

New concepts and best practices for management of pre- and post-transplantation cancer

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Abstract

Solid-organ transplant recipients are at increased risk of developing cancer compared with the general population. Tumours can arise *de novo*, as a recurrence of a preexisting malignancy, or from the donated organ. The ATOS (Aula sobre Trasplantes de Órganos Sólidos; the Solid-Organ Transplantation Working Group) group, integrated by Spanish transplant experts, meets annually to discuss current advances in the field. In 2011, the 11th edition covered a range of new topics on cancer and transplantation. In this review we have highlighted the new concepts and best practices for managing cancer in the pre-transplant and post-transplant settings that were presented at the ATOS meeting. Immunosuppression plays a major role in oncogenesis in the transplant recipient, both through impaired immunosurveillance and through direct oncogenic activity. It is possible to transplant organs obtained from donors with a history of cancer as long as an effective minimization of malignancy transmission strategy is followed. Tumour-specific wait-periods have been proposed for the increased number of transplantation candidates with a history of malignancy; however, the patient's individual risk of death from organ failure must be taken into consideration. It is important to actively prevent tumour recurrence, especially the recurrence of hepatocellular carcinoma in liver transplant recipients. To effectively manage post-transplant malignancies, it is essential to proactively monitor patients, with long-term intensive screening programs showing a reduced incidence of cancer post-transplantation. Proposed management strategies for post-transplantation malignancies include viral monitoring and prophylaxis to decrease infection-related cancer, immunosuppression modulation with lower doses of calcineurin inhibitors, and addition of or conversion to inhibitors of the mammalian target of rapamycin.

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1. Introduction

Improved methodology, availability of more effective immunosuppressive drugs, refined immunosuppressive regimens, perfected logistics in organ handling, and

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accumulated clinical knowledge have caused a gradual decrease in organ rejection over the years and, consequently, overall post-transplant patient survival has risen notably, with 1-year renal graft survival rates rising to over 90% [1,2]. Other solid-organ transplants also have excellent short-term graft survival rates: in 2008 at 1 year, post-transplantation graft survival rates were 87.2% for heart, 84.1% for liver, and 83.0% for lung transplant recipients [3]. However, in the past 20 years the long-term survival rates have changed very little, with minor changes in the yearly graft attrition rate of 5–10 years post-transplant for kidney (7.5–6.6), heart (6.4–5.1), liver (4.7–4.3), and lung (10.9–10.1) [3–5].

Chronic rejection and long-term complications of immunosuppression, such as nephrotoxicity, cardiovascular disease, infection, and malignancy are largely responsible for this lack of long-term improvement. Transplant recipients are at increased risk of developing malignancies because of longer life expectancy and chronic exposure to immunosuppressive agents, which not only impair normal immune function but may also have direct pro-oncogenic activity. Furthermore, long-term immunodeficiency places the transplant recipient at risk of oncoviral infection conducive to malignancy. Indeed, cancer incidence among transplant recipients is greater than in the general population [6–12].

A recent large study in 175,732 solid-organ transplant recipients (58.4% for kidney, 21.6% for liver, 10.0% for heart, and 4.0% for lung) from the US Scientific Registry of Transplant Recipients (1987–2008) and 13 regional cancer registries reported that the overall cancer risk was elevated, with 10,656 cases and an incidence of 1,375 per 100,000 person-years (standardized incidence ratios [SIR]: 2.10 [95% CI, 2.06–2.14]) [13].

After transplantation, cancer risk varies from no increase for several common cancers, to a many-fold increase for a number of virus-associated cancers. Overall, the most common malignancies in the post-transplant setting are non-melanoma skin cancer (SIR: 28.6), post-transplant lymphoproliferative disorder (PTLD) (SIR of non-Hodgkin's lymphoma [NHL], the primary PTLD: 8.1), Kaposi's sarcoma (KS) (SIR: 208.0), and anogenital cancers (SIR for vulva and vagina: 22.8 and SIR for penis: 15.8) (Table 1) [6,8,14,23,31–33].

In addition to the higher incidence, cancer usually progresses at a faster rate, has a worse prognosis, and is more refractory to treatment [34,35] in these patients. Although cardiovascular disease is still the predominant cause of mortality in patients with functioning grafts [36], it is expected that cancer will become the leading cause of death within the next 2 decades [34,37]. Therefore, it is imperative to streamline effective preventive, diagnostic, and

Table 1
Common post-transplant tumours in transplant recipients. [13,14].

Common malignancies	SIR Renal [8,13,14]	SIR Liver [9,13,15,16]	SIR Heart [13,14,17–20]	SIR Lung [13,21,22]
All cancers excluding non-melanoma skin cancer	2.4–3.9	2.2	2.5	3.6
Non-melanoma skin cancers	16.6	6.6	18.5	16.1
Melanoma	1.4–6.3			
Non-Hodgkin's lymphoma	12.5	13.3	19.8	30.0
Hodgkin's lymphoma	7.4	8.9	11.4	5.0
Kaposi's sarcoma	17.1	144	10–22	
Lip	65.6	20.0	60	
Oral cavity	4.2	10.0	5.0	5.0
Anogenital cancer (anus, vulva, perineum)	10.0	3.3	7.5	20.0
Breast	1.0–1.5	0.8	0.8–2.4	0.3
Colorectal	1.4–2.4	2.3	1.1	1.1
Uterine cervix	1.6–5.7		14.3	
Kidney	6.7–7.9	1.8	2.9–14.4	2.5
Liver		43.3	1.2–3.3	
Lung	1.5–2.8	1.6–2.0	0.95–2.1	5.9–6.1
Multiple myeloma	3.3	0.8	3.2	2.6
Common risk factors	Renal transplant-specific [8,23–25]	Liver transplant-specific [26–29]	Heart transplant-specific [18,30]	
Immunosuppression (type and dose)	Chronic viral infection	HCV infection	Time-from-transplant Multiple transplantations	
Conventional risk factors, i.e., age, smoking, male	Genetic risk factors	Alcoholic cirrhosis.		
EBV seronegativity	Treatment with cytotoxic agents	Azathioprine first year post-transplant		
Sun exposure	Splenectomy	Cyclosporine treatment in patients ≤50 years or with C ₂ monitoring (?)		
Pre-transplant malignancy	Diabetes			
	Hypersensitised patients			

HCV=hepatitis C virus; SIR=standardised incidence ratio; EBV=Epstein–Barr virus.

treatment measures in patients who are undergoing solid-organ transplantation.

The Spanish transplant ATOS (Aula sobre Trasplantes de Órganos Sólidos; the Solid-Organ Transplantation Working Group) Group meets annually to discuss current advances in the field of transplantation. In 2011, the 11th meeting of the ATOS Group focused on the mechanisms of oncogenesis in transplantation and the role of immunosuppression, assessment of epidemiologic, diagnostic, and risk factors associated with the development of post-transplantation malignancies, management strategies for decreasing the recurrence of pre-transplant malignancies, and the minimization of malignancy transmission from donor organs. In this article we aim to describe the new concepts and review the best practices for the management of pre- and post-transplantation cancer.

2. Mechanism of oncogenesis in transplantation and the role of immunosuppression

In the general population, cancer is characterised by six multistep biological hallmarks that include sustained proliferative signalling, evasion of growth suppressors, resistance to cell death, enabled replicative immortality, induced angiogenesis, and activated invasion and metastasis [38]. Two additional emerging hallmarks involved in the pathogenesis of the majority of cancers have been recently proposed: immuno-evasion and reprogrammed energy metabolism. Tumorigenesis in transplant recipients also follows this multifactorial pattern, with immuno-evasion playing a large role. Specific oncogenic mechanisms involve impaired immune activity against oncoviruses, impaired immunosurveillance of neoplastic cells, DNA damage and disruption of the DNA repair mechanism, and the upregulation of cytokines [39]. Tumorigenic lesions progressively grow, reaching a steady-state level of proliferating and apoptosing cells [40]. Vascularisation of the tumour to guarantee its blood supply is required to convert an *in situ* carcinoma into a rapidly growing malignancy. The initiation of angiogenesis has to occur to ensure exponential tumour growth [40]. This angiogenic switch leads to the overexpression of proangiogenic signals, such as vascular endothelial growth factor (VEGF), resulting in increased survival, proliferation, migration, and vascular permeability [40,41].

The causes of post-transplant malignancy are multifactorial (immunosuppression, oncogenic viruses, oncogenic effects of immunosuppression, chronic disease), with chronic immunosuppressive therapy having a large role, as shown by the elevated incidence of cancer observed in most medical conditions associated with immunosuppression [6,42], and the correlation between the length of exposure and intensity of immunosuppression with the incidence of cancer [43,44].

The high incidence of post-transplant malignancies and their aggressive progression are thought to be due to the

resulting impairment of the organ recipient's immunosurveillance system [45]. Through cancer immunoediting, the immune system protects the host against development of nonviral malignancies and helps determine tumour immunogenicity. This consists of three phases: elimination or cancer immunosurveillance, equilibrium (a period of immune-mediated latency of existing malignant cells), and escape (tumour progression and metastasis) [46,47]. In immunocompetent individuals, immunosurveillance functions as a tumour suppressor and protects the immunocompetent host from the development of neoplasia. In organ transplant recipients, acquired immunodeficiency upon immunosuppressive therapy results in a lower threshold for immunosurveillance, allowing malignant cells to proliferate. There have been reports that transplant recipients receiving organs from donors who had previously been cured of a malignancy later went on to develop the donor's malignancy, suggesting that the cancer cells had been in equilibrium with the donor's fully functional immune system, but the post-transplant immunosuppression provided the stimulus for the malignant cells to escape the immune system and proliferate [48,49].

Chronic immunosuppression predisposes transplant patients to a variety of viral infections; some can induce oncogenesis and result in PTLD by the Epstein–Barr virus (EBV), KS (human herpes simplex virus type 8 [HHV-8]), or skin and/or cervical cancers (human papillomavirus [HPV]) (Table 2). Oncoviruses act on various cellular signalling pathways, leading to immortalization and proliferation of the infected cells by disrupting the mitotic checkpoint upon infection of the host cell [51–53]. Upon cellular infection, virally encoded gene products can functionally inhibit or lead to the proteasomal degradation of many tumour suppressor proteins. Virally infected cells can either be eliminated via cell-mediated apoptosis or establish long-term persistent chronic infections that can lead to oncogenesis.

Table 2
Viruses with oncogenic potential [50].

Virus	Malignancy
Human papillomaviruses (HPV)	Cervical carcinoma Non-melanoma skin cancer Anogenital cancer
Human polyomaviruses (BKV, JCV, SV40, MCV)	Mesotheliomas Brain tumours Merkel cell carcinoma
Epstein–Barr virus (EBV)	PTLD Nasopharyngeal carcinoma
Human herpesvirus (HHV8)	Kaposi's sarcoma Primary effusion lymphomas
Hepatitis B virus (HBV)	Hepatocellular carcinoma
Hepatitis C virus (HCV)	
Human T-cell lymphotropic virus type 1 (HTLV-1)	T-cell leukaemias
<i>Helicobacter pylori</i>	Gastric carcinoma

MCV=Merkel cell polyomavirus; PTLD=post-transplant lymphoproliferative disorder.

There are indirect and direct viral strategies of oncotransformation [51–53]. The indirect strategies include the inactivation of tumour suppressor genes, such as *Rb* and *p53*, blocking of apoptosis, immuno-evasion, and impairment of cell-mediated immunity. The direct oncogenic viral strategies include expression of viral oncoproteins, activation of oncogenes (*c-myc*), promotion of cellular proliferation, induction of cytokine release, immunosuppression, and angiogenesis. In addition to predisposing transplant recipients to a higher risk of viral infection, calcineurin inhibitors (CNI) also increase the expression of EBV growth and virus-inducing factors (interleukin[IL]-1, IL-6, and transforming growth factor [TGF]- β), promote EBV replication, and increase immunoresistance by promoting the expression of anti-apoptotic genes [54].

Treatment with immunosuppressant agents not only causes impaired immunosurveillance of emerging malignant cells and multiplies the risk of oncoviral infection, it also displays direct pro-oncogenic activity in the case of CNIs (Fig. 1) [45,55,56]. There are various mechanisms by which CNIs may promote tumorigenesis and tumour growth, such as the induction of cancer cell invasiveness [45], the inhibition of DNA repair mechanisms [57,58] and apoptosis [58], the promotion of transcription and functional expression of the TGF- β 1 gene leading to tumour cell invasion and metastatic potential [59], and the promotion of tumour

angiogenesis via the stimulation of VEGF [56,60]. To overcome this problem, immunosuppressive agents with low oncogenic or even anti-oncogenic properties are being clinically developed [42,56,61,62].

3. Pre-transplant cancer

3.1. Donors with cancer: Challenges and recommendations

Transmission from the donor is a rare but clinically significant complication in solid-organ transplantation [63]. Donor-derived disease transmission potentially complicates less than 1% of all transplant procedures, but when a transmission occurs, significant morbidity and mortality can result [64]. The literature related to donor-derived malignancy transmission is limited to anecdotal reports, registry series, and retrospective studies [64]. The inconsistent reporting to transplant cancer registries, with overestimation in some cases (Israel Penn International Transplant Tumor Registry [IPTTR]) and underreporting in others (Organ Procurement and Transplantation Network [OPTN]) further complicates interpretation of donor-transmitted cancer data. Depending on registries, 0.5%–3% of donors have a history of cancer, and transmission from these donors has been demonstrated in 0.02%–6% of recipients [63–69]. This figure is much higher in the IPTTR registry, which by its

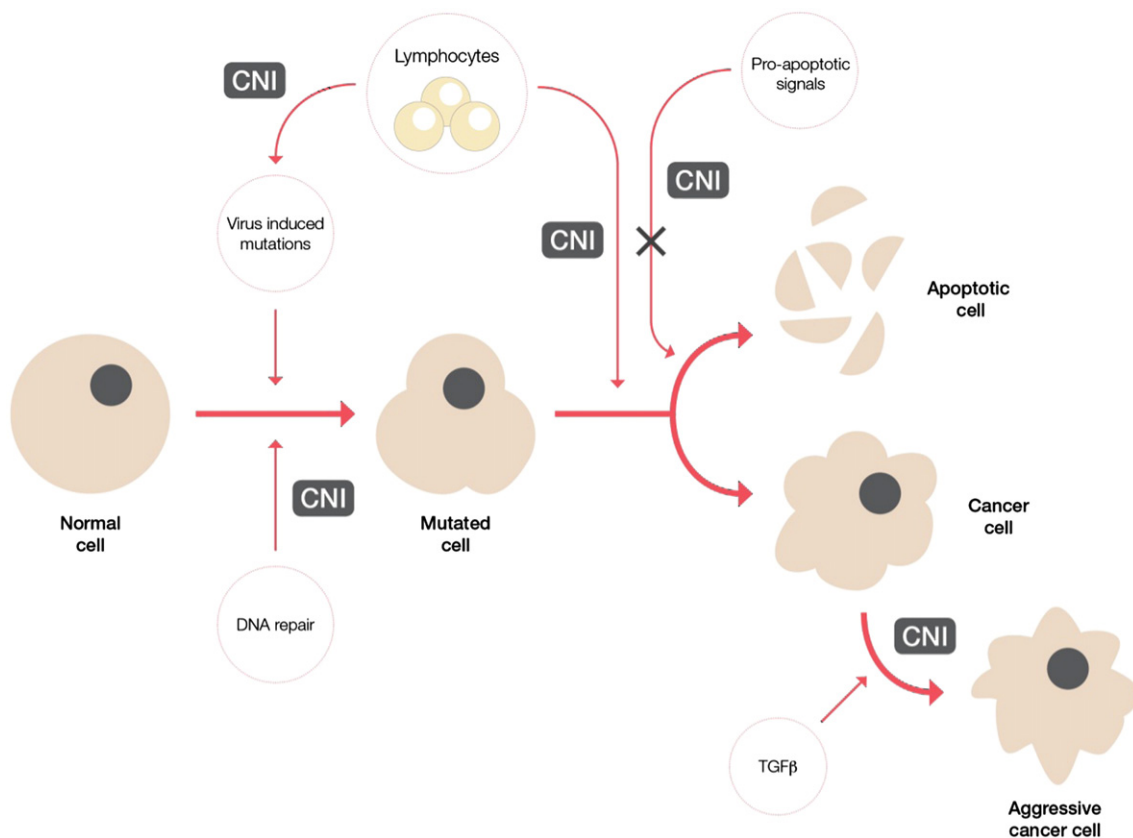


Fig. 1. Immunosuppression-driven oncogenesis. Adapted from Gutierrez-Dalmau and Campistol 2007 [42]. CNI=calcineurin inhibitors; TGF β =transforming-growth factor β .

nature is subject to reporting bias and tends to overestimate tumour transmission. High tumoural transmission was found among recipients of organs from donors with renal carcinoma (63%), melanoma (77%), and choriocarcinoma (93%). Other tumours transmitted were lung (41%), colon (19%), breast (29%), prostate (29%), and KS (67%) [70]. The threat of donor-to-recipient transmission varies, depending on which organ is being transplanted. Data from OPTN indicate that the liver, kidney, and heart (in this order) carry the highest risk [71,72].

Given the impact of donor-transmitted malignancy on the outcome of organ transplantation, detection of malignancy is an important measure of donor suitability. Not all malignancies, however, constitute an absolute contraindication to donation. Organ donation is usually not excluded in the presence of low-grade skin cancers, low-grade solid-organ tumours with a greater than 5-year documented tumour-free interval, and primary brain tumours that have not been treated with previous surgery. Donor kidneys with small cell renal carcinoma and low histological grade can be managed with excision and transplantation, with a low risk of tumour recurrence in the recipient [73,74]. Similarly, organs from donors with carcinomas *in situ* and non-metastasizing central nervous system (CNS) tumours are usually suitable for transplantation [75,76]. The United Network of Organ Sharing (UNOS) donor acceptance criteria guidelines require that medical suitability of the organ donor be determined by an assessment of several donor parameters, with specific recommendations to screen for malignancy to minimize the transmission of malignant donor cells to the transplant recipient (Table 3) [77–80]. As with other donor selection criteria, it is crucial that potential recipients are warned of the risk, and that any organ might transmit malignancy, particularly if it is from a donor with a known history of malignancy, and that the recipient is fully informed and closely involved in the decision-making process. Recently, the subcommittee to examine donor-related malignancy transmission (Malignancy Subcommittee) of the Disease Transmission Advisory Committee (DTAC) of OPTN/UNOS suggested risk categorisations for specific tumour types (Table 4) [81]. Benign tumours for which malignancy was excluded were reported to have no significant risk of

disease transmission. As mentioned in the section above, the transmission of malignant cells from the donor to the transplant recipient when the donor did not have an overt malignancy suggests that the malignant cells were never completely removed from the donor's body, remaining in a dormant state and/or in equilibrium with the donor's immunocompetent immune system [49,67,71]. The immunosuppression in the recipient provided the stimulus to overcome the immune defense and enter into the phase of "escape" and formation of a full-blown cancer [46].

3.2. Solid-organ transplantation candidates with cancer or a history of malignancy

When placing a patient on the waiting list for a solid-organ transplant, it is important to consider if there is a history of malignancy. The impact of immunosuppression on cancer recurrence must be weighed against the risk of death from organ failure without transplantation. The eligibility criteria for transplant candidates have broadened, increasing the age limits and widening the number of indications, and as a result, the number of transplant candidates with a history of previous malignancy is growing. The consensus is that tumour type and stage of disease must be considered, and a series of recommendations has been proposed concerning waiting periods between diagnosis and cancer treatment that aim to facilitate decision-making prior to proceeding with transplantation in these patients (Table 5) [82–84]. The individual prognosis of each malignancy in terms of 5-year survival rates should be considered and should not fall below the general 5-year life expectancy after solid-organ transplantation. In non-renal organ transplantation, available data and outcome of recipients who previously had a malignancy are generally limited, hindering the establishment of organ-specific disease-free intervals between cancer remission and transplantation [85]. In general, the recommendations for renal transplant candidates are followed for other organ transplants; however, non-renal transplant candidates with underlying high-risk disease and comorbidity are unlikely to be able to endure the waiting period recommended for some cancers. Therefore, providing that the cancer is adequately controlled and the malignancy stage itself does not have a poor prognosis, transplantation in the non-renal transplant population may be considered before completion of the waiting period with informed consent of the candidate [86].

Table 3
Recommendations for malignancy screening in potential donors.

Malignancy-specific recommendations for screening [77–79]

- Complete medical history to include previous diagnosis of neoplasia
- Unexplained intracranial haemorrhage (to rule out a metastasis as the cause)
- In women, menstrual disorders, as a metastatic choriocarcinoma may be the underlying cause
- Physical examination should rule out any possible skin malignancies
- Laboratory analysis for detection of tumour markers; it is recommended that blood samples be stored for future analysis
- Radiology tests
- Pathologic examination of extracted organs

3.2.1. Transplantation as treatment for organ-specific malignancy

Transplantation is not the main indication for treatment of malignant tumours; however, transplantation can be considered in very well selected lung carcinomas and unresectable heart tumours, such as cardiac angiosarcomas [87] and cholangiocarcinoma [88]. It is acceptable in unresectable chemosensitive hepatoblastoma, epithelioid haemangioendothelioma, liver metastasis of neuroendocrine tumours, and in hepatocellular carcinoma (HCC) [88].

Table 4

Suggested risk categorisations for specific tumour types by the Malignancy Subcommittee of the Disease Transmission Advisory Committee of the OPTN/UNOS. Adapted from Nalesnik et al. 2011 [81].

Risk category	Recommended clinical use	Tumours
Minimal risk (<0.1% transmission)	Clinical judgement	Basal cell carcinoma, skin SCC, skin without metastases <i>In situ</i> non-melanoma skin carcinoma <i>In situ</i> cervical carcinoma <i>In situ</i> vocal cord carcinoma <i>In situ</i> bladder carcinoma (nonrenal transplant only) Solitary papillary thyroid carcinoma, ≤0.5 cm Minimally invasive follicular carcinoma, thyroid, ≤1.0 cm (Resected) solitary renal cell carcinoma, ≤1.0 cm (Resected) solitary renal cell carcinoma, >1.0 cm ≤2.5 cm Low grade CNS tumour (WHO grade I or II) Primary CNS mature teratoma Solitary papillary thyroid carcinoma, 0.5–2.0 cm Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure
Low risk (0.1%–1% transmission)	Use in recipients at significant risk without transplant	<i>In situ</i> breast carcinoma <i>In situ</i> colon carcinoma (Resected) solitary RCC T1b, 4–7 cm History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90% and 99%
Intermediate risk (1%–10% transmission)	Use of these donors is generally not recommended except in circumstances where recipient's expected survival without transplantation is very short	Malignant melanoma Breast carcinoma >stage 0 (active) Colon carcinoma >stage 0 (active) Choriocarcinoma CNS tumour with shunt, surgery, irradiation, or metastasis CNS tumour WHO grade III or IV Leukaemia or lymphoma History of melanoma, leukaemia or lymphoma, small-cell lung/neuroendocrine carcinoma History of treated non-CNS malignancy (≥5 years prior) with <90% probability of cure Metastatic carcinoma Sarcoma Lung cancer (stages I–IV) RCC >7 cm
High risk (>10% transmission)	Use of these donors is discouraged except in rare and extreme circumstances	

CNS=central nervous system; OPTN=Organ Procurement and Transplantation Network; UNOS=United Network of Organ Sharing; SCC=squamous cell carcinoma; RCC=renal cell carcinoma; WHO=World Health Organization.

3.2.1.1. Hepatocellular carcinoma and expanded Milan criteria. Liver transplantation offers the best long-term oncologic results in patients with HCC [89]. HCC is the fifth most common cancer worldwide [90], and has rates that have risen significantly in Western Europe, North America, and Oceania [91]. It develops in the context of cirrhosis in 80% of patients. Liver transplantation for HCC in the late 1980s and early 1990s achieved poor results, with 5-year survival ranging from 20% to 36% attributed to selection of recipients with advanced stage cancer [92]. In 1996, Mazzaferro and colleagues proposed the Milan criteria that translated to a patient survival rate of 75% at 4 years (Table 6) [84,95]. In the past decade, post-transplant survival rates in patients beyond Milan criteria have nearly matched those of patients fitting the criteria [93,96–99]. A study by Yao and colleagues at the University of California, San Francisco (UCSF) concluded that a modest expansion of the criteria could

maintain survival while increasing the number of transplantation candidates [93,97–99]. The UCSF criteria [93] have been independently validated based on either tumour pathology or radiological staging [100–102]. A recent study by Mazzaferro and colleagues using the “up-to-seven” criteria reported 5-year survival similar to patients selected according to the Milan criteria [94], and the authors suggested that more patients with HCC could be candidates for transplantation if the Milan criteria were replaced with a more precise estimation of survival contouring individual tumour characteristics and use of the “up-to-seven” criteria. A recent prediction model using the Barcelona Clinic Liver Cancer (BCLC) staging that assesses prognosis of patients with HCC found that the patients' BCLC stage was able to significantly predict the 5-year liver transplant benefit in patients with HCC without absolute contraindications to liver transplantation [103]. Importantly, they noted that liver

Table 5
Proposed malignancy-free delay periods before transplantation.

Time	European guidelines [82]	American guidelines [83]
No delay	Incidental RCC Basal-cell skin cancers	Incidental RCC Basal-cell skin cancers Bladder carcinoma <i>in situ</i>
Less than 2 years	<i>In situ</i> carcinomas Small single focal neoplasms Low-grade bladder cancer Excised SCC Prostate (1–2 years)	
2 years (also includes cancers otherwise not listed)	Lymphoma Thyroid Testicular Symptomatic renal	Invasive bladder Symptomatic renal Testicular Thyroid Prostate Lymphoma
More than 2 years	Malignant melanomas (>2 years) Breast cancer (>3 years) Colorectal cancer (>5 years) Invasive cervical cancer (4–5 years) Invasive bladder (>5 years)	Breast cancer (2–5 years) Malignant melanoma (2–5 years) Colorectal cancer (0–5 years, depends on stage)

SCC=squamous cell carcinoma; RCC=renal cell carcinoma.

transplantation provided survival benefit in patients with advanced liver cirrhosis and in patients with intermediate HCC, regardless of the tumour number–size criterion, provided there was no macroscopic vascular invasion and extra-hepatic disease. The authors suggested that the use of BCLC could help improve the selection process for liver transplantation by increasing the homogeneity of the organ allocation system between patients with HCC and those with other indications for transplantation [103].

Another method for allowing patients with HCC outside the Milan criteria to become transplant candidates is to downstage the tumours before transplantation [104,105]. Radiofrequency ablation, ethanol injection, selective internal radiation therapy, and transarterial chemoembolisation are locoregional therapies currently used in HCC downstaging. A complete response after transarterial chemoembolisation has been associated with excellent post-transplantation

outcomes in patients with HCC that exceeded the Milan criteria [106]. A recent systematic review of the literature reported the outcome of patients with HCC outside the Milan criteria who underwent successful downstaging before liver transplantation to determine the survival and recurrence rates [105]. Of the 720 patients in eight selected observational studies who received downstaging treatment, 305 (42%) were successfully downstaged, of whom 186 (26%) underwent transplantation. Patients downstaged to within the Milan criteria achieved survival results similar to patients originally within the Milan criteria, with 3-year survival 79%–100% and 5-year survival 55%–94%. Recurrence rates were similar at 2 years post-transplantation [105]. Long-term multicentre clinical studies might be necessary to establish a definitive consensus on the benefits of pre-transplantation HCC tumour downstaging.

3.2.1.2. Bronchoalveolar cell carcinoma. Unlike liver transplantation for HCC, there is only anecdotal evidence that lung transplantation may be beneficial as a treatment option in some patients with lung cancer, such as those with extensive bronchoalveolar cell carcinoma [107–109]. This tumour is a subtype of non-small-cell lung cancer with unique clinical and pathologic characteristics that is generally localized to the lung and does not usually metastasize [110]. Surgical resection yields a good long-term outcome, but when the disease is diffuse or bilateral, survival beyond 2 years from diagnosis is rare, and single- and double-lung transplantation has been proposed as a curative measure [111]. Although data are scarce, a few reports suggest that lung transplantation may be an option for unresectable or recurrent bronchoalveolar cell carcinoma confined to the lungs, although recurrence of the original tumour within the donor lungs was common at 4 years post-transplantation [112,113].

4. Post-transplant cancer

Post-transplantation incidence of malignancies is increased in solid-organ transplant recipients versus the general population [7,14,17,114]. The 25-year cumulative cancer incidence after renal transplantation was 49% for all tumours and 40% excluding non-melanoma skin cancers [23]. Similar qualitative data have been obtained for other

Table 6
Tumour staging for patients with HCC.

	Milan criteria [84]	UCSF criteria [93]	Up-to-seven criteria [94]
Definition	1 tumour ≤ 5 cm or 2–3 tumours ≤ 3 cm and no vascular invasion and/or extrahepatic spread	1 tumour ≤ 6.5 cm or 2–3 tumours ≤ 4.5 cm, with a total diameter ≤ 8 cm and no vascular invasion and/or extrahepatic spread	7=sum of the size of the largest tumour [in cm] and the number of tumours
5-year survival	73%	75%	71%

HCC=hepatocellular carcinoma; UCSF=University of California, San Francisco.

organs [115,116]. Reports of post-transplantation malignancies include recurrence of pre-transplant malignancies or *de novo* cancers.

4.1. Recurrence of pre-transplant cancer

Risk of cancer recurrence among patients treated for the disease before transplantation is inversely proportional to the length of time bridging both events [86,117]. Because chronic immunosuppressive therapy is associated with an increase in malignant disease, the current notion is that a history of malignancy puts the patient at high risk for relapse after transplantation. However, there is little reliable evidence that immunosuppression uniformly alters the risk of a patient with malignancy in remission [85,117]. Rates of risk of cancer recurrence after transplantation in patients with preexisting malignancies are listed in Table 7.

4.1.1. Recurrence of HCC in liver transplantation recipients

Despite the 5-year 60%–80% disease-free survival rate in liver transplant recipients with unresectable early HCC, approximately 3.5%–21% of liver transplant recipients will experience a post-transplant HCC recurrence, which has a very poor prognosis [119]. Recurrence of HCC in liver transplant recipients is thought to occur either via occult undetected extrahepatic metastases or via the release of

tumoural cells during the transplantation procedure, with migration to the liver graft (40%–70% of recurrence cases) or other organs [120]. There are relatively few studies aiming to prevent recurrence of HCC in liver transplant recipients. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, seem to improve disease-free and survival-rates, although large prospective trials that are specifically designed to look at rates of HCC recurrence are lacking [121–123]. The SiLVER Study is an ongoing open-label prospective randomised controlled trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for HCC to evaluate whether immunosuppression with sirolimus can reduce HCC recurrence (NCT00355862) [124]. A recent small study that evaluated the combination of an mTOR inhibitor and sorafenib, a multikinase antiangiogenic inhibitor, in patients with recurrent HCC following liver transplant concluded that this regimen could be effective despite notable toxicity [125]. A recent article has proposed several strategies to decrease the engraftment of circulating tumour cells to decrease the risk of recurrence and increase eligibility criteria for transplantation in patients with more advanced HCC (Table 8) [120]. Results from ongoing randomised clinical trials with mTOR inhibitors in patients with HCC are expected to provide specific guidance on their use in this population [124].

4.2. Common post-transplantation *de novo* malignancies

Post-transplant *de novo* malignancies are frequent in all solid-organ recipients, although they are more frequent among heart and lung recipients owing to strong immunosuppression regimens. Age- and sex-adjusted 10-year incidence of *de novo* cancers is twice that of the general population, with the incidence of nonmelanoma skin cancer being 13 times higher [14]. As mentioned earlier, viral infection is a major risk factor for multiple types of cancer (Table 2). Common risk factors contributing to development of post-transplant cancer are listed in Table 1. In addition, a recent study reported that the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) after kidney transplantation among smokers was associated with an increased risk for respiratory/intrathoracic organ cancers, the SIR was significantly higher with ACE-inhibitor/ARB use (1.65 vs 1.09 for no ACE inhibitor/ARB use; $P=0.033$) [129]. Multivariate analysis showed that ACE-inhibitor/ARB treatment was not associated with an increased risk of respiratory cancers in nonsmokers. But in patients with a history of smoking, the risk of respiratory tumours was 7.10 in patients treated with ACE inhibitor/ARBs compared with 2.77 in those without ACE-inhibitor/ARB use ($P<0.001$), a 2.5-fold higher risk on top of the increase from smoking *per se*.

Most common post-transplant malignancies include non-melanoma skin cancer, lymphoma and PTLN, and KS, as

Table 7

Risk of recurrence after renal or liver transplantation in patients with preexisting malignancies [117].

Risk of recurrence	Renal transplant recipients [85,118]	Liver transplant recipients [85]
Low recurrence rate (0%–10%)	Incidental RCC (0%) Lymphomas (10%) Testicular, uterine cervical (5%), thyroid (7%) carcinomas	Incidental RCC (0%) Lymphomas (6%) Malignant melanoma (0%) Cervix carcinoma (0%) Endometrial carcinoma (0%) Myeloproliferative disorder (7%)
Intermediate recurrence rate (11%–25%)	Colorectal cancer (20%) Prostate cancer Breast cancer (24%) Carcinoma of the uterine body Wilms' tumours	Thyroid carcinoma (25%) Colorectal cancer (19%) Non-melanoma skin cancer (24%) Breast cancer (33%)
High recurrence rate (<26%)	Non-melanoma skin cancer (60%) Melanoma skin cancer (29%) Symptomatic RCC (30%) Bladder carcinoma Sarcomas Myelomas	Oral squamous carcinoma (33%)

RCC=renal cell carcinoma.

Table 8

Proposed strategies to decrease the release and engraftment of circulating tumour HCC cells and prevent post-liver transplant recurrence. Adapted from Toso et al., 2011 [120].

Strategy	Definition
Selecting recipients with low pre-transplant levels of circulating HCC cells	Selection cut-off based both on morphology (total tumour volume $\leq 115 \text{ cm}^3$) and biology (AFP $\leq 400 \text{ ng/mL}$) appears to exclude patients with more aggressive HCC [126]
Decreasing the peritransplant release of HCC cells	Use of the “no touch” technique for liver resection during surgery because liver and HCC mobilisations potentially increase the risk of HCC cell release
Preventing the engraftment of circulating HCC cells in the liver	Early liver graft injury increases the risk of metastases Tumour invasiveness is linked to the acute-phase liver graft injury Protective strategies to prevent ischaemia-reperfusion lesions could potentially decrease recurrences
Using anticancer drugs	Licartin ([^{131}I] metuximab injection) significantly improved survival [127] mTOR inhibitors have shown protective effects in preclinical, single-center, and registry-based studies [128] Sorafenib ($\pm$ mTOR inhibitors) should be assessed after liver transplantation in patients with high risk of recurrence [125] Heparanase inhibition via low-molecular-weight heparins or PI-88 could prevent tumour invasion and metastasis
Tumour-customised immunosuppression via cytotoxic activity of natural killer (NK) cells	Excessive immunosuppression should be avoided

AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma; mTOR=mammalian target of rapamycin.

well as a number of other solid tumours, particularly in the lung (Table 1).

4.2.1. Non-melanoma skin cancer

Solid-organ transplant recipients are up to 250-times more likely to develop non-melanoma skin cancer (mainly squamous cell carcinoma [SCC] but also basal) than people without transplants. Risk factors for skin cancer include sun exposure, age, previous history of neoplasia, and immunosuppression. Treatment with cyclosporine accelerates the overall development of skin cancers [8,130], whereas treatment with azathioprine increases the risk of SCC; on the other hand, administration of mycophenolate mofetil (MMF) reduces the risk [18,131]. Specific recommendations for immunosuppressive therapies for the treatment of skin cancer are lacking, although mTOR inhibitors have been associated with reduced cancer incidence [132,133].

4.2.2. PTLD/lymphoma

PTLD/lymphoma is a heterogeneous group of diseases characterised by excessive proliferation of lymphoid cells that frequently results from infection or reactivation of latent EBV [134,135]. PTLT is mainly associated with EBV infection, either through an EBV seronegative recipient who received an EBV seropositive organ from the donor or through a primary infection in EBV negative recipients, usually children [136]. PTLT occurrence also depends on the type of organ transplantation, with intestinal transplantation having the highest rates, followed by heart, lung, liver, and kidney [136].

There is a close relationship between immunosuppression dose-intensity and PTLT incidence [137–141]. Patients who are heavily immunosuppressed are at increased risk of developing PTLT [141] and, conversely, recipients who

receive less immunosuppression have a lower risk [142]. The type of immunosuppression regimen is also a risk factor for PTLT development, with a higher risk in patients who receive T-cell depleting antibodies, such as OKT3 or anti-thymocyte globulin, in cases where immunosuppression must be higher to prevent acute rejection, and in patients who are receiving maintenance immunosuppression with three agents. Treatment with cyclosporine has also been reported to accelerate the development of lymphoproliferative disease [8,130]. Treatment with belatacept, a selective co-stimulation blocker recently approved for renal-transplant recipients, results in an increased frequency of PTLT, specifically, PTLT involving the central nervous system [143,144]. The majority of PTLT events were diagnosed within the first 12 months post-transplant in patients who were EBV seronegative and in patients who received higher doses of belatacept. There were no new cases of PTLT between years 2 and 3 [145].

4.2.3. Kaposi's sarcoma

Risk of KS is increased 500-fold in solid-organ recipients compared with the general population, and represents approximately 4% of all post-transplant tumours [146,147]. KS is a multifocal angioproliferative neoplasm driven by HHV-8 infection. Two mechanisms have been described: HHV-8 contamination from the donor organ and HHV-8 reactivation in recipients seropositive for HHV-8 [148–151]. HHV-8 is a complex DNA virus, and infection can result in deregulation of cell growth and survival, angiogenesis, inflammation, and modulation of immune system in favour of tumour growth [152]. In vitro, HHV-8 up-regulates VEGFR, causing long-term proliferation and survival of endothelial cells [153]. Blocking the interaction between

VEGF and its receptor has been shown to abolish VEGF-induced proliferation, therefore inhibiting the progression of KS [154]. KS oncogenesis involves the stimulation of tuberlin phosphorylation, promoting the activation of the mTOR pathway [153] and contributing to cell survival, growth, and production of angiogenic factors. mTOR plays an essential role in the expression of the replication and transcription activator (RTA), the lytic switch protein of HHV-8. A recent study reported that an mTOR inhibitor was able to block lytic reactivation of HHV-8 in vitro [155].

Because the course of KS depends on the level of immunosuppression, the treatment cornerstone is to taper down immunosuppressive regimens to the lowest possible level associated with regression of lesions [156]. Specific local or, less frequently, systemic treatment modalities can be used, such as chemotherapy. Recently, sirolimus has proven effective in the treatment of KS among kidney recipients; it inhibits disease progression while providing effective immunosuppression [157]. Studies are ongoing to assess whether immunosuppression by mTOR inhibitors can provide prevention in high-risk patients.

4.2.4. Others

4.2.4.1. Anogenital cancer. Transplant recipients have an increased incidence of tumours of the anogenital region (anus, vulva, perianal region, penis, scrotum or perineum). They are most frequently reported in women and in recipients with multiple sexual partners, infection with HPV, a history of genital herpes, the presence of skin cancers, and a high level of immunosuppression. HPV is one of the most frequent infections in transplant recipients and various types are associated with skin, cervix, penis, or anogenital carcinomas [158]. The prevalence of anogenital warts increases with the length of graft survival, and up to 50% of renal transplant recipients with graft survival >5 years have anogenital warts [159].

4.2.4.2. Renal cancer. The risk of renal cancer is most elevated in kidney transplant recipients; however, it is also increased in liver transplant recipients and heart recipients [13]. Renal tumours that develop in solid organ transplant recipients may differ from the tumours that develop in the general population [160]. In general the renal cancers that develop in organ recipients are smaller asymptomatic renal masses that are low grade and low stage tumours with a favourable prognosis [160,161]. Removal of the small renal masses is usually done with surgical treatment. In order to diagnose the tumours at an early stage a regular yearly abdominal ultrasound screening is recommended [161,162].

4.3. Spanish Post-Heart Transplant Tumour Registry

In an attempt to overcome shortcomings commonly associated with single-centre studies, the Spanish post-heart transplant tumour registry incorporates data from all heart transplant units across the national territory [116]. Similar

to other organs, risk of malignancy among recipients of heart transplants is greater than in the non-transplanted population. Interestingly, they also show that while skin cancer is still the most common post-transplant malignancy, PTLD is no longer the second most common malignancy, probably because of the introduction of prophylactic therapy against EBV. A study on the influence of induction therapy, immunosuppressive regimen, and antiviral prophylaxis on development of lymphomas after heart transplantation reported that induction increased the risk of lymphoma if antiviral prophylaxis was not used (regardless of induction agent and antiviral agent), but did not increase the risk if antiviral prophylaxis with acyclovir or ganciclovir was used in a multivariate analysis that controlled for age group, sex, pre-HT smoking, and immunosuppression in the first 3 months with MMF and/or tacrolimus [163].

4.4. Effective management of post-transplant cancer

Management of transplant patients varies depending on the type of organ transplanted. Because of increased tumour risk and comorbidity, limitations in therapeutic intervention, and lower life expectancy in solid-organ transplant recipients, specific preventive and management recommendations can differ from those for the general population.

4.4.1. Screening

In general, careful long-term screening protocols are recommended for early detection of malignancies because this is associated with increased chance of survival. Lymphoma (PTLD) and solid-organ tumours must be screened through regular visits to the doctor at pre-scheduled intervals, particularly in the first years after transplantation (Table 9) [164]. Two studies of intensive overall screening protocols for tumour surveillance in liver transplant recipients have shown a significantly improved survival (Table 10) [174,175]. Early detection of pre-cancerous skin lesions through skin self-examination leads to early referrals to the dermatologist and results in better prognosis relative to other neoplasms [165].

4.4.2. Prevention

To reduce cancer risk, sun exposure should be minimized with sunblock and clothing, and premalignant lesions, such as warts and actinic keratoses, should be treated early. Administration of low-dose retinoids could be useful in treating premalignant lesions and reducing skin cancer risk. Other general preventive measures include smoking cessation, following a balanced diet plan, and getting enough exercise.

4.4.2.1. Prevention of viral infections. Because the post-transplantation risk of certain cancers is linked to infection with viruses, prevention and control of viral infections are crucial, particularly in patients who develop a primary viral infection and in chronic carriers of EBV, HHV-8, HPV, hepatitis B virus (HBV), and hepatitis C virus (HCV).

Table 9

Proposed prevention, screening, and prophylaxis programs to reduce post-transplantation malignancies based on specific risk factors.

Cancer site (refs)	Active protection	Screening	
		Type	Frequency
Skin [164–166]	Photoprotection	Skin autoexam	Monthly
	Retinoids	Dermatologist visit	Annually
Lymphomas [167]	mTOR inhibitors (?)		
	HPV vaccine (?)		
	EBV viral load monitoring		
	Acyclovir prophylaxis		
	Reduction in immunosuppression		
Cervix [164,168]	HPV vaccine	Pap smear	Annually
Breast [169]		Mammography	Every 2 years
Prostate [166,170]		Digital rectal exam and prostate-specific antigen	Annually
Colorectal [171,172]		Fecal occult blood test	Annually
		Sigmoidoscopy	Every 5 years
		Colonoscopy	Every 10 years
		Laryngoscopy	Annually
Head and neck [27,164]	No tobacco		
	HPV vaccine (?)		
Lung [173]	No tobacco	Chest X-ray and CT	Annually
Kidney and urothelia [27,164]	No tobacco	Sedimentation and echography	Annually

CT=computed tomography; EBV=Epstein–Barr virus; HPV=human papillomavirus; mTOR=mammalian target of rapamycin; Pap=Papanicolaou.

Measures to prevent and control post-transplantation infections include careful screening of recipients and donors for infectious disease, prophylactic antiviral therapy, meticulous postoperative care, judicious use of immunosuppression, laboratory and other diagnostic tests, and early treatment of infections. The potential for pre-transplant vaccination to prevent HPV-related SCC should be explored in transplant recipients. Regarding prophylaxis, use of acyclovir to treat cytomegalovirus has been shown to reduce

the incidence of lymphoma in renal and heart transplant recipients [114,176].

Antiviral agents may be necessary to avoid the risk of complications such as lymphoma when using induction therapy with antibody-based therapies (e.g., muromonab-CD3 and the anti-CD25 antibodies basiliximab and daclizumab) during the first weeks after post-transplantation [9,176–178]. In this respect, cytomegalovirus prophylaxis during induction therapy (with agents other than IL-2

Table 10

Intensive screening protocols for tumour surveillance in liver transplant recipients. Adapted from Chak et al 2010 [26].

Reference	Traditional screening*	Intensive screening*	Results
Finkenstedt 2009 [174]	● Chest X-ray ● Abdominal US ● Chest and abdominal CT[†] ● Mammography and urologic screening[‡]	● Chest and abdominal CT ● PSA ● Gynaecologic screening ● Skin examination ● Colonoscopy[§]	Improved median overall survival in the intensive screening group (11.3 vs 3.1 years, $P=0.001$)
Herrero 2009 [175]	● None	● Chest X-ray ● Abdominal US ● Mammography (every 2 years) ● Colonoscopy[¶] ● ENT clinic visit (>20 pack year smoking) ● CT scan (>20 pack year smoking) ● PSA (age>55)	At 25-month median follow-up, survival in intensive screening group was 100% with 11 malignancies vs 25% survival with 28 malignancies ($P=0.002$)

CT=computed tomography; ENT=ear, nose, and throat; PSA=prostate-specific antigen; US=ultrasound.

* Each test was performed annually unless otherwise noted.

[†] Only in patients with history of malignancy.[‡] According to standard of care.[§] Performed 3 years after surgery and every 5 years thereafter.[¶] Performed 1 year after surgery in patients with prior adenoma and repeated every 2–4 years if more adenomas were found. If no adenomas were found, colonoscopy was repeated every 10 years in patients >50 years old.

inhibitors) reduces the incidence of PTLT in kidney transplant recipients [176]. Data from the Spanish Tumour Registry presented at the ATOS meeting showed a similar trend in heart transplant recipients. In Spain, 60% of patients undergo induction therapy and 50% receive viral prophylaxis, which could explain why the incidence of PTLT among patients in this registry is almost half that described elsewhere [114].

4.4.3. mTOR inhibitors

In recent years, mTOR inhibitors, such as sirolimus or everolimus, have been approved for immunosuppression of transplant recipients. Compared with CNI-mediated immunosuppression, mTOR inhibitors have shown strong anti-angiogenic effects that inhibit tumour growth [56,60,179].

Furthermore, mTOR inhibitors can directly target cancer cells by inhibiting their dependence on the mTOR pathway for cell growth and survival. Both in the RMR study and CONVERT trials, which assessed the conversion to a sirolimus-based CNI-free immunosuppression regimen, the malignancy rates post-conversion were significantly lower in the group who converted to treatment with mTOR inhibitors [132,133]. A multivariate analysis of post-transplant malignancies in 33,249 renal transplant recipients showed that the risk of developing *de novo* malignancies was significantly higher in the group of patients receiving CNI-based immunosuppression compared with the group receiving mTOR inhibitors (with or without CNIs) [180].

Conversion from CNIs to mTOR inhibitors or inclusion of mTOR inhibitors in a CNI-based immunosuppressive

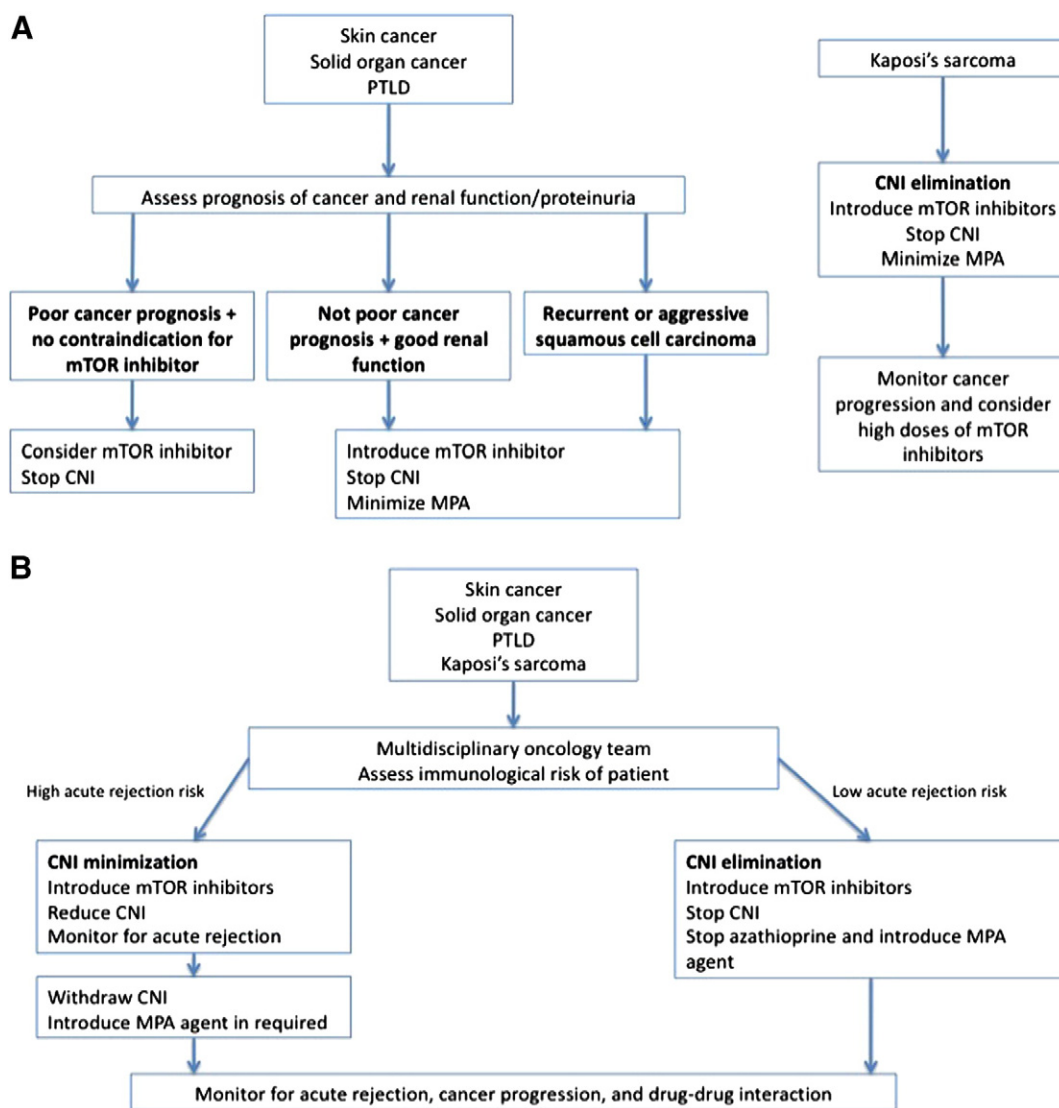


Fig. 2. Algorithm for management of common post-transplantation malignancies in renal transplant recipients (A) and heart transplant recipients (B). Adapted from Campistol 2009 [185] and Epailly et al 2011 [186]. CNI=calcineurin inhibitor; MPA=mycophenolic acid; PTLT=post-transplant lymphoproliferative disorder; mTOR=mammalian target of rapamycin.

regimen is one of the strategies recommended upon appearance of post-transplant malignancy [61,181,182]. This conversion has been particularly effective in reducing KS progression [157]. There is an ongoing prospective multicentre trial in Europe (NCT00133887) that is studying renal transplant recipients who developed a first post-transplant SCC with CNIs, to determine whether conversion to sirolimus-based immunosuppression can decrease the subsequent recurrence of SCC [183]. In renal transplantation, mTOR-inhibitor based therapies have reported a lower risk of tumour development compared with other therapy groups [133,180]. A recent meta-analysis of 56 studies in renal transplant recipients comparing *de novo* CNI-sparing regimens with CNI-based regimens suggested that reducing the exposure to CNI immediately after renal transplantation could result in improved clinical outcomes; however, data on malignancy rates were not reported [184].

4.4.4. Treatment algorithm for post-transplant malignancies

Algorithms for treatment of post-transplant malignancies in renal transplant (Fig. 2A) or heart transplant (Fig. 2B) recipients have been proposed [185,186]. The key aspect of these treatment algorithms is to modulate immunosuppression to reduce the burden of net immunosuppression. Minimization or elimination of CNIs forms the basis of treatment for post-transplantation malignancies. On the other hand, it is important to maintain sufficient immunosuppression to guarantee normal graft function and to prevent the risk of organ rejection. In many cases, a simple reduction or elimination of CNIs only brings about tumoural regression in 20% of patients, indicating that it might also be important to add an mTOR inhibitor to the immunosuppression regimen.

4.5. Malignancy in paediatric solid-organ transplantation

Paediatric transplant recipients have a 10-fold higher risk of developing cancer than an age-matched population, and even higher, depending on the type of tumour (e.g., 200-fold and 46-fold higher risk for skin cancer and non-Hodgkin's lymphoma, respectively). In a large retrospective cohort study of 18,911 young kidney transplant recipients, malignancy-related deaths occurred at a median age of 21.0 (interquartile range [IQR] 15.8–28.0), and a median of 7.0 (IQR 3.0–12.9) years after the first transplant [187]. Malignancy-related deaths were 5.5 times more common in patients with graft function than in patients on dialysis because of graft failure. The risk of non-Hodgkin lymphoma after liver transplantation is much higher in children compared with adults: SIR 123 (95% confidence interval [CI], 3.12–686) for recipients aged less than 17 years, 55.7 (95% CI, 6.74–201) for ages 17–39 years and 9.42 (95% CI, 3.06–22.0) for ages >40 years [9]. In registries of paediatric transplantation, PTLTD accounted for the majority of malignancies, followed by skin cancer [10,188–190]. The incidence of PTLTD in the paediatric population depends on the organ transplanted: intestinal transplantation (30%), heart transplantation (15%), liver (5%–15%), and kidney (1%–2%) [191–194]. Mortality from paediatric PTLTD can be quite high (50%–90%) [195]. Most PTLTD cases are EBV-related B-cell tumours resulting from impaired immunity due to immunosuppressive therapy. PTLTD is classified into four major categories: early lesion, monomorphic PTLTD, polymorphic PTLTD, and classical Hodgkin's lymphoma (CHL)-type PTLTD (Table 11) [196]. Timely and accurate diagnosis based on histological examination of biopsy tissue is essential for early intervention. Patients in whom primary EBV infection develops after transplantation should be managed with a reduction in immunosuppression and with

Table 11
WHO categorisation of PTLTD and treatment recommendations [196–198].

Stage	Definition	Treatment
Early lesions	Infectious mononucleosis-like hyperplasia Plasmacytic hyperplasia	Reduction in immunosuppression Consider antiviral treatment Consider rituximab if no response to above after 6 weeks
Polymorphic lymphoproliferative disorders		Reduction in immunosuppression Consider antiviral treatment Consider rituximab if no response to above after 6 weeks Consider chemotherapy if no response to rituximab
Monomorphic lymphoproliferative disorders (by lymphoma classification)	B-cell neoplasms - Diffuse large B-cell lymphoma - Burkitt/Burkitt-like lymphoma - Plasmacytoma-like lesions - Plasma cell myeloma T-cell lymphomas (unusual) - Peripheral T-cell lymphoma, not otherwise specified	Reduction in immunosuppression Rituximab Chemotherapy
Hodgkin's lymphoma/Hodgkin's lymphoma-like lymphoproliferative disorders		Reduction in immunosuppression Rituximab Chemotherapy

WHO=World Health Organization; PTLTD=post-transplant lymphoproliferative disorder.

close surveillance for the development of PTLT [199,200]. Screening of EBV viral load has been shown to significantly reduce PTLT-related mortality in paediatric liver transplant recipients [167]. Antiviral drugs targeting EBV replication may be beneficial in patients with early or polymorphic PTLT [201]. Several phase II studies and retrospective studies have confirmed the efficacy of rituximab in PTLT, especially in CD20+PTLT, with early treatment showing better results [196,197,202]. Patients with localized PTLT can be treated with surgery, radiotherapy, or rituximab, whereas patients with systemic polymorphic PTLT should receive chemoimmunotherapy or rituximab. Patients should be closely monitored for EBV viral load with EBV-polymerase chain reaction. Continuation of reduction in immunosuppression and viral load monitoring or rituximab maintenance are recommended after achieving a complete response to first-line therapy [197].

5. Conclusions

The important points discussed at the 2011 ATOS meeting summarising the new concepts and best practices for understanding and effectively managing cancer and solid organ transplant recipients are described in Box 1.

Box 1

New concepts and best practices

Epidemiology

- Recipients of a kidney, liver, heart, or lung transplant are at increased risk of developing infection-related and unrelated post-transplant malignancies.

Oncogenesis

- CNI-based chronic immunosuppression causes impaired immunosurveillance, allowing malignant cell proliferation that multiplies the risk of oncoviral infection, and displays direct pro-oncogenic activity.
- Oncoviruses, such as EBV, HHV-8, and HPV, play a significant role in the development of post-transplant malignancies

Donors with cancer

- It is important to detect malignancies in donor organs; however, suggested risk categorisations for specific tumour types in organ donors illustrate that not all malignancies constitute an absolute contraindication to donation.

Transplantation candidates with a history of malignancy

- Broader eligibility criteria for transplantation have increased the number of transplant candidates with a history of previous malignancy. Tumour-specific wait periods between resolution of cancer by treatment and transplantation have been proposed; however, the patient's risk of death from organ failure without transplantation must be taken into consideration.

- Liver transplantation offers the best long-term results for patients with HCC. More patients with HCC could be candidates for transplantation if the current Milan criteria were replaced with the “up-to-seven” criteria or if patients were treated with locoregional therapies that downstage their tumours to within the Milan criteria before transplantation.

Recurrence of pre-transplant cancer

- There is a broad range of cancer recurrence rates after transplantation in patients with preexisting malignancies that differ slightly according to the organ transplanted.
- There are few studies on the prevention of recurrence of HCC in liver transplant recipients. mTOR inhibitors seem to improve disease-free and survival-rates, although large prospective trials are lacking.

De novo malignancies

- To reduce and effectively manage post-transplant malignancies, active monitoring and follow-up of patients are essential. Long-term screening protocols are recommended for early detection of post-transplantation malignancies. Intensive overall screening protocols for tumour surveillance in liver transplant recipients have shown a significantly improved survival versus traditional screening programs.

Viral monitoring and prophylaxis

- o Viral infection control is particularly important in patients who develop a primary viral infection and in chronic carriers of EBV, HHV-8, HPV, HBV and HCV.
- o Screening of EBV viral load and introduction of prophylactic antiviral therapy against EBV have been shown to significantly reduce PTLT-related mortality.

Immunosuppression modulation

- o Reduction in immunosuppression, conversion from CNIs to mTOR inhibitors, and inclusion of mTOR inhibitors in a CNI-based immunosuppressive regimen are some of the strategies recommended upon diagnosis of a post-transplant malignancy.
- o mTOR inhibitors are the first class of immunosuppressants to be associated in the long-term with a significant decrease in post-transplant *de novo* malignancies, and can be recommended as a cornerstone immunosuppressant for renal transplant recipients who had a pre-transplant malignancy or developed *de novo* cancer post-transplant, e.g., KS or recurrent skin cancers.

Paediatric organ transplantation

- o PTLT accounts for the majority of malignancies in paediatric organ transplantation, because children are usually EBV negative at transplantation.
- o EBV viral load should be monitored, and if viral load increases, early antiviral therapy against EBV

should be administered. Patients in whom primary EBV infection develops should be managed with a reduction in immunosuppression and close surveillance for the development of PTLT.

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