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EDITORIAL

Cancer post kidney transplant: the question of risk

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The risk of developing a cancer is one of the most feared and challenging complications after successful kidney transplantation. Sadly, cancer incidence is increased post kidney transplantation [1, 2] and remains a major cause of morbidity and mortality for kidney recipients. Post-transplant malignancies may be derived from the donor or the recipient, with each scenario involving different considerations. In this issue of the Journal of Nephrology, two studies report on each of these scenarios.

The risk of donor transmitted cancers is fortunately low, and the risk of morbidity and mortality from such donor derived cancers varies based on malignancy type [3, 4]. A previous systematic review was undertaken in 2013, but there have been a number of studies published since this time [3]. A thorough understanding of the newer literature associated with donor cancer transmission is imperative to balance the risk of cancer transmission and mitigate against the risk of non-utilisation of life sustaining organs. In this issue of the Journal of Nephrology, Eccher et al. [4] analysed case reports and series of donor-transmitted cancer until August 2019. They reviewed 234 recipients from 128 papers. The rarity of these transmissions occurring, means that most of the literature in this area will be case series thus there will be a degree of reporting bias and clinical heterogeneity necessitating some caution in interpretation of these results.

The most commonly transmitted cancers were lymphoma, renal cell cancer, melanoma and non-small cell lung cancer (NSCLC). Melanoma and NSCLC had the worst prognosis with renal cell cancer and lymphoma being more favourable. As expected, the most adverse prognostic factor was the presence of metastases. Interestingly, most diagnoses were made in the first 2 years post transplantation confirming the need for particular vigilance in recipient assessment over this time period.

In regards to the different types of cancer, melanoma continues to be an insidious malignancy with diagnosis occurring late after transplantation with limited ability to predict the risk of recurrence. Renal cell carcinoma, conversely, had a more favourable prognosis and was mostly identified in the first year. It was treated predominantly with tumour or transplant nephrectomy, though some were merely observed. As the authors acknowledge in their discussion, distinguishing between donor derived lymphomas and post-transplant lymphoproliferative disease continues to pose challenges to the clinician. Prediction of which recipients will develop lymphomas is difficult. The number of donor derived brain tumour such as glioblastomas, is low, which is pleasing given this is frequently found in potential donors. The relative lack of gastro-intestinal malignancies reported with transmission in the current era is also reassuring. When it comes to deceased kidney donor transplant assessment, these data confirm our current practice, that potential donors with a history of melanoma or lymphoma are generally excluded from donation. Conversely, this paper provides reassurance that renal cell cancers are relatively indolent, and the risk of transmission of gastrointestinal cancer and glioblastomas is rare.

For recipients with a history of cancer, risk of recurrence and mortality post malignancy varies based on a number of individual factors [1, 2]. The literature on the impact of cancer on mortality is in the elderly age group is conflicting [1, 5, 6]. To avoid cancer recurrence with immunosuppression, individuals with a cancer history are required to undergo a period of remission before being added to the transplant waiting list. For the elderly, this prospect of cancer recurrence, however, needs to be balanced with the risk of remaining on dialysis, the possibility of acquiring morbidity, and thus decreasing transplantation eligibility. The length of time a potential recipient must be cancer free

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before transplantation differs both for the different cancers and depending on the place of practice [7].

In this issue, Tessari et al. [6] compared cancer related death post kidney transplantation relative to the general population. The authors undertook a competing risk analysis in an Italian multicentre retrospective cohort study of 6789 patients from 1980–2012. For the different age ranges, they calculated cause specific cumulative incidence and hazard rates of death, as well as standardized mortality ratios (SMR).

Compared to the general population, for recipients 10 years post kidney transplant, the SMRs were greater in the younger age ranges compared to the older age ranges. The rate of cancer related death did not increase with recipient age, unlike cardiovascular and infection related death. Surprisingly, female kidney transplant recipients lost the survival advantage seen in the general population whereby females live longer than men. This study shows that male and female transplant recipients have a similar cumulative incidence of death.

Whilst reassuring that the malignancy rate in the elderly is not increased, the SMR in transplant recipients under 40 is staggering. Attentive monitoring for malignancy in this age group is particularly important. In terms of what cancer screening should be done, there is substantial variability in practice internationally [8]. For example, in Australia, we have a higher incidence of skin cancers, and thus have a focus on posttransplant skin screening. We recommend taking into account the country and patient specific risk profiles to tailor screening policies.

As for cancer remission times before waitlisting, our practice is to follow the KDIGO Evaluation and Management of Transplant candidate guidelines [7]. There is variability between international guidelines and this lack of agreement likely reflects relative low level evidence. We do not tailor these waitlist times depending on recipient age or patient preferences. Tessari et al.'s study challenges this "one size fits all" approach.

These papers fundamentally highlight the question of individualised risk. This holds true for both scenarios covered in these papers: potential donors or potential recipients with a past history of cancer. Deceased donor kidneys are a scarce and finite resource. From a societal point of view, the utilitarian argument advocates that the kidney should be transplanted into the person who will survive the longest and thus provide the greatest benefit. You may, on average, get a greater benefit from accepting more risks with donors and recipients, by transplanting more people. The trade off, however, is that this may lead to more harm through the transmission or recurrence of malignancy. To mitigate the risk of malignancy-related harm to recipients, the use of mandatory cancer remission waiting times and only accepting organs from donors with negligible cancer risk have been adopted.

From an individual kidney recipients' point of view, however, there are many factors to consider when deciding to be listed for transplantation. Factors such as poor quality of life on dialysis, being highly sensitised, and lack of vascular access options may lower the threshold for accepting a shorter waiting time and a higher risk of malignancy. Many patients see the of risk of cancer as acceptable compared to remaining on life-long dialysis [9]. This is particularly important for elderly kidney recipients, where the risk of morbidity and mortality from remaining on dialysis may outweigh the risk of recurrence of low-intermediate risk cancers. Also, as Tessari et al. highlight, the competing causes of death post transplantation in this group mean that the relative importance of cancer is diminished. When assessing a potential donor, there is also the issue of individualised risk for the recipient. Individual, time dependent factors, may mean that accepting a higher malignant risk donor that is available immediately may be less risky than waiting for a potential lower malignant risk offer.

This argument is simpler when patients have a living donor option, as the impact on society and utility do not have to be accounted for. When it comes to living donation, too, we are more willing to accept greater risks for recipients with other comorbidities such as diabetes or cardiovascular disease. We are more likely to transplant a recipient with greater number of, or severity of, comorbidities if they have a live donor. This raises the question, should we also apply this same principle to recipients with a past history of cancer?

So, where does this leave the practicing clinician? The purpose of waiting times are to minimise risk to recipients and ensure that the benefit of a scare resource is maximised. We currently practice with fixed waiting times than are not tailored to the individual recipient. This paper raises the issue that, whilst mandatory waiting times following malignancy provide guidance, perhaps individual circumstances and preferences need to be accounted for when accepting donor organs and when listing patients for transplantation. Ultimately, when making decisions about kidney transplantation, it is advantageous to have as much information as possible to allow patients and clinicians to make the most informed shared decision. These papers help with these complex decisions by increasing our knowledge of risk. Further work is required to individualise risk assessments, particularly for elderly patients whose risk of mortality from malignancy may be low. Given the increasing age of donors and recipients, the issue of cancer in organ allocation is a risk that will be encountered more and more. Utilising the information from these papers may allow us to move from rigid "one size fits all" guidelines to "bespoke" guidelines, recognising that in our patients, not all factors are the same for the individual.

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Compliance with ethical standards

Conflict of interest All the authors declared no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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