Transplant International

REVIEW

Assessment of kidney transplant suitability for patients with prior cancers: is it time for a rethink?

Wai H. Lim[1,2], Eric Au[3,4,5], Anoushka Krishnan[1] & Germaine Wong[3,4,5]

1 Department of Renal Medicine, Sir Charles Gairdner Hospital, Nedlands, WA, Australia
2 School of Medicine, University of Western Australia, Perth, WA, Australia
3 Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia
4 Centre for Transplant and Renal Research, Westmead Hospital, Sydney, NSW, Australia
5 Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia

Correspondence
Wai H. Lim, Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, WA 6009, Australia.
Tel.: +61864572799;
fax: +61864573942;
e-mail: wai.lim@health.wa.gov.au

SUMMARY

Kidney transplant recipients have up to a 100-fold greater risk of incident cancer compared with the age/sex-matched general population, attributed largely to chronic immunosuppression. In patients with a prior history of treated cancers, the type, stage and the potential for cancer recurrence post-transplant of prior cancers are important factors when determining transplant suitability. Consequently, one of the predicaments facing transplant clinicians is to determine whether patients with prior cancers are eligible for transplantation, balancing between the accelerated risk of death on dialysis, the projected survival benefit and quality of life gains with transplantation, and the premature mortality associated with the potential risk of cancer recurrence post-transplant. The guidelines informing transplant eligibility or screening and preventive strategies against cancer recurrence for patients with prior cancers are inconsistent, underpinned by uncertain evidence on the estimates of the incidence of cancer recurrence and the lack of stage-specific outcomes data, particularly among those with multiple myeloma or immune-driven malignancies such as melanomas. With the advent of newer anti-cancer treatment options, it is unclear whether the current guidelines for those with prior cancers remain appropriate. This review will summarize the uncertainties of evidence informing the current recommendations regarding transplant eligibility of patients with prior cancers.

Transplant International 2019; 32: 1223–1240

Key words
Prior cancers, transplant suitability, myeloma, melanoma, kidney transplant

Received: 11 June 2019; Revision requested: 16 July 2019; Accepted: 31 July 2019; Published online: 28 August 2019

Introduction

Kidney transplantation is often the treatment of choice for a proportion of patients with end-stage kidney disease (ESKD), conferring a significant survival advantage and improvement in quality of life compared to dialysis treatment [1,2]. Advances in the management of cardiovascular disease (CVD) have resulted in a substantial reduction in CVD mortality in kidney transplant recipients, but despite improved access to cancer screening and novel treatment options, cancer remains a major cause of morbidity and mortality in this population [3,4]. In Australia, cancer has surpassed CVD as the most frequent cause of mortality in kidney transplant recipients, with similar trends observed worldwide [4,5]. Even though cancer is a feared complication for kidney transplant recipients, many patients would still consider this as an acceptable risk in the trade-off between the risk of dying from cancer versus remaining on lifelong dialysis treatment [6].

doi:10.1111/tri.13486

With a greater accessibility to the growing armamentarium of novel anti-cancer therapies combined with improved overall survival of cancer patients in the general population, the current recommendations and clinical practice for determining transplant suitability of patients with prior treated advanced cancers may no longer be applicable. This review will focus on a few of the controversial aspects of transplanting patients with prior cancers, including those with ESKD attributed to multiple myelomas.

Epidemiology of cancer incidence and mortality after kidney transplantation

Several large population cohort studies have consistently shown that cancer incidence is up to 100-fold higher in solid organ transplant recipients compared to age- and gender-matched general population, particularly for oncogenic virus-related cancers [7,8]. Even though all solid organ transplant recipients have an excess risk of a large number of cancers post-transplant, there are organ-specific differences where the absolute risks of certain types of cancers are higher in subgroups of organ transplant recipients (e.g. the risk of renal cell cancer is higher in patients who have received kidney transplants). Impairment of cell-mediated immunity arising from chronic exposure to immunosuppression is a major contributing factor in the pathogenesis of certain cancers post-transplant, particularly cancers attributed or suspected to be related to a viral aetiology such as Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV-8) [9,10]. In addition, there is an increased risk of other cancer subtypes such as melanoma, and lung and renal cell cancers, where uraemia, inflammation and/or ability of cancer cells to escape immune surveillance are likely to be important in the development of these cancers. In contrast, the risks of common cancers such as breast and prostate cancers are not increased in kidney transplant recipients.

The prognosis of kidney transplant recipients who have developed incident cancer is relatively poor, with the risk of cancer mortality substantially greater compared to age-matched general population [11–13]. In two large contemporaneous population cohorts of kidney transplant recipients from the United Kingdom (UK, 2001–2012) and Australia and New Zealand (1980–2014), standardized mortality ratios (SMRs) were substantially higher in kidney transplant recipients of either gender and across all age groups, with SMRs highest for younger recipients [12,13]. Relative to the general population, the greatest SMRs of cancer deaths were non-Hodgkin lymphoma [10.7, 95% confidence interval (95% CI) 8.9–12.7], kidney cancers (7.8, 95% CI 5.9–10.0) and melanoma (5.8, 95% CI 4.5–7.3) for kidney transplant recipients in Australia and New Zealand [12], whereas in the UK, lung cancer and lymphoma were the most common cause of cancer deaths in men and women, respectively [13]. There was no significant increased risk of cancer death from breast cancer in women or prostate cancer in men. Similar findings have been corroborated in population cohorts from Canada and Hong Kong [14,15].

Cancer recurrence post-kidney transplant in patients with prior cancers

The risk of cancer recurrence post-transplant in patients with prior cancer remains poorly described. In a population cohort study of 2840 kidney transplant recipients from Australia and New Zealand who have developed cancer post-transplant between 1965 and 2012, 80 (2.8%) had a history of prior cancers, with 23 (0.8%) and 57 (2.0%) recipients who experienced cancer recurrence or had developed a second new cancer, respectively [16]. The most frequent recurring cancers after transplantation included urinary tract cancers (30%), followed by breast cancers (26%), melanoma (13%) and female genital tract cancers (13%). However, it appears that the cumulative cancer-specific and patient survivals were similar between recipients who had developed *de novo* cancers and those who had experienced cancer recurrence, but these findings, however, were limited by the small event rates. In a French cohort study of 143 patients with prior renal cell cancer, cancer recurrence rate post-kidney transplant was 9% (13 of 143 patients), with over 75% of patients who had experienced cancer recurrence died during the follow-up period [17]. In a systematic review of 57 studies (37 studies in the meta-analyses) reporting on cancer recurrence in solid organ transplant recipients (19 studies in kidney transplant recipients), the proportion of patients (395 recurrences in 5838 patients) who had experienced recurrent cancer ranged between 0.4% and 22% (the latter from Israel Penn registry, a voluntary reporting registry) [18,19], with the pooled proportion of patients with recurrence of 5.0% (95% CI 3.2–7.6%). Thirteen of the 57 studies were in abstract form and 17 of the remaining 44 studies were deemed to be of low quality. The pooled estimates for site-specific recurrence rate for all solid organ transplant recipients were uncertain and imprecise. The highest recurrence rate was reported for lung cancer (5.4 events per 100 person-year, 95% CI 1.7–16.6),

gastrointestinal cancer (4.7 events per 100 person-year, 95% CI 1.7–12.4), cervical cancer (3.9 events per 100 person-year, 95% CI 1.6–9.3), kidney cancer (2.2 events per 100 person-year, 95% CI 0.8–6.2), breast cancer (2.0 events per 100 person-year, 95% CI 1.3–3.3) and melanoma (1.9 events per 100 person-year, 95% CI 0.8–4.7). In studies confined to only kidney transplant recipients (maximum of four studies for each site-specific cancer), the cancer recurrence rate per person-year of follow-up was highest for kidney cancer (seven recurrences per 334 person-year of follow-up), melanoma (7 per 235 person-years), breast cancer (4 per 83 person-years), cervical cancer (3 per 98 person-years), gastrointestinal cancer (2 per 20 person-years) and thyroid cancer (2 per 36 person-years) [20]. It is noteworthy that the pattern and frequency of cancer recurrence after kidney transplantation is dissimilar between studies, but is likely to reflect differing approaches in data reporting of cancer recurrence (i.e. reports of cumulative incidences, relative/absolute recurrence rates); dissimilar risk factors (e.g. analgesic nephropathy as cause of ESKD is more common in Australia and parts of Europe, which predispose to a greater risk of renal cell and bladder cancers) [21–23], availability and/or uptake of cancer screening programmes, differences in country-specific patient characteristics/ethnicity, potential differences in the geographical distribution of oncogenic viruses; and the inclusion of other nonkidney solid organ transplant recipients in the studies. Nonetheless, it is likely that the reporting of cancers to country-specific transplant registries is often incomplete, which may lead to an underestimation (and differences between countries) of the cancer recurrence risk.

Recommendation for transplant eligibility and 'optimal' waiting time prior to transplant wait-listing

The current recommendation regarding medical suitability of patients with prior cancers and the duration of waiting time between the treatment of prior cancer (s) and time to wait-listing/transplantation is primarily extrapolated (and arbitrarily established) from the data of potential cancer recurrence in the general population. Therefore, the benefit and cost of cancer recurrence relative to the projected patient and allograft survival compared to no transplantation are not explicitly considered and the risk of cancer recurrence is anticipated to be increased (but relatively unknown) in the setting of chronic immunosuppression. Given that the risk of cancer recurrence and recurrent cancer-related mortality appears low from previous epidemiological studies [16], it is unclear whether the current recommendation is justified or whether we are too restrictive in determining the transplant eligibility of patients with prior cancers, and whether a lesser waiting time may be appropriate in certain cancers where the survivals have substantially improved in the general population. Nevertheless, clinicians and patients will need to be cognizant that treatment for cancer recurrence in kidney transplant recipients is exceedingly dissimilar to the general population, taking into consideration the potential drug interaction between chemotherapeutic agents with immunosuppressive regimen, modification of immunosuppressive regimen in the presence of chemotherapeutic agents, combined cumulative toxicities (including infectious complications) of the addition of chemotherapeutic agents to immunosuppressive regimen, suboptimal kidney allograft function necessitating reduction in the dose of chemotherapeutic agents (which may reduce the efficacy of treatment) and the potential to induce kidney allograft rejection and premature allograft failure as a result of under-immunosuppression (reducing or withdrawal of specific immunosuppressive agent or as a result of inducing acute rejection with the use of immune-stimulatory therapy) [24]. Not infrequently, clinicians and patients must decide on the 'paradoxical' trade-off between sustaining allograft function and the adequate treatment of cancer recurrence at the expense of a functioning allograft.

The recommended waiting time for candidates with prior solid organ cancers varied between 2 and 5 years, depending on the cancer types and stage. Table 1 shows a number of guidelines highlighting the transplant eligibility of patients with selected prior cancers where there is a notable disparity in the recommendations. To assess the quality of each individual guideline, the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument should be used. The various domains of the AGREE II include the scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence [25]. Each item was rated on a 7-point scale ranging from strongly disagree (score 1) to strongly agree (score 7). The domain score was obtained by summing all scores of the individual items per domain and then standardizing the total as a percentage of the maximum possible score for that domain. The American Society of Transplantation (AST) and European Renal Best Practice (ERBP) guidelines (specifically evaluating the section relating to prior cancers) would have rated relatively well across the six domains, whereas for the Caring for

Australasians with Renal Impairment (CARI) guidelines, the quality of the domains was considered inadequate and under-developed. Nevertheless, none of the guidelines were able to assess in detail all types and stages of cancers, which may reflect the lack of supporting data for many of these cancers.

The 2018 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline on the evaluation and management of candidates for kidney transplantation is currently available for public review and is likely to incorporate updated guidelines regarding suitability of transplant wait-listing for patients with prior cancers. In contrast to the reported updated recurrence rate of cancers in the general population [26], the recurrence rates for patients with prior cancers remain poorly defined and with data primarily from the Israel Penn registry in the 1990s, which therefore does not take into account the cancer histology, updated staging and classification, evolution of improved treatments and survival of patients with these cancers [18,27]. Table 2 shows the cancer stage-specific survival, recurrence rate and prognostic characteristics in the general population ± kidney transplant recipients, along with a proposed recommendation based on the available data. Given the uncertainties, the recommended transplant suitability and waiting time must be individualized, informed by a multidisciplinary specialty team-centred approach involving the haematologists and oncologists (where appropriate) and engagement of the patients, based not solely on cancer staging but also on prognostic characteristics of the tumour (genetic, clinical and biochemical/haematological), expected survival on dialysis versus transplantation, projected risk of disease recurrence and the beliefs and expectations of both clinicians and patients regarding the benefits of kidney transplantation.

By way of an example, the guidelines consider the staging of prior breast cancer as a simplistic classification of localized versus advanced and the recommendation applicable to the stage of the cancer when it is first diagnosed. In addition, the standardized tumour, node and metastases (TNM) classification system, which

Table 1. Eligibility guidelines for kidney transplantation for patients with treated prior early and advanced cancers.

	Guidelines			
Cancer type/stage	AST 2001 [27]	CST 2005 [28]	ERBP 2013 [29]	CARI 2013 [30]
Breast cancer				
Stage 0–2 (early)	√(2)	√(2–5)	?	√(2)
Stage 3–4 (advanced)	√(5)	X	?	X
Colorectal cancer				
Duke C	√(2–5)	√(5)	??	√(5)
Duke D	?	?		X
Melanoma				
In situ	√(2)	√(2)	?	√(2)
Invasive	√(5)	√(5)	√(5)	√(5)
Renal cell cancer				
Early/symptomatic	√(0–2)*	√(0–2)	√(1)	√(5)
Large/invasive	√(5)*	√(5)	?	?
Multiple myeloma	?	X	?	X
Lymphoma	√(2)	√(2)	√(1–3)	√(2)
Lung cancer				
Localized	√(2)	√(2)	√(5)	?
Invasive	?	?	?	?
Thyroid cancer†	√(2)	√(2)	√(1–3)	√(2)
Bladder cancer				
Invasive	√(2)	√(2)	?	√(2)
Nonmelanoma skin cancers				
Localized	√(0)	√(0)	√(0)	√(0)
Invasive	?	?	?	?

CST, Canadian Society of Transplantation; ERBP, European Renal Best Practice; √(0) denotes no waiting time, √(2) denotes waiting time of at least 2 years, √(5) denotes waiting time of at least 5 years, √(2–5) denotes waiting time of at least 2–5 years, X denotes contraindication for transplantation, ? denotes no recommendation or unknown; *Symptomatic renal cell cancer ≥2 years after surgical removal, large (≥5 cm) and/or invasive renal cancers 5 years of waiting time, no waiting time required if <5 cm discovered incidentally, †Tumour invasiveness not specified.

Table 2. Survival, recurrence and prognostic features of site-specific cancer types in the general population and kidney transplant recipients.

Cancer type	SEER* (5-year survival)	AJCC (5-year survival)	Recurrence rate (general population)	Recurrence rate (kidney transplant)	Prognostic features	Recommendation
Breast cancer [31,32]	Localized – 99% Regional – 85% Distant – 27%	Overall survival: Stage I – 94–97% Stage IIA – 88–97% Stage IIB – 91–100% Stage IIIA – 67–100% Stage IIIC – 33–84%	10-year recurrence rate: T1N0 stage – LR rates 4.6%, RR 2.3% and DM 7.8%. T2N1 stage – LR rates 6.2%, RR 5.2% and DM 19.6%. Recurrence risk reduces with increasing time.	23%	Hormone receptor status, HER-2 receptor status, gene expression (Oncotype DX® and the MammaPrint®), histological grade and ploidy and cell proliferation	Stage I/II ● Stage III ● Stage IV ●
Colorectal cancer [33,34]	Localized – 90% Regional – 71% Distant – 14%	Overall survival: Stage I – 83% Stage II – 70% Stage III – 58%	5-year recurrence rate: Stage I – 5% Stage II – 12% Stage III – 33%	21% (mortality rate from recurrence 63%)	Tumour location, grade, size, number of LNs involvement	Stage I/II ● Stage III ● Stage IV ●
Melanoma [35,36]	Localized – 98% Regional – 64% Distant – 23%	*In situ* – 99–100% Stage I – 97–99% Stage II – 82–94% Stage III – 32–93%	Crude 5-year recurrence/ progression-free survivals: Stage I – 85% Stage II – 59% Stage III – 17% Stage IV – 13%	21%	Tumour thickness, presence of ulceration, mitotic index, extent of nodal metastases, extent of satellitosis and in-transit disease, presence of tumour ulceration, LDH level	Stage I ● Stage II/III ● Stage IV ●
Renal cell cancer [17,37,38]	Localized – 93% Regional – 69% Distant – 12%	Overall survival: Stage I – 81% Stage II – 74% Stage III – 53% Stage IV – 8%	Recurrence rate (80% recurs within 3 years): T1 tumour – 7% T2 – 26% T3 – 39%	27% (1% if incidental cancer; cumulative incidence of recurrence: 8% at 5 years and 15% at 10 years)	Age, LDH level, serum calcium level, haematological parameters, tumour biology and stage, histological clear cell type, extent of 'm' = nodal and distant metastases	Stage I/II ● Stage III ● Stage IV ●

Table 2. Continued.

Cancer type	SEER* (5-year survival)	AJCC (5-year survival)	Recurrence rate (general population)	Recurrence rate (kidney transplant)	Prognostic features	Recommendation
Lung cancer [39–43]	*SCLC* Localized – 29% Regional – 15% Distant – 3% *NSCLC* Localized – 60% Regional – 33% Distant – 6%	*SCLC* Stage I – 46–54% Stage II – 34–36% Stage III – 8–26% Stage IV – 7% *NSCLC* Stage I – 53–68% Stage II – 36–41% Stage III – 7–20% Stage IV – 3%	NSCLC: 30% to 55% of patients develop recurrence Population cohort (all lung cancer subtypes) – recurrence rates: Stage IA to IB – about one-third of patients had a recurrence Stage IIA – 61.2% Stage IIB – 57.9% Stage IIIA – 62.8%	Unknown	Age, nodal involvement, performance status, weight loss, tumour size, LDH level, sodium level,	Stage I 🟠 Stage II–IV ⚫
Lymphoma [44–46]	*NHL* Localized – 72% Regional – 72% Distant –55% *HD* Localized – 92% Regional – 93% Distant –78%	*NHL* Risk categories: Low – 73% Low-intermediate – 51% High-intermediate – 43% High – 26% All subtypes: Stage I – 70% Stage II – 72% Stage III – 58% Stage IV – 57% *HD* Stage I – >90% Stage II – >90% Stage III – ≥80% Stage IV – ≥65%	Recurrence variable (up to 50% for aggressive lymphoma)	11%	Age, cell type, tumour bulk, extranodal involvement, LDH level, performance status, presence of B symptoms and response to initial treatment	All stages 🟠 'Aggressive' 🔴

Table 2. Continued.

Cancer type	SEER* (5-year survival)	AJCC (5-year survival)	Recurrence rate (general population)	Recurrence rate (kidney transplant)	Prognostic features	Recommendation
Thyroid cancer [47–49]	*Papillary* Localized – 100% Regional – 100% Distant – 78% *Follicular* Localized – 100% Regional – 96% Distant – 56% *Anaplastic* Localized – 30% Regional – 13% Distant – 3%	10 years disease-specific survival: Stage I – 98–100% Stage II – 85–95% Stage III – 60–70% Stage IV – <50%	Up to 20% (for papillary and follicular cancers)	7%	Age, tumour size, ≥2 lymph nodes involvement, bilateral tumours	Stage I/II ● Stage III ● Stage IV or anaplastic ●
Bladder cancer [50–52]	Localized – 69% Regional – 35% Distant – 5%	Stage I – 85–90% Stage II – 30–45% Stage III – 15–30% Stage IV – 10%	Overall 2-year, 5-year and 10-year recurrence rates: 61%, 69% and 74%, respectively	29%	Age, female gender (higher risk), Black race, undifferentiated or higher grade tumour	Stage I ● Stage II–IV ●
NMSC (SCC) [53–55]	Not reported	No nodal involvement – 96% Nodal involvement + adequate treatment – 72% Nodal involvement + no treatment – 25–35%	Variable, with recurrence rate of 7% ay 5 years (majority within 2 years). 'Higher risk' tumour higher recurrence rate (perineural invasion 19%)	48%	Size, cancer borders, primary/recurrent cancer, presence of immunosuppression, pathology (tumour differentiation; thickness/depth; perineural, vascular or lymphatic involvements), location, size, growth pattern	Localized – none Invasive ● Nodal/distant metastasis ●

AJCC, American Joint Committee on Cancer; DM, distant metastasis; HD, Hodgkin disease; HER-2, human epidermal growth factor receptor-2; LDH, lactate dehydrogenase; LR, local recurrence; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; NSCLC, non-small-cell lung cancer; RR, regional recurrence; SCC, squamous cell cancer (skin); SCLC, small cell lung cancer; SEER, The Surveillance, Epidemiology and End Results. ● Waiting time of at least 1 year; ● Waiting time of at least 5 years; ● Contraindication for transplantation unless exceptional clinical circumstances. *Survival data extracted from American Society of Cancer website (ref. [22]).

Table 3. Kidney transplant outcomes of patients with multiple myeloma in the era of autologous stem cell transplantation.

	Number of cases (follow-up time)	Time from diagnosis to kidney transplantation (pretransplant treatment)	Relapse post-transplant (time from kidney transplant to relapse and treatment)	Allograft and patient outcomes
Shah *et al*. [95]	*N* = 5 ISS III (median follow-up 55 months)	Median 27 months (high-dose melphalan and ASCT)	2/5 relapsed (median 11 months) and died (median of 52 months) post-transplant despite chemotherapy	80% at 4 years
Batalini *et al*. [96]	*N* = 4 with MIDD (unknown, 2/4 CR at time of transplant)	Median 2.6 years after treatment (high-dose melphalan and ASCT)	Not reported	Not reported
Le *et al*. [97]	*N* = 4 LD transplants, 2/4 cases LCDD kidney biopsy (f/up range 16–58 months)	Range 20–66 months (high-dose melphalan and ASCT)	1/4 stable disease (not CR prior to transplant), bortezomib → lenalidomide maintenance	Survivals 100% at f/up
Hassoun *et al*. [98]	*N* = 2 LCDD (f/up range 26–70 months)	Treatment to transplant 14–46 months (high-dose melphalan and ASCT)	None	Survivals 100% at f/up
Sanchez-Quintana *et al*. [99]	*N* = 2 (1 LCDD, 1 MM; f/up range 3–4 years)	Treatment to transplant 4 years (ASCT with CR or VGPR pretransplant)	None, both received lenalidomide maintenance	Survivals 100% at f/up
Girnius *et al*. [100]	*N* = 2 (1 MIDD; f/up 1 and 5 years)	Not reported (high-dose melphalan and ASCT)	None	Survivals 100% at f/up
Khoriaty *et al*. [101]	*N* = 1 MM (f/up 1 year)	3.5 years (high-dose melphalan and ASCT)	None	Survival 100% at f/up
Royer *et al*. [102]	*N* = 1 LCDD (f/up 50 months)	36 months (high-dose melphalan and ASCT)	None	Survival 100% at f/up
Lorenz *et al*. [103]	*N* = 1 LCDD (f/up 23 months)	9 months (high-dose melphalan and ASCT)	None	Survival 100% at f/up
Bansal *et al*. [104]	*N* = 1 MIDD (f/up 2 years)	<1 year (high-dose melphalan and ASCT)	None	Survival 100% at f/up

ASCT, autologous stem cell transplant; CR, complete response; f/up, follow-up; ISS, Multiple Myeloma International Staging System; LCDD, light-chain deposition disease; LD, live donor; MM, multiple myeloma; MIDD, monoclonal immunoglobulin deposition disease; VGPR, very good partial response.

considers in more details the size, nodal involvement and spread of the tumours (for breast cancer: stages IA, IB, IIA/B, IIIA–C and IV), provides a more accurate description and prognosis of the cancers. Other factors such as age, performance status, response to treatment and presence of certain tumour characteristics [such as hormone receptor and human epidermal growth factor receptor-2 (Her2) status for breast cancer] will influence prognosis, further compounding the complex decision when determining whether patients with prior cancers are suitable for transplantation (Table 2). The current guideline recommendations are often based on low or ungraded quality of clinical evidence extrapolated from cohort studies and/or the opinions of the expert committee, and therefore, clinicians, in collaboration with haematologists and oncologists, should consider these guidelines as a supportive adjunct in the clinical decision-making when considering the eligibility of patients with prior cancers for transplantation.

Screening and surveillance for patients with prior cancers

In a critical appraisal of the clinical cancer screening guidelines for kidney transplant recipients, Wong *et al.* [56] indicated that the current recommendations for cancer screening in kidney transplant recipients were exclusively extrapolated from study findings in the general population (with no randomized controlled trials undertaken in the kidney transplant recipients), and as such, there were insufficient data to inform cancer screening guidelines in kidney transplant recipients pre- and post-transplant. Complex simulation model has shown a modest benefit of cancer screening in kidney transplant recipients, with the incremental cost-effectiveness ratio of cancer screening for colorectal, breast and prostate cancers in an average risk nondiabetic White population between $25 000 and $57 000USD per life-years saved [57]. There may be incremental benefits in higher risk transplant recipients, but given the assumptions and limitations of the model as well as the imprecise estimation of life expectancy of these patients, the evidence to support cancer screening in this population remains weak. Similar magnitude of benefits and uncertainties have been shown in a model of implementing routine ultrasound screening to detect asymptomatic renal cell cancer in kidney transplant recipients [58]. One recent prospective cohort study showed that faecal occult blood testing (FOBT) was an accurate screening test to detect advanced colorectal neoplasia in kidney transplant recipients; with test sensitivity, specificity, positive predictive value and negative predictive value of 97%, 82%, 26% and 98%, respectively [59]. Nevertheless, there are continuing uncertainties relating to the diagnostic test performance of other population-based cancer screening techniques including cervical cancer screening test and mammography; the competing risks of cardiovascular and infection-related mortality; the projected reduced survival of patients with ESKD; and the beliefs and concerns of patients regarding cancer screening relative to their health needs and priorities, and therefore, the strengths of the current recommendations for cancer screening in the kidney transplant recipients remain indeterminate [56,60]. Consequently, the timing, optimal imaging technique and frequency of targeted cancer screening to verify persistent cancer clearance prior to and during wait-listing, or the timing and frequency of targeted cancer screening after kidney transplantation remain unknown, although most clinicians would recommend for more frequent targeted screening in these patients in the absence of definitive evidence or guidelines. In a systematic review comprising of 16 cohort studies (inclusive of all solid organ transplant recipients, with eight cohort studies in kidney or kidney–liver and kidney–pancreas transplant recipients), patients with prior cancer were found to have up to a twofold greater risk of developing *de novo* cancers post-transplantation [hazard ratio (HR) 1.92; 95% CI 1.52–2.42] [61]. Given the current available evidence, adherence to age-specific population-based screening should be encouraged, but there are insufficient data to suggest that more frequent targeted or general cancer screening will be cost-effective or of clinical benefit in kidney transplant recipients with prior cancers.

Management approach of patients with prior cancers post-kidney transplantation

The direct and indirect carcinogenic effects of the cumulative burden of immunosuppressive agents are well established, which involves a complex interplay of an altered immune balance favouring a reduction in tumour immune surveillance and the activation of human oncogenic-type viruses [62]. Consequently, clinicians often advocate a lower cumulative burden of immunosuppression for patients with prior cancers, either by allocating donor kidneys associated with a lower immunological risk [e.g. better human leucocyte antigen (HLA)-matched kidneys or the absence of pre-transplant donor-specific anti-HLA antibody], thereby allowing the use of reduced-intensity

Table 4. Survival rates of patients with malignant melanoma in the general population and after kidney transplantation.

	General population [113,114] (5-year survival rate)*	Survival (kidney transplant recipients with *de novo* melanoma versus matched cohort from general population) [110] 5-year survival from melanoma diagnosis	
		Kidney transplant	Matched cohort
AJCC staging			
In situ	99–100%	–	–
Stage I		78% (stage I)†	98% (stage I)†
Stage IA (<0.8 mm)	99%	Adjusted HR melanoma-specific death 3.55 (95% CI 1.09, 11.54)	Referent
Stage IB (0.8–2 mm)	97%		
Stage II		35% (stage II)†	62% (stage II)†
Stage IIA (2.01–4 mm)	94%	Adjusted HR melanoma-specific death 1.30 (95% CI 0.49, 3.45)	Referent
Stage IIB (>4 mm)	87%		
Stage IIC (>4 mm + ulceration)	82%		
Stage III		20% (stage III/IV)†	32% (stage III/IV)†
Stage IIIA	93%		Referent
Stage IIIB	83%	Adjusted HR melanoma-specific death 1.21 (95% CI 0.27, 5.41)	
Stage IIIC	69%		
Stage IIID	32%		
Stage IV	15–20%		

95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; HR, hazard ratio; mm, millimetres. *Survival rate from time of diagnosis in people with malignant melanoma between 2008 and 2014. †Approximate estimates only.

immunosuppressive regimen, or by avoiding the excess utilization of potent immunosuppressive agents such as T-cell-depleting antibody which has shown to be associated with a heightened risk of incident cancer post-transplant [63,64]. However, the critical balance between maintaining an adequate amount of 'lower burden' immunosuppressive regimen versus the risk of acute and chronic rejection is often difficult to achieve or predict; and frequent immunological risk assessment post-transplant such as the monitoring of *de novo* donor-specific anti-HLA antibody or protocol biopsy to detect subclinical rejection may assist in the clinical decision-making process of individualizing immunosuppression for these patients.

Mammalian target of rapamycin (mTOR) inhibitor has been shown to possess antiviral and anti-tumour properties, with epidemiological and trial data showing that maintenance treatment with mTOR inhibitor in kidney transplant recipients significantly reduced the risk of skin and possibly nonskin cancers [65–67]. Several systematic reviews of randomized controlled trials have shown that the early conversion from CNI treatment to mTOR inhibitor (±low-dose CNI) reduced the risk of incident cancer post-kidney transplant, compared to CNI treatment regimen, but this risk reduction was observed predominantly for nonmelanoma skin cancers (NMSC) [68,69]. Several randomized controlled trials have also shown that mTOR inhibitor was effective in the secondary prevention of NMSC in kidney transplant recipients, but the long-term tolerability of mTOR inhibitor remains relatively poor [70–72]. In addition, several studies have shown that switching from CNI treatment to mTOR inhibitor may be effective in tumour regression in patients who have developed post-transplant lymphoproliferative disease (PTLD), but this approach has yet to be tested in a randomized controlled trial [73,74]. Given the continuing uncertainty regarding the efficacy of mTOR inhibitor in reducing the risk of nonskin cancers, the preferential use of mTOR inhibitor immunosuppressive regimen cannot be recommended for all patients with prior cancers; with the clinical decision based on the expected benefit as opposed to the potential long-term adverse effect of mTOR inhibitor including a higher risk of allograft failure, mortality, development of *de novo* donor-specific anti-HLA antibody and a higher

Table 5. Incidence of recurrent melanoma after kidney transplantation in patients with prior history of melanoma.

Author (year)	Study type	Recurrence (time)	Outcome
Dahle [115] (1963–2010)	Single centre Norway (kidney only)	3 of 20 (unknown)	Similar survival prior cancers (all cancers) versus no prior cancers, higher risk of cancer deaths
Hellstrom [116] (1982–2013)	Single centre Sweden (kidney only)	1 of 6 (unknown)	No cancer death reported
Viecelli [16] (1965–2012)	ANZDATA Registry (kidney only)	3 of 8 (unknown)	1 melanoma recurrence death
Unterrainer [117] (1984–2016)	CTS registry (kidney only)	8 of 164 (unknown)	Similar graft and patient survivals prior melanoma versus no prior cancers, higher risk of cancer deaths with HR of 2.56 (95% CI 1.51–4.34) up to 10 years
Chapman [118] (1963–1999)	ANZDATA Registry (kidney only)	2 of 19	Not reported
Brewer [119] (1967–2007)	Mayo Clinic databases, OPTN, IPITTR (kidney only)	2 of 59	2× recurrences (1 nodal and 1 lung)
Matin [120] (1976–2007)	Europe SCOPE network (kidney only)	0 of 9	Follow-up 14 years postmelanoma. Interval from melanoma to transplant range: 0.4–33 years. Breslow thickness range: 0.5–18 mm (3 no records)
Puza [121] (2001–2016)	Duke University, US. All solid organs)	2 of 12 (median time 5.3 years). 1 *in situ* and 1 stage IIIA	None with recurrence died from cancer. Median time between melanoma diagnosis and transplantation was 4.13 years (range: 1.1–13.3 years).
Acuna [122] (1991–2010)	CORR registry (all solid organs)	Not reported	All-cause mortality: pretransplant melanoma (HR 1.76; 95% CI 1.12–2.77) versus matched cohort without pretransplant cancer
Arron S [123] (1987–2010)	SRTR database (all solid organs)	336 (112 *in situ* and 224 invasive)	Pretransplant melanoma: death because of melanoma (adjusted HR 27, 95% CI 11–64; $P < 0.0001$), all-cause mortality (adjusted HR 1.3, 95% CI 1.0–1.5; $P = 0.02$); incident melanoma after transplant (adjusted HR 5.4, 95% CI 2.9–9.8; $P < 0.0001$)
Kang [124] (2005–2013)	UNOS database (kidney only)	398 with pretransplant melanoma	Pretransplant melanoma: post-transplant cancer (any) (adjusted SHR 1.77, 95% CI 1.30–2.40; $P < 0.001$); post-transplant skin cancer (adjusted SHR 1.93, 95% CI 1.38–2.69; $P < 0.01$)
Dapprich [125] (1978–2007)	Mayo clinic database (all solid organs)	0/12 recurrence. Pretransplant AJCC: stage 0 ($n = 4$), IA ($n = 3$), IB ($n = 2$), IV ($n = 1$); unknown ($n = 2$)	No deaths from melanoma/cancer. Median time from melanoma to transplantation 3.8 years
Penn [126] (1968–1995)	IPITTR (all solid organs)	6/31 recurrence ($n = 3$ within 2 years post-transplant, $n = 2$ between 2 and 5 years)	Not reported

95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; ANZDATA Registry, Australia and New Zealand Dialysis and Transplant registry; CORR, Canadian Organ Replacement Register; CTS, Collaborative Transplant Study; HR, hazard ratio; IPITTR, Israel Penn International Transplant Tumor Registry; mm, millimetres; OPTN, Organ Procurement and Transplantation Network; SCOPE, Skin Care in Organ Transplant Patients, Europe; SHR, subdistribution hazard ratio; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

risk of antibody-mediated rejection compared to CNI treatment [75–79].

In patients who have developed *de novo* cancers during prior kidney transplants, the clinical decision regarding medical suitability and duration of cancer waiting time when considering repeat transplantation should be similar to the current recommendations of those with a history of cancers prior to the initial transplantation. For certain transplant-specific cancers such as Kaposi's sarcoma and PTLD, successful repeat transplantation has been consistently reported although reports of cancer recurrence (for both Kaposi's sarcoma and PTLD) have been infrequently reported [80–86]. However, the timing of repeat transplantation, the optimal immunosuppressive regimen (or whether to consider using mTOR inhibitor as initial immunosuppression) or whether certain prior cancer-specific characteristics (e.g. Epstein-Barr virus [EBV] positivity, initial response to treatment) influence the re-transplant outcomes of patients with prior Kaposi's sarcoma and PTLD remains poorly defined.

'High-risk' pretransplant cancers: multiple myeloma and nonlocalized melanoma

The current guidelines suggest that patients with multiple myeloma or with nonlocalized melanoma should not be considered for kidney transplantation, with the assumption that the survival of these patients will be severely reduced post-transplant as a result of cancer recurrence. In the presence of improved survival of patients with multiple myeloma and advanced malignant melanoma, combined with the availability of novel anti-neoplastic agents and increasing number of reports of acceptable short- and medium-term outcomes post-transplant in patients with these cancers, there are increasing challenges to the long-standing paradigm of excluding patients with multiple myeloma and nonlocalized malignant melanoma who have achieved complete cancer remission for kidney transplantation.

Kidney transplantation in patients with multiple myeloma

With the evolution and availability of more potent anti-neoplastic agents combined with improved survival of patients with multiple myeloma [87,88], kidney transplantation is now a practical and conceivably an underutilized treatment option. Prior case reports describing the outcome of patients treated with chemotherapy (e.g. dexamethasone, bortezomib) to achieve clinical remission prior to kidney transplantation have largely been disappointing, with high rates of disease relapses (up to 70%) requiring further treatment. In patients who had experienced recurrence, the time to relapse post-transplant varied between 3 months and over 3 years, with a proportion dying from disease recurrence or treatment-related infective complications [89–94]. The change in treatment strategy to include preconditioning chemotherapy followed by high-dose alkylating agent and autologous stem cell transplant (ASCT) to achieve complete remission prior to kidney transplantation has resulted in favourable short- to intermediate-term outcomes and low rates of relapse, suggesting that treatment strategy to include ASCT may be necessary to achieve sustained clinical remission post-transplant ($n = 23$ cases; Table 3). Nonetheless, there are several questions which remain unanswered: (i) the 'optimal' time of clinical remission post-ASCT prior to kidney transplantation, (ii) clinical or haematological risk factors for disease relapse after kidney transplant, (iii) consideration of the timing for kidney transplantation and differences in post-transplant outcomes between those who have achieved complete versus very good partial response, (iv) clinical benefit in maintenance anti-myeloma treatment post-kidney transplant and (v) kidney transplant eligibility of patients with disease affecting extrarenal organs (e.g. heart). It is likely that the answers to these questions may be partly addressed as more cases of patients with multiple myeloma are considered for kidney transplantation and longer-term outcomes are ascertained.

Kidney transplant eligibility of patients with advanced malignant melanoma

Malignant melanoma is the most fatal type of skin cancer affecting the general population, with global incidence steadily increasing over the last decade [105,106]. Tumour characteristics such as cancer stage, presence of ulceration and thickness of the tumour have prognostic significance, and patients with more invasive disease have a higher risk of cancer recurrence and melanoma-specific mortality [107]. In patients who have received solid organ transplants, the risk of developing *de novo* melanoma is twice that of age- and gender-matched general population, likely resulting from the chronic suppression of cell-mediated immunity attributed to lifelong immunosuppressive therapy [7,108,109]. There is consistent epidemiological evidence to suggest that kidney transplant recipients with melanoma have significantly higher Clark's level and pathological staging,

with up to four times the risk of cancer mortality compared to the general population (Table 4) [12,110]. Consequently, clinicians are often reluctant to consider kidney transplantation in patients with prior history of melanoma, with those with invasive melanoma [American Joint Committee on Cancer (AJCC) stage II and above] considered absolute contraindication for transplantation. Given the improved survival and treatment options for patients with melanoma in the general community [111], there is considerable debate regarding the acceptability of patients with more advanced treated melanoma for transplantation. In the general population, 40% of patients with treated melanoma and without metastatic disease will experience cancer recurrence, typically within the first 12 (for local and nodal recurrences) to 24 (for distant metastasis) months [112].

Table 5 shows the current evidence summarizing the risk of cancer recurrence after kidney transplantation in those with a prior history of melanoma. The recurrence risk in those with prior melanoma varies between 0% and 35%, but intermediate- to long-term allograft and patient survivals are poorly defined. It is noteworthy that details relating to the pathological staging of melanoma pretransplant, treatment and the timing between melanoma diagnosis/treatment and transplantation are inadequately described, with the majority of the cohorts having included patients prior to 2000. The current recommendations regarding the suitability and waiting time for patients with prior melanoma remain inconsistent and largely extrapolated from population cohort studies from earlier eras, with an over-simplified broad classification staging system and other prognostic factors (Table 1). With the available data, it is difficult to ascertain whether the current recommendations are appropriate (given the low rates of melanoma recurrence post-transplant in current clinical practice) or whether the guidelines are too restrictive in excluding those patients with higher staged melanomas who may still derive a relative survival benefit from transplantation compared to dialysis treatment or death from melanoma recurrence.

Implications for future research

In the absence of adequate clinical evidence to support the recommendations of transplant eligibility or waiting time across all cancer types, the creation of a global repository of patients with all cancer types (including accurate records of the updated histology, prognostic factors, staging and classification and response to treatment) for patients with EKSD (dialysis and transplantation) will help inform future clinical guidelines. There continues to be uncertainty as to the applicability of age- and gender-specific general population cancer screening guidelines to patients with ESKD pre- and post-transplantation and future research examining the test performance of cancer screening in this population should be prioritized [59], including the appropriateness and cost-effectiveness of screening renal tract ultrasound (to detect renal cell carcinoma) and lung imaging (to detect lung cancer particularly in higher risk population such as former/current smokers) given the higher incidence of these cancers in patients with ESKD [58]. In addition, a greater emphasis on attaining effective consumer engagement along with a transparent public consultative process in clinical practice guideline development is critical, particularly on the standpoints of eligibility and 'acceptable' waiting times for patients with prior cancers (for both potential live and deceased donor kidney transplantation). Nevertheless, the integration of quality and diverse consumer participation in clinical guideline development or in healthcare research remains in its infancy, and the conception of a framework to establish optimal consumer engagement to inform evidence-based healthcare guidelines and research is needed [127,128].

Conclusion

The continuing dilemma facing organ transplant programmes is the imbalance between donor supply and demand, and therefore, each transplant programme will continue to prioritize and accept for transplantation only patients who are deemed clinically suitable to receive an organ. Patient preferences for how organs should be allocated is often not aligned with that of the community or clinicians, and often, the refusal to accept patients for transplantation who are otherwise suitable with the exception of a history of treated advanced cancer is often centred on the concern that cancer recurrence is likely to be at an increased risk and will lead to premature mortality and substantial reduction in the utility of the allograft, although the basis of this recommendation originates from outdated and poor-quality data. This decision ignores the rights and ability of the patients to provide informed consent for treatment, balancing the projected survival benefit of transplantation (including improvement in quality of life) versus the likelihood of cancer recurrence, which is difficult to quantify accurately.

There is generally a lack of comparative data of the outcomes of patients with prior cancers if the waiting

time after cancer treatment to transplantation was reduced, but evidence to support or refute such an approach is lacking and unlikely to be forthcoming. For patients without potential live kidney donors, a large proportion of patients on the deceased donor transplant waiting list will be required to wait on average of 2–5 years before transplantation for nonlocalized cancers, and clinical and transplant allocation programmes should consider factoring in the projected waiting time (for a kidney transplant) and patient survival when determining the 'most appropriate' waiting time prior to wait-listing for patients with prior cancers. The decision to consider transplantation for those with prior treated advanced cancers should be individualized with wider consultation with the broader multidisciplinary team including haematologist or oncologist, clearly outlining the projected risk associated with cancer recurrence and the potential treatment options and outcomes if cancer does recur post-transplantation.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgements

Wai H Lim is supported by a Clinical Research Fellowship from the Raine Foundation, University of Western Australia, and Health Department of Western Australia. Germaine Wong is supported by a National Health and Medical Research Council Career Development Fellowship.

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, *et al*. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
2. Tonelli M, Wiebe N, Knoll G, *et al*. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011; **11**: 2093.
3. Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation* 2010; **89**: 851.
4. Awan AA, Niu J, Pan JS, *et al*. Trends in the causes of death among kidney transplant recipients in the United States (1996–2014). *Am J Nephrol* 2018; **48**: 472.
5. ANZDATA Registry. *41st Report. Chapter 3: Mortality in End Stage Kidney Disease*. Adelaide, SA: Australia and New Zealand Dialysis and Transplant Registry, 2018.
6. Howell M, Wong G, Rose J, Tong A, Craig JC, Howard K. Eliciting patient preferences, priorities and trade-offs for outcomes following kidney transplantation: a pilot best-worst scaling survey. *BMJ Open* 2016; **6**: e008163.
7. Vajdic CM, McDonald SP, McCredie MR, *et al*. Cancer incidence before and after kidney transplantation. *JAMA* 2006; **296**: 2823.
8. Engels EA, Pfeiffer RM, Fraumeni Jr JF, *et al*. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011; **306**: 1891.
9. Le J, Gantt S, Practice ASTIDCo. Human herpesvirus 6, 7 and 8 in solid organ transplantation. *Am J Transplant* 2013; **13**(Suppl 4): 128.
10. LaCasce AS. Post-transplant lymphoproliferative disorders. *Oncologist* 2006; **11**: 674.
11. Au E, Wong G, Chapman JR. Cancer in kidney transplant recipients. *Nat Rev Nephrol* 2018; **14**: 508.
12. Au EH, Chapman JR, Craig JC, *et al*. Overall and Site-specific cancer mortality in patients on dialysis and after kidney transplant. *J Am Soc Nephrol* 2019; **30**: 471.
13. Farrugia D, Mahboob S, Cheshire J, *et al*. Malignancy-related mortality following kidney transplantation is common. *Kidney Int* 2014; **85**: 1395.
14. Acuna SA, Fernandes KA, Daly C, *et al*. Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. *JAMA Oncol* 2016; **2**: 463.
15. Cheung CY, Lam MF, Chu KH, *et al*. Malignancies after kidney transplantation: Hong Kong renal registry. *Am J Transplant* 2012; **12**: 3039.
16. Viecelli AK, Lim WH, Macaskill P, *et al*. Cancer-specific and all-cause mortality in kidney transplant recipients with and without previous cancer. *Transplantation* 2015; **99**: 2586.
17. Cognard N, Anglicheau D, Gatault P, *et al*. Recurrence of renal cell cancer after renal transplantation in a multicenter french cohort. *Transplantation* 2018; **102**: 860.
18. Penn I. Evaluation of transplant candidates with pre-existing malignancies. *Ann Transplant* 1997; **2**: 14.
19. Oliveira GH, Hardaway BW, Kucheryavaya AY, Stehlik J, Edwards LB, Taylor DO. Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation. *J Heart Lung Transplant* 2012; **31**: 805.
20. Acuna SA, Huang JW, Dossa F, Shah PS, Kim SJ, Baxter NN. Cancer recurrence after solid organ transplantation: a systematic review and meta-analysis. *Transplant Rev (Orlando)* 2017; **31**: 240.
21. Chang SH, Mathew TH, McDonald SP. Analgesic nephropathy and renal replacement therapy in Australia: trends, comorbidities and outcomes. *Clin J Am Soc Nephrol* 2008; **3**: 768.
22. McCredie M, Stewart J, Smith D, Supramaniam R, Williams S. Observations on the effect of abolishing analgesic abuse and

reducing smoking on cancers of the kidney and bladder in New South Wales, Australia, 1972-1995. *Cancer Causes Control* 1999; **10**: 303.
23. Stewart JH, Buccianti G, Agodoa L, *et al*. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003; **14**: 197.
24. Lipson EJ, Bagnasco SM, Moore Jr J, *et al*. Tumor regression and allograft rejection after administration of anti-PD-1. *N Engl J Med* 2016; **374**: 896.
25. Brouwers MC, Kho ME, Browman GP, *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**: E839.
26. American Cancer Society. Cancer. 2019. https://www.cancer.org/cancer.html2019
27. Kasiske BL, Cangro CB, Hariharan S, *et al*. The evaluation of renal transplantation candidates: clinical practice guidelines. *Am J Transplant* 2001; **1**(Suppl 2): 3.
28. Knoll G, Cockfield S, Blydt-Hansen T, *et al*. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. *CMAJ* 2005; **173**: S1.
29. European Renal Best Practice Transplantation Guideline Development Group. ERBP guideline on the management and evaluation of the kidney donor and recipient. *Nephrol Dial Transplant* 2013; **28**: ii1-ii71.
30. Campbell S, Pilmore H, Gracey D, Mulley W, Russell C, McTaggart S. KHA-CARI guideline: recipient assessment for transplantation. *Nephrology* 2013; **18**: 455.
31. van Maaren MC, Strobbe LJA, Smidt ML, Moossdorff M, Poortmans PMP, Siesling S. Ten-year conditional recurrence risks and overall and relative survival for breast cancer patients in the Netherlands: taking account of event-free years. *Eur J Cancer* 2018; **102**: 82.
32. Giuliano AE, Connolly JL, Edge SB, *et al*. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; **67**: 290–303.
33. Osterman E, Glimelius B. Recurrence Risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum* 2018; **61**: 1016.
34. Hari DM, Leung AM, Lee JH, *et al*. AJCC cancer staging manual 7th edition criteria for colon cancer: do the complex modifications improve prognostic assessment? *J Am Coll Surg* 2013; **217**: 181.
35. Rockberg J, Amelio JM, Taylor A, Jorgensen L, Ragnhammar P, Hansson J. Epidemiology of cutaneous melanoma in Sweden-Stage-specific survival and rate of recurrence. *Int J Cancer* 2016; **139**: 2722.
36. Bartlett EK, Karakousis GC. Current staging and prognostic factors in melanoma. *Surg Oncol Clin N Am* 2015; **24**: 215.
37. Bukowski RM, Negrier S, Elson P. Prognostic factors in patients with advanced renal cell carcinoma: development of an international kidney cancer working group. *Clin Cancer Res* 2004; **10**: 6310S.
38. Finley DS, Pantuck AJ, Belldegrun AS. Tumor biology and prognostic factors in renal cell carcinoma. *Oncologist* 2011; **16**(Suppl 2): 4.
39. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. *Transl Lung Cancer Res* 2014; **3**: 242.
40. Consonni D, Pierobon M, Gail MH, *et al*. Lung cancer prognosis before and after recurrence in a population-based setting. *J Natl Cancer Inst* 2015; **107**: djv059.
41. Chansky K, Detterbeck FC, Nicholson AG, *et al*. The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2017; **12**: 1109.
42. Crvenkova S. Prognostic factors and survival in non-small cell lung cancer patients treated with chemoradiotherapy. *Open Access Maced J Med Sci* 2015; **3**: 75.
43. Fukui T, Itabashi M, Ishihara M, *et al*. Prognostic factors affecting the risk of thoracic progression in extensive-stage small cell lung cancer. *BMC Cancer* 2016; **16**: 197.
44. Armitage JO. Staging non-Hodgkin lymphoma. *CA Cancer J Clin* 2005; **55**: 368.
45. Cancer Research UK. Non-Hodgkin lymphoma (NHL) survival by stage at diagnosis. 2013. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/survival
46. Canadian Cancer Society. Survival statistics for Hodgkin lymphoma. 2019. http://www.cancer.ca/en/cancer-information/cancer-type/hodgkin-lymphoma/prognosis-and-survival/survival-statistics/?region=on
47. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (Eighth Edition): what changed and why? *Thyroid* 2017; **27**: 751.
48. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; **97**: 418.
49. Hwangbo Y, Kim JM, Park YJ, *et al*. Long-term recurrence of small papillary thyroid cancer and its risk factors in a Korean multicenter study. *J Clin Endocrinol Metab* 2017; **102**: 625.
50. Cancer Research UK. Bladder cancer. 2019. https://www.cancerresearchuk.org/about-cancer/bladder-cancer/survival2019
51. Mungan NA, Aben KK, Schoenberg MP, *et al*. Gender differences in stage-adjusted bladder cancer survival. *Urology* 2000; **55**: 876.
52. Chamie K, Litwin MS, Bassett JC, *et al*. Recurrence of high-risk bladder cancer: a population-based analysis. *Cancer* 2013; **119**: 3219.
53. Fahradyan A, Howell AC, Wolfswinkel EM, Tsuha M, Sheth P, Wong AK. Updates on the management of non-melanoma skin cancer (NMSC). *Healthcare (Basel)* 2017; **5**: 82.
54. Khan K, Mykula R, Kerstein R, *et al*. A 5-year follow-up study of 633 cutaneous SCC excisions: rates of local recurrence and lymph node metastasis. *J Plast Reconstr Aesthet Surg* 2018; **71**: 1153.
55. Brantsch KD, Meisner C, Schonfisch B, *et al*. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol* 2008; **9**: 713.
56. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? *Clin J Am Soc Nephrol* 2008; **3**(Suppl 2): S87.
57. Kiberd BA, Keough-Ryan T, Clase CM. Screening for prostate, breast and colorectal cancer in renal transplant recipients. *Am J Transplant* 2003; **3**: 619.
58. Wong G, Howard K, Webster AC, Chapman JR, Craig JC. Screening for renal cancer in recipients of kidney transplants. *Nephrol Dial Transplant* 2011; **26**: 1729.

59. Wong G, Hope RL, Howard K, *et al*. One-time fecal immunochemical screening for advanced colorectal neoplasia in patients with CKD (DETECT study). *J Am Soc Nephrol* 2019; **30**: 1061.
60. James LJ, Wong G, Craig JC, *et al*. Beliefs and attitudes to bowel cancer screening in patients with CKD: a semistructured interview study. *Clin J Am Soc Nephrol* 2017; **12**: 568.
61. Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. Outcomes of solid organ transplant recipients with preexisting malignancies in remission: a systematic review and meta-analysis. *Transplantation* 2017; **101**: 471.
62. Wong G, Chapman JR, Craig JC. Death from cancer: a sobering truth for patients with kidney transplants. *Kidney Int* 2014; **85**: 1262.
63. Lim WH, Turner RM, Chapman JR, *et al*. Acute rejection, T-cell-depleting antibodies, and cancer after transplantation. *Transplantation* 2014; **97**: 817.
64. Opelz G, Naujokat C, Daniel V, Terness P, Döhler B. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. *Transplantation* 2006; **81**: 1227.
65. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883.
66. Khokhar NZ, Altman JK, Platanias LC. Emerging roles for mammalian target of rapamycin inhibitors in the treatment of solid tumors and hematological malignancies. *Curr Opin Oncol* 2011; **23**: 578.
67. Campistol JM, Eris J, Oberbauer R, *et al*. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581.
68. Wolf S, Hoffmann VS, Habicht A, *et al*. Effects of mTOR-Is on malignancy and survival following renal transplantation: A systematic review and meta-analysis of randomized trials with a minimum follow-up of 24 months. *PLoS One* 2018; **13**: e0194975.
69. Lim WH, Eris J, Kanellis J, *et al*. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant* 2014; **14**: 2106.
70. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transplant* 2012; **12**: 1146.
71. Dantal J, Morelon E, Rostaing L, *et al*. Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results. *J Clin Oncol* 2018; **36**: 2612.
72. Euvrard S, Morelon E, Rostaing L, *et al*. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med* 2012; **367**: 329.
73. Ashrafi F, Shahidi S, Ebrahimi Z, Mortazavi M. Outcome of rapamycin therapy for post-transplant-lymphoproliferative disorder after kidney transplantation: case series. *Int J Hematol Oncol Stem Cell Res* 2015; **9**: 26.
74. Boratynska M, Smolska D. Inhibition of mTOR by sirolimus induces remission of post-transplant lymphoproliferative disorders. *Transpl Int* 2008; **21**: 605.
75. Liefeldt L, Brakemeier S, Glander P, *et al*. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. *Am J Transplant* 2012; **12**: 1192.
76. de Sandes-Freitas TV, Felipe CR, Campos EF, *et al*. Subclinical lesions and donor-specific antibodies in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen followed by early conversion to sirolimus. *Transplantation* 2015; **99**: 2372.
77. Gatault P, Bertrand D, Buchler M, *et al*. Eight-year results of the Spiesser study, a randomized trial comparing de novo sirolimus and cyclosporine in renal transplantation. *Transpl Int* 2016; **29**: 41.
78. Badve SV, Pascoe EM, Burke M, *et al*. Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients. *Clin J Am Soc Nephrol* 2016; **11**: 1845.
79. Knoll GA, Kokolo MB, Mallick R, *et al*. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014; **349**: g6679.
80. Karras A, Thervet E, Le Meur Y, Baudet-Bonneville V, Kessler M, Legendre C. Successful renal retransplantation after post-transplant lymphoproliferative disease. *Am J Transplant* 2004; **4**: 1904.
81. Caillard S, Cellot E, Dantal J, *et al*. A French cohort study of kidney retransplantation after post-transplant lymphoproliferative disorders. *Clin J Am Soc Nephrol* 2017; **12**: 1663.
82. Birkeland SA, Hamilton-Dutoit S, Bendtzen K. Long-term follow-up of kidney transplant patients with posttransplant lymphoproliferative disorder: duration of posttransplant lymphoproliferative disorder-induced operational graft tolerance, interleukin-18 course, and results of retransplantation. *Transplantation* 2003; **76**: 153.
83. Bohelay G, Arzouk N, Levy P, *et al*. Outcome of second kidney transplantation in patients with previous post-transplantation Kaposi's sarcoma: a French retrospective study. *Clin Transplant* 2017; **31**: e13091.
84. Segoloni GP, Giraudi R, Messina M, *et al*. No recurrence of Kaposi's sarcoma in a case of renal retransplantation under a calcineurin inhibitor free immunosuppressive regimen: first report. *Transpl Int* 2007; **20**: 395.
85. Euvrard S, Kanitakis J, Bosshard S, *et al*. No recurrence of posttransplantation Kaposi's sarcoma three years after renal retransplantation. *Transplantation* 2002; **73**: 297.
86. Johnson SR, Cherikh WS, Kauffman HM, Pavlakis M, Hanto DW. Retransplantation after post-transplant lymphoproliferative disorders: an OPTN/UNOS database analysis. *Am J Transplant* 2006; **6**: 2743.
87. Fonseca R, Abouzaid S, Bonafede M, *et al*. Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia* 2017; **31**: 1915.
88. Decourt A, Gondouin B, Delaroziere JC, *et al*. Trends in survival and renal recovery in patients with multiple myeloma or light-chain amyloidosis on chronic dialysis. *Clin J Am Soc Nephrol* 2016; **11**: 431.
89. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis* 2004; **43**: 147.
90. Huskey JL, Heilman RL, Khamash H, Fonseca R. Kidney transplant in the era of modern therapy for multiple myeloma. *Transplantation* 2018; **102**: 1994.
91. van Bommel EF. Multiple myeloma treatment in dialysis-dependent patients: to transplant or not to

transplant? *Nephrol Dial Transplant* 1996; **11**: 1486.
92. Lum EL, Kogut N, Pham T, Danovitch GM, Bunnapradist S. Kidney transplantation in patients with active multiple myeloma: case reports. *Transplant Direct* 2017; **3**: e200.
93. De Lima JJ, Kourilsky O, Meyrier A, Morel-Maroger L, Sraer JD. Kidney transplant in multiple myeloma. Early recurrence in the graft with sustained normal renal function. *Transplantation* 1981; **31**: 223.
94. Iggo N, Palmer AB, Severn A, *et al*. Chronic dialysis in patients with multiple myeloma and renal failure: a worthwhile treatment. *Q J Med* 1989; **73**: 903.
95. Shah S, Ibrahim M, Delaney M, *et al*. Risk of relapse of multiple myeloma following kidney transplantation. *Clin Kidney J* 2019; **12**: 216.
96. Batalini F, Econimo L, Quillen K, *et al*. High-dose melphalan and stem cell transplantation in patients on dialysis due to immunoglobulin light-chain amyloidosis and monoclonal immunoglobulin deposition disease. *Biol Blood Marrow Transplant* 2018; **24**: 127.
97. Le TX, Wolf JL, Peralta CA, Webber AB. Kidney transplantation for kidney failure due to multiple myeloma: case reports. *Am J Kidney Dis* 2017; **69**: 858.
98. Hassoun H, Flombaum C, D'Agati VD, *et al*. High-dose melphalan and auto-SCT in patients with monoclonal Ig deposition disease. *Bone Marrow Transplant* 2008; **42**: 405.
99. Sanchez Quintana A, Rull PR, Atienza JB, McDonnell CN. Renal transplant in plasma cell dyscrasias with lenalidomide treatment after autologous stem cell transplantation. *Nephrology* 2013; **18**: 641.
100. Girnius S, Seldin DC, Quillen K, Dember LM, Segal A, Sanchorawala V. Long-term outcome of patients with monoclonal Ig deposition disease treated with high-dose melphalan and stem cell transplantation. *Bone Marrow Transplant* 2011; **46**: 161.
101. Khoriaty R, Otrock ZK, Medawar WA, Khauli RB, Bazarbachi A. A case of successful double sequential bone marrow and kidney transplantations in a patient with multiple myeloma. *Nephrol Dial Transplant* 2006; **21**: 3585.
102. Royer B, Arnulf B, Martinez F, *et al*. High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int* 2004; **65**: 642.
103. Lorenz EC, Gertz MA, Fervenza FC, *et al*. Long-term outcome of autologous stem cell transplantation in light chain deposition disease. *Nephrol Dial Transplant* 2008; **23**: 2052.
104. Bansal T, Hossain R, McKane W, Snowden JA. Safety and efficacy of high dose melphalan and autologous stem cell transplantation prior to renal allograft in end-stage renal failure secondary to monoclonal immunoglobulin deposition disease. *Cell Ther Transplant* 2011; **3**: e.000091.01. https://doi.org/10.3205/ctt-2011-en-000091.01
105. Guy Jr GP, Thomas CC, Thompson T, *et al*. Vital signs: melanoma incidence and mortality trends and projections – United States, 1982–2030. *MMWR Morb Mortal Wkly Rep* 2015; **64**: 591.
106. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. *J Invest Dermatol* 2016; **136**: 1161.
107. Balch CM, Gershenwald JE, Soong SJ, *et al*. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; **27**: 6199.
108. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**: 59.
109. Vajdic CM, van Leeuwen MT, Webster AC, *et al*. Cutaneous melanoma is related to immune suppression in kidney transplant recipients. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2297.
110. Vajdic CM, Chong AH, Kelly PJ, *et al*. Survival after cutaneous melanoma in kidney transplant recipients: a population-based matched cohort study. *Am J Transplant* 2014; **14**: 1368.
111. Suteu O, Blaga ML, Nicula F, *et al*. Incidence trends and survival of skin melanoma and squamous cell carcinoma in Cluj County, Romania. *Eur J Cancer Prev* 2017; **26 Joining forces for better cancer registration in Europe**: S176.
112. Salama AK, de Rosa N, Scheri RP, *et al*. Hazard-rate analysis and patterns of recurrence in early stage melanoma: moving towards a rationally designed surveillance strategy. *PLoS One* 2013; **8**: e57665.
113. American Cancer Society. Survival rates for melanoma skin cancer. 2019. https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanoma-skin-cancer-by-stage.html
114. AIMS Foundation. Understanding melanoma. 2014. https://www.aimatmelanoma.org
115. Dahle DO, Grotmol T, Leivestad T, *et al*. Association between pretransplant cancer and survival in kidney transplant recipients. *Transplantation* 2017; **101**: 2599.
116. Hellstrom V, Lorant T, Dohler B, Tufveson G, Enblad G. High posttransplant cancer incidence in renal transplanted patients with pretransplant cancer. *Transplantation* 2017; **101**: 1295.
117. Unterrainer C, Opelz G, Dohler B, Susal C, Collaborative Transplant S. Pretransplant cancer in kidney recipients in relation to recurrent and de novo cancer incidence posttransplantation and implications for graft and patient survival. *Transplantation* 2019; **103**: 581.
118. Chapman JR, Sheil AG, Disney AP. Recurrence of cancer after renal transplantation. *Transplant Proc* 2001; **33**: 1830.
119. Brewer JD, Christenson LJ, Weaver AL, *et al*. Malignant melanoma in solid transplant recipients: collection of database cases and comparison with surveillance, epidemiology, and end results data for outcome analysis. *Arch Dermatol* 2011; **147**: 790.
120. Matin RN, Mesher D, Proby CM, *et al*. Melanoma in organ transplant recipients: clinicopathological features and outcome in 100 cases. *Am J Transplant* 2008; **8**: 1891.
121. Puza CJ, Barbas AS, Mosca PJ. Outcomes of patients with a pretransplant history of early-stage melanoma. *Melanoma Res* 2018; **28**: 471.
122. Acuna SA, Sutradhar R, Kim SJ, Baxter NN. Solid organ transplantation in patients with preexisting malignancies in remission: a propensity score matched cohort study. *Transplantation* 2018; **102**: 1156.
123. Arron ST, Raymond AK, Yanik EL, *et al*. Melanoma outcomes in transplant recipients with pretransplant melanoma. *Dermatol Surg* 2016; **42**: 157.
124. Kang W, Sampaio MS, Huang E, Bunnapradist S. Association of pretransplant skin cancer with posttransplant malignancy, graft failure and death in kidney transplant

recipients. *Transplantation* 2017; **101**: 1303.
125. Dapprich DC, Weenig RH, Rohlinger AL, *et al*. Outcomes of melanoma in recipients of solid organ transplant. *J Am Acad Dermatol* 2008; **59**: 405.
126. Penn I. Malignant melanoma in organ allograft recipients. *Transplantation* 1996; **61**: 274.
127. Tong A, Lopez-Vargas P, Howell M, *et al*. Consumer involvement in topic and outcome selection in the development of clinical practice guidelines. *Health Expect* 2012; **15**: 410.
128. Miller CL, Mott K, Cousins M, *et al*. Integrating consumer engagement in health and medical research – an Australian framework. *Health Res Policy Syst* 2017; **15**: 9.