al. [134]	Iran	1992–2012	1700	–	5.5	38 (2.2%)	PTLD – 63%; gastrointestinal cancer – 10.5%	–
Sérée et al. [101]	France	1993–2012	11226	–	–	1200 (10.7%)	Lung cancer – 15.6%; esophagus, stomach, colon – 11.8%; larynx cancer 6.3%; oral cavity/pharynx – 6%	All solid tumors – 2.2

End of Table

1	2	3	4	5	6	7	8	9
Jain et al. [87]	USA	1996–2006	1000	6.5 ± 1	3	57 (5.7%)	Skin cancer (including melanoma) – 38.6%; lung cancer – 14%; oropharynx – 12.2%	–
Chatrath et al. [1]	USA	1997–2004	534	5.7 ± 3.2	4 ± 2.2	80 (15%)	Solid tumors – 50%; skin cancer – 30%; hematological – 20%	3.1
Yeh et al. [135]	Taiwan	1997–2011	2127	4.2	–	111 (5.2%)	–	1.5
Park et al. [136]	South Korea	1998–2008	1952	3.5 ± 2.8	3.4 ± 2.4	44 (2.3%)	Stomach – 25%; colon – 20.4%; breast – 9%	Men – 7.7; women – 7.3
Egeli et al. [137]	Turkey	1998–2016	429	8.6	5.3	9 (2%)	Lung cancer – 44.4%	–
Kobayashi et al. [138]	Japan	1999–2022	70	12.1	–	8 (11.4%)	Lung cancer – 50%; PTLD – 37.5%; skin cancer – 12.5%	–
Lucidi et al. [139]	Italy	2000–2015	789	6.75	4	67 (5.5%)	Lung cancer – 16.4%, head and neck – 16.4%; PTLD – 13.4%, breast – 7.4%	–
Mangus et al. [140]	USA	2001–2011	1275	–	–	180 (14%)	Skin cancer – 59.4%, gastrointestinal tumors – 10.5%	–
Yu et al. [141]	China	2005–2011	569	3.5 ± 2.2	–	18 (3.2%)	PTLD – 16.7%	–
Antinucci et al. [142]	Argentina	2006–2014	159	1.1	1.3	12 (7.5%)	Skin cancer – 33.3%	–
Tiwari et al. [143]	India	2006–2017	2100	3.5	–	21 (1%)	Oropharyngeal cancer – 33.3%; lung cancer – 19%; SCC – 9.5%	–

The risk of developing KS in recipients of solid organ transplants is estimated to be up to 500 times greater than in the general population [19].

Although the vast majority of reported cases present with cutaneous lesions, visceral involvement has also been documented and is typically associated with a poorer prognosis [22].

Hematologic Malignancies

PTLD typically develops within the first year following transplantation; however, onset may occur as early as 20 days post-transplant or, conversely, several decades later.

High levels of immunosuppression are considered a major risk factor for early PTLD development. Early-onset PTLD is characterized by the proliferation of B-lymphocytes infected with Epstein-Barr virus (EBV) and is associated with profound suppression of T-cell-mediated immunity, which is intended to prevent graft rejection [25].

In contrast, late-onset PTLD is generally associated with a more aggressive clinical course, monoclonal lymphoid proliferation, and the absence of EBV genetic material in tumor cells [26–28].

Solid Organ Tumors

Solid organ tumors are diagnosed in approximately 1% of LT recipients annually. The cumulative incidence of these malignancies ranges from 3% to 15% at various time points following transplantation [3, 29]. In LT (recipients, the risk of developing solid tumors is estimated to be 2–5 times higher than in the general population [30]. Unlike PTLD, solid organ tumors typically develop more than one year after transplantation, are exceedingly rare in pediatric patients, and occur more frequently in older recipients [3]. An increased risk has been observed in individuals with a history of alcoholic liver disease (ALD) and primary sclerosing cholangitis (PSC) [31]. Recent evidence indicates that solid tumors have become the most common type of malignancy in post-LT patients, surpassing both skin cancers and PTLD in incidence [32].

SKIN CANCER

Risk Factors

Several risk factors contribute to the development of skin cancer in LT recipients. These include advanced age, prolonged and intensive immunosuppressive therapy, infection with human papillomavirus (HPV), and signi-

ficant exposure to ultraviolet (UV) radiation. Individuals with a tendency to sunburn – particularly those with Fitzpatrick skin phototypes II and III – are at increased risk, as are patients with a history of actinic keratosis or prior malignancies, including hepatocellular carcinoma (HCC) and other cancers [15–17, 33, 34].

Additional risk factors include CD4+ lymphocytopenia, male sex, blue eye color, red hair, and fair (Caucasian) skin phenotype, as well as the use of induction therapy with monoclonal antibodies [3, 16, 35]. Furthermore, an elevated risk of skin cancer has been reported in patients who undergo LT for PSC or ALD, compared with those transplanted for other underlying liver conditions [14, 16, 34, 36, 37].

Cyclosporine A is considered one of the most significant predictors of cutaneous malignancies. Patients receiving cyclosporine tend to develop skin cancer earlier than those treated with tacrolimus [16]. Moreover, cyclosporine A has been identified as an independent and specific risk factor for post-transplant malignancies [34, 38]. Azathioprine has also been associated with an increased risk of cutaneous squamous cell carcinoma in organ transplant recipients, including those who have undergone heart transplantation [39–41]. Nevertheless, the overall degree of immunosuppression is likely the principal determinant of cancer risk, rather than any single immunosuppressive agent [20, 42].

The primary etiological factor in Kaposi's sarcoma (KS) is infection with HHV-8, although co-infections such as hepatitis B virus, cytomegalovirus, and Epstein-Barr virus may also contribute to disease development [43, 44]. Severe immunosuppression is strongly associated with the onset of KS [18]. Accordingly, individualized adjustment of immunosuppressive therapy represents a key strategy for KS prevention [34].

Although clinical trials investigating novel therapeutic approaches for KS are ongoing, current evidence suggests that the most effective strategy is the substitution of calcineurin inhibitors (e.g., cyclosporine and tacrolimus) with mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus [19, 34, 45, 46].

Screening and Prevention

Currently, evidence regarding the effectiveness of surveillance strategies for skin malignancies following LT remains limited. Nevertheless, sustained oncological vigilance is essential, and individualized screening programs should be implemented for patients with identified risk factors [47]. Individuals with a history of risk factors, such as smoking and alcohol use, require more frequent and targeted monitoring. At a minimum, surveillance should be consistent with established oncological screening protocols for the general population [47].

All LT recipients should undergo a comprehensive dermatological examination at least once annually [29, 47, 49, 50]. For patients with additional risk factors, more frequent evaluations – every 3–6 months – are recommended, particularly in those with a prior history of skin cancer or as determined by the treating physician [17, 32, 47–49]. Clinicians should maintain a high index of suspicion when assessing suspicious skin lesions and promptly perform biopsy or excision when malignancy is suspected, even at an early stage [3, 48].

Furthermore, patients must be informed about their elevated risk of skin cancer and educated on preventive measures. These include consistent use of sunscreen, wearing protective clothing and hats, and the use of sunglasses to minimize ultraviolet exposure [13, 29, 47].

In a prospective cohort study involving 779 patients who had undergone total prostatectomy, 105 malignant tumors were detected in 96 (12.3%) of them. The most common were skin cancer (17%), lung cancer (16%), oropharyngeal tumors (11%), and prostate cancer (11%). Patients with early tumor detection had favorable clinical outcomes. The implementation of an intensive follow-up protocol increased the rate of early diagnosis of *de novo* tumors from 4.9% to 13% and improved treatment outcomes [51].

Screening for KS is a complex challenge, as HHV-8 viral load levels in patients are often low and detectable in fewer than half of cases. Furthermore, there are no standardized serological tests [41, 52–54].

Treatment

In general, the treatment of malignant neoplasms in LT recipients involves standard methods – surgery, chemotherapy, and radiation therapy – just as in immunocompetent patients. However, a key difference lies in the need to adjust immunosuppression, particularly for tumors sensitive to the level of immunosuppression, such as KS and PTLC [18].

- **SCC (squamous cell carcinoma):** Superficial lesions may be managed with cryotherapy, electrocoagulation, or curettage, whereas invasive forms require wide surgical excision. These tumors are characterized by an aggressive clinical course, with a high risk of recurrence and metastasis [55, 56].
- **BCC (basal cell carcinoma):** Surgical excision remains the standard of care. In patients with recurrent disease, reduction of immunosuppressive therapy may decrease the risk of new lesions. Radiation therapy can be considered in elderly patients or those unsuitable for surgery. For low-risk lesions, electrodesiccation and curettage are appropriate options. Additional effective treatments include photodynamic therapy, imiquimod, and 5-fluorouracil [56].
- **Malignant melanoma:** Management involves surgical excision, with or without sentinel lymph node biopsy, along with consideration of reducing immunosuppressive therapy [55, 56].

– **Merkel cell carcinoma:** Localized disease is treated similarly to that in immunocompetent patients. In metastatic cases, temporary discontinuation of cyclosporine A may provide clinical benefit; however, the overall prognosis in immunocompromised patients remains poor [55, 56].
– **Kaposi's sarcoma:** There are no standardized treatment guidelines. Therapeutic approaches include surgical resection, radiation therapy, intralesional chemotherapy, reduction or discontinuation of immunosuppressive therapy, and systemic chemotherapy [57]. In some cases, complete remission has been achieved following reduction of immunosuppression or conversion to sirolimus [19, 31, 58, 59]. The efficacy of mTOR inhibitors is attributed to their antiangiogenic effects, including suppression of vascular endothelial growth factor (VEGF) production and inhibition of endothelial cell proliferation [60, 61]. Additionally, they may inhibit human herpesvirus 8 (HHV-8) replication by modulating viral protein expression [62].

If modification of immunosuppressive therapy proves ineffective, systemic chemotherapy is indicated. The first-line agent is pegylated liposomal doxorubicin, which achieves complete or partial remission in approximately 70% of patients [56, 63]. Other effective agents include vinblastine, bleomycin, taxanes, etoposide, and gemcitabine. Additionally, some studies suggest that prophylactic administration of ganciclovir or other antiviral agents in high-risk patients may offer clinical benefit [56, 64].

HEMATOLOGICAL (LYMPHOPROLIFERATIVE) NEOPLASMS

Risk Factors

Advances in immunosuppressive regimens and supportive care have significantly improved overall survival among LT recipients. However, this increased survival has been accompanied by a higher incidence of *de novo* malignancies. Intensive immunosuppression contributes to profound immunodeficiency and is a major risk factor for the development of post-transplant lymphoproliferative disorders (PTLDs), with a cumulative incidence of approximately 1–2% within the first five years following LT [65].

The risk of PTLD is highest during the first year after transplantation. The type of immunosuppressive agent also plays a critical role: the use of tacrolimus has been associated with a higher risk of PTLD compared to cyclosporine, another calcineurin inhibitor [66]. In particular, drugs that suppress T-cell function are more strongly implicated in the pathogenesis of PTLD.

Most post-transplant lymphoproliferative disorders (PTLDs) are of B-cell origin and are strongly associated with the Epstein–Barr virus (EBV). In EBV-seronegative recipients receiving organs from EBV-seropositive donors, the risk of PTLD development is significantly increased due to the absence of pre-existing immunity [67]. Serological mismatch involving Cytomegalovirus (CMV) may also contribute to an elevated risk. EBV-negative PTLDs are less common and exhibit distinct biological and clinical characteristics. In some cases, these may be linked to previously acquired but undetected EBV infection (Fig. 2) [68].

A single-center study conducted in Germany reported a higher incidence of hematological malignancies in patients who underwent transplantation for Hepatitis C [69]. This association was also supported by findings from a systematic review, which suggested that chronic B-cell stimulation during HCV infection may contribute to lymphomagenesis [70, 71]. However, a large retrospective study from France did not demonstrate a statistically significant association between HCV infection and an increased incidence of hematological malignancies following HCV-related LT [72].

Immunosuppressive therapy, which is essential for preventing graft rejection, disrupts the body's natural antitumor defense mechanisms. In particular, suppression of the T-cell–mediated immune response impairs immune surveillance of atypical cells. Persistent viral infections in the setting of immunosuppression (e.g., EBV, HHV-8), further promote the proliferation of infected cells and their transformation into tumor cells. At the same time, the reduced capacity to eliminate cells with DNA mutations facilitates the accumulation of genetic abnormalities. Together, these processes create a tumor-promoting microenvironment that supports oncogenesis and progression of malignancy.

Clinical Presentation

PTLD typically presents with general symptoms, including fever, night sweats, weight loss, and lymphadenopathy. Extranodal involvement occurs in approximately 50% of cases and may affect organs such as the liver, lungs, and central nervous system (CNS). Laboratory abnormalities may include unexplained cytopenias, elevated lactate dehydrogenase (LDH), hyperuricemia, hypercalcemia, and the presence of monoclonal protein.

According to current classification systems, PTLDs are divided into four main types: non-destructive (early lesions), polymorphic, monomorphic, and classical Hodgkin lymphoma [73]. Early (non-destructive) PTLD is characterized by benign, polyclonal lymphoid proliferation without disruption of normal tissue architecture. Polymorphic PTLD comprises a heterogeneous population of lymphoid cells that do not meet the diagnostic criteria for defined B-cell or T/NK-cell lymphomas observed in immunocompetent individuals. In contrast, monomorphic PTLD fulfills the criteria for established lymphoid malignancies, including diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cell myeloma,

and T-cell lymphomas. Classical Hodgkin lymphoma is the rarest subtype of PTLD.

Poor prognostic factors include a high International Prognostic Index, bulky disease, Epstein–Barr virus negativity, and involvement of the central nervous system or bone marrow, as well as early disease onset following transplantation [74].

Screening and Prevention

There are currently no standardized guidelines for PTLD screening following solid organ transplantation, and surveillance protocols vary across institutions. Early tapering or discontinuation of immunosuppressive therapy, in combination with antiviral prophylaxis, may reduce the risk of PTLD development. Maintaining the lowest effective concentration of immunosuppressive agents – sufficient to prevent graft rejection – also contributes to lowering PTLD incidence.

Whenever possible, transplantation from EBV-positive donors to EBV-negative recipients should be avoided due to the significantly increased risk of disease. Regular monitoring of EBV DNA levels in peripheral blood, with timely adjustment of immunosuppressive therapy in response to rising viral load, may help prevent the onset of PTLD [75].

In selected cases of viral reactivation, administration of the anti-CD20 monoclonal antibody rituximab may be indicated. As the majority of PTLD cases occur within the first year after transplantation, intensified monitoring is particularly important during this period, with the possibility of gradual de-escalation over time.

Treatment

In patients who have undergone T-cell–depleting therapy and present with systemic symptoms in the absence of infectious or rejection-related causes, PTLD should be strongly suspected and ruled out. Diagnostic evaluation includes measurement of lactate dehydrogenase (LDH) levels, positron emission tomography–computed tomography (PET-CT), and assessment of EBV viral load. In cases where central nervous system (CNS) involvement is suspected, brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis are recommended.

The primary goal of treatment is to achieve complete remission while minimizing side effects. Antiviral therapy has not demonstrated efficacy in EBV-positive PTLD. In many cases, initial management with reduction of immunosuppression is effective, typically involving discontinuation of antimetabolites (e.g., azathioprine, mycophenolate mofetil) and a 25–50% reduction in calcineurin inhibitor dosage. Close multidisciplinary collaboration with the transplant team is essential.

Treatment strategies are guided by PTLD subtype. Early (non-destructive) lesions may regress completely within 3–5 weeks following reduction of immunosuppression alone [76]. Polymorphic PTLD generally requires treatment with rituximab, with escalation to chemotherapy in refractory cases. Monomorphic PTLD is

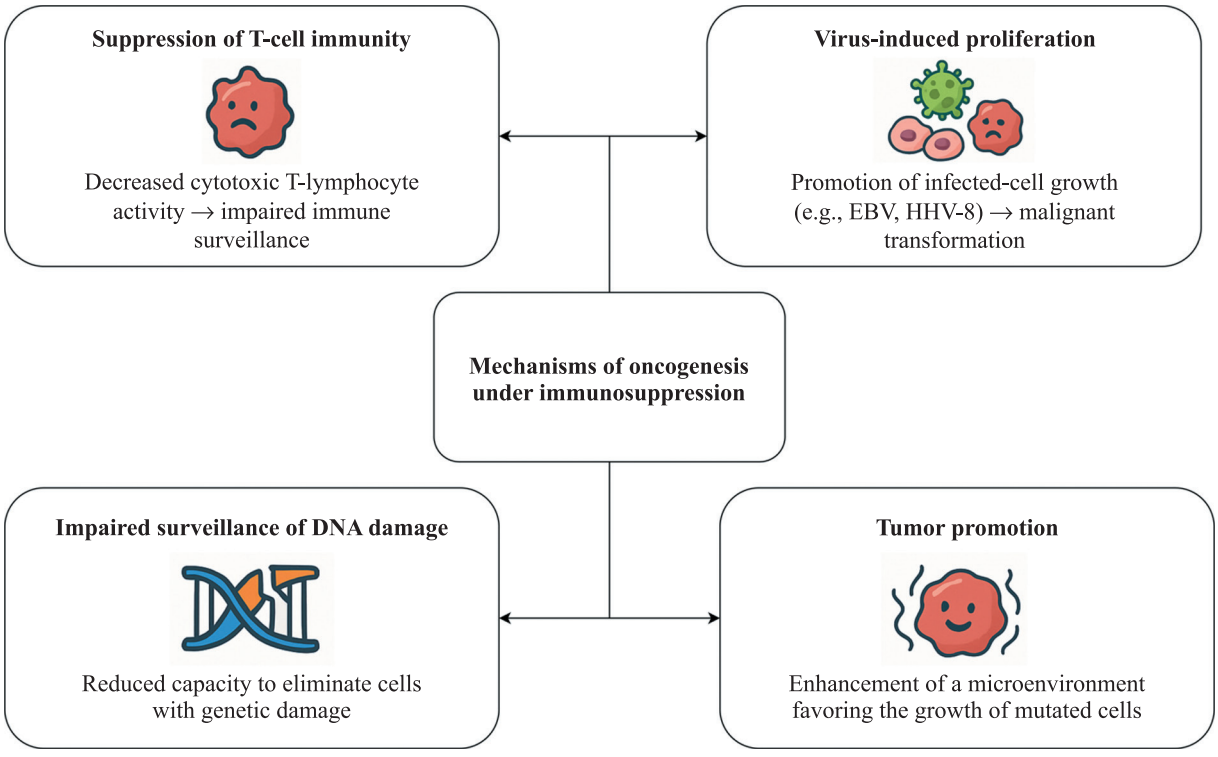

Fig. 2. Key mechanisms of oncogenesis during immunosuppression

managed with first-line chemoimmunotherapy regimens. In some centers, following completion of chemotherapy, patients are transitioned to mTOR inhibitors combined with low-dose prednisolone, with complete withdrawal of calcineurin inhibitors and antimetabolites.

Combination therapy with rituximab and reduction of immunosuppression has been shown to significantly improve overall survival, reaching 73% compared with 33% for reduction of immunosuppression alone [77]. In the PTLD-1 study, a sequential treatment approach consisting of four cycles of rituximab followed by CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) achieved complete remission in 57% of patients [78].

Patients who achieved remission after initial rituximab therapy were continued on maintenance treatment, whereas non-responders were escalated to R-CHOP. Notably, approximately 25% of patients were able to avoid chemotherapy altogether, and the median overall survival reached 6.6 years [79]. For highly aggressive disease, particularly in cases with BCL2 and MYC rearrangements, the R-EPOCH regimen may be considered [80].

Alternative combinations, such as rituximab with ibrutinib or with brentuximab vedotin, have not demonstrated superior efficacy and are associated with increased toxicity, especially in the case of brentuximab vedotin [81, 82]. Surgical intervention is rarely indicated and is generally reserved for selected cases, particularly with gastrointestinal involvement complicated by risk of obstruction or perforation.

PTLD relapse following chemotherapy is a major clinical challenge. In a retrospective study of patients with relapsed EBV-positive PTLD, the median overall survival was only 4.1 months [83]. The phase III ALLELE trial evaluated tabelecleucel, an allogeneic, HLA-matched EBV-specific T-cell therapy, which achieved complete remission in 12 of 43 patients and subsequently led to its approval by the European Medicines Agency in 2022 [84]. Brentuximab vedotin may also be considered in the management of relapsed disease.

Epigenetic therapy, including the combination of the histone deacetylase inhibitor nanatinostat with valganciclovir, has been explored in selected cases and demonstrated a partial response in 1 of 4 patients [85]. Additional salvage options include platinum-based chemotherapy regimens, chimeric antigen receptor T-cell (CAR-T) therapy, and autologous stem cell transplantation, with selection guided by disease biology and patient clinical status.

SOLID MALIGNANT TUMORS

Risk Factors

Head and neck tumors (upper respiratory and digestive tracts)

These tumors are associated with smoking and alcohol abuse. They develop from the tissues of the upper respiratory and digestive tracts, including the lips, oral cavity, tongue, nasal cavity, pharynx, larynx (vocal cords), esophagus, and trachea. Patients with alcoholic cirrhosis who undergo LT exhibit a significantly increased risk of developing oropharyngeal cancer compared with those transplanted for other indications [20, 29]. Evidence from a single-center study demonstrated that no cases of oropharyngeal cancer were observed in patients without a history of smoking or alcoholism [86]. Smoking is strongly associated with malignancies of the tongue and larynx, and its carcinogenic effects – well established in the general population – are equally relevant in LT recipients [87].

Disentangling the individual contributions of smoking and alcohol as independent risk factors is difficult, as alcohol enhances the carcinogenic effects of tobacco, and concurrent use of both substances is common [18].

Lung cancer

The main risk factors for lung cancer (LC) in transplant recipients include prolonged post-transplant survival, alcoholic cirrhosis as the indication for LT, and a long history of smoking [44, 88, 89].

Among patients transplanted for alcoholic cirrhosis, the risk of developing LC is approximately 2–4 times higher than in those transplanted for other indications [1, 29]. Data from the U.S. National Institute of Diabetes and Digestive and Kidney Diseases database indicate that these patients exhibit the highest cumulative incidence of LC, reaching 2.0% and 4.8% at 5 and 10 years post-transplantation, respectively, compared with 0.15% and 1.3% in patients with non-alcohol-related indications for LT [37].

Consistent with findings in the general population, smoking remains a major independent risk factor for LC in LT recipients [1, 18, 44, 87]. Notably, the incidence of LC is significantly higher among patients transplanted for alcoholic cirrhosis than among those transplanted for other underlying conditions [18, 90].

Tumors of the gastrointestinal tract

Major risk factors include prolonged follow-up duration, alcoholism, primary sclerosing cholangitis (PSC) with or without inflammatory bowel disease (IBD), obesity, diabetes mellitus, and metabolic dysfunction–associated steatohepatitis (MASH).

In patients with PSC, the risk of colorectal cancer after transplantation significantly exceeds that of the

general population, reaching comparable 10-year population risk levels as early as 5.75 years in men and 3.25 years in women. The presence of concomitant IBD further doubles this risk (OR = 2.06; 95% CI: 1.03–4.15; P = 0.042) [91].

Both PSC and MASH are also associated with an elevated risk of pancreatic cancer. The increased incidence of post-transplant gastric cancer may be attributable to the combined effects of chronic immunosuppression and underlying cirrhosis [92].

A retrospective study involving 9,724 patients identified the following as significant predictors of recurrent hepatocellular carcinoma (HCC): donor age >60 years, donor diabetes, body mass index (BMI) ≥35 kg/m^2, severe graft steatosis, and organ procurement following cardiac death with prolonged ischemia time [93].

Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as well as continued exposure to environmental carcinogens, remain significant risk factors.

Urogenital System

Evidence indicates that kidney transplant recipients have an increased risk of both kidney and bladder cancers compared with the general population [6, 7, 94]. Individuals with a prior history of renal cell carcinoma, von Hippel–Lindau syndrome, chronic kidney disease, or polycystic kidney disease are at particularly high risk.

Bladder cancer in transplant recipients is often characterized by a more aggressive clinical course and poorer prognosis than in non-transplanted individuals [95]. In contrast, although prostate cancer may occur in this population, transplant recipients do not appear to have an increased disease-specific mortality compared with the general population [96].

Gynecological Tumors

Female liver transplant recipients are at increased risk of developing cervical and vulvar cancer. This elevated risk is strongly associated with a prior history of cervical dysplasia and persistent HPV infection. Immunosuppression contributes to the reactivation of oncogenic HPV strains and impairs viral clearance, thereby increasing the risk of neoplasia [97].

Screening and Prevention

All LT recipients should be counseled on the importance of complete abstinence from smoking and alcohol use, given their significant contribution to post-transplant malignancy risk. For lung cancer screening, adherence to standard population-based protocols is recommended, as intensified screening strategies have not shown a survival benefit in this population [98, 99]. Annual oral cavity examinations are advised for all recipients, while high-risk individuals (smokers, those with HPV infection) should undergo a comprehensive annual otorhinolaryngological (ENT) evaluation [49, 100].

Patients with IBD should undergo annual colonoscopy. In contrast, individuals with PSC without concomitant IBD are advised to undergo colonoscopy every 3–5 years [101, 102]. For patients with MASH or a history of HCC after the age of 50 years, colonoscopic screening every 5 years is recommended [49, 91].

According to the European Association of Urology guidelines, annual renal ultrasonography is recommended for high-risk individuals, including those with a prior history of renal cell carcinoma, von Hippel–Lindau syndrome, or autosomal dominant polycystic kidney disease [103].

Screening for cervical and vulvar cancer should follow protocols for immunocompromised women [104].

Treatment

The initial step in the management of *de novo* solid tumors in LT recipients is to reduce immunosuppressive therapy to the lowest effective dose. Although randomized controlled trials are lacking, retrospective studies suggest that conversion from calcineurin inhibitors to mTOR inhibitors is associated with a 55–75% reduction in mortality [105, 106].

Surgical management generally follows the same oncological principles as in the general population. However, transplant recipients are at increased risk of postoperative complications, including infections and higher 90-day mortality rates [107].

If detected early, lung cancer can be radically resected surgically. In patients with significant comorbidities, sublobar resection combined with radiotherapy may be considered [108]. For advanced-stage disease, treatment strategies align with standard approaches, including surgical resection for non-small cell lung cancer and chemoradiotherapy for small cell lung cancer [109].

For esophageal and gastric cancer, esophagectomy or gastrectomy are indicated depending on tumor location. In early-stage disease, endoscopic resection may be a viable option [110, 111]. Surgical and endoscopic resection, chemotherapy, and radiation therapy are also used [112, 113].

Pancreatic cancer is primarily managed surgically, sometimes in combination with neoadjuvant therapy; however, outcomes remain poorer compared with sporadic cases.

Tumors of the upper respiratory tract (oral cavity, oropharynx, and larynx) typically require surgical intervention, frequently combined with chemotherapy and/or radiotherapy. Early detection significantly improves survival rates [114].

CONCLUSION

Skin cancers, PTLDs, and solid organ tumors are the most common *de novo* malignancies following LT and are among the leading causes of morbidity and mortality in this population. Their development is primarily driven by chronic immunosuppression and persistent infection with oncogenic viruses. Additional important risk factors include advanced age, male sex, smoking, alcohol abuse, and underlying conditions such as PSC and inflammatory bowel disease.

In recent years, substantial progress has been made in the development of screening guidelines. Nevertheless, further improvements in patient outcomes will depend on reducing immunosuppression or using alternative medications, as well as strict adherence to risk-adapted screening protocols. Screening measures should be individualized, taking into account each patient's specific risk profile.

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