Pre-existing malignancies in renal transplant candidates-time to reconsider waiting times

Position Statement

Pre-existing malignancies in renal transplant candidates – time to reconsider waiting times !

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Introduction

Transplantation has evolved as the gold standard for renal replacement therapy based on better life quality and important survival benefits compared to hemo- and peritoneal dialysis. [1, 2] Consequently a major treatment goal for patients with end-stage renal disease (ESRD) is offering renal transplantation for as many patients as possible.

In preparation for a kidney transplant, potential candidates must undergo pre-transplant screening programmes that include a precise immunological work-up and focus on pre-existing medical conditions such as cardiovascular diseases, infections and the presence of any active and/or history of malignancy [3] Serious medical conditions or a high number of comorbidities, increase the risk for dying during or shortly after transplantation and therefore can prohibit or postpone the patient´s acceptance onto the waiting list.

New epidemiological data, recent developments in oncology and changes in immunosuppressive therapy may allow a re-evaluation of current practice for listing of patients with a variety of tumour entities. Albeit important, it is beyond the scope of this position statement to go into a detailed discussion of all individual malignancies, as different genomic properties, tumor stages and treatment opportunities/modalities may nowadays significantly influence the decision processes. We focused on solid tumors and try to provide a general overview on evolving issues.

In recipients with a pre-transplant malignancy, cancer mortality seems about doubled to tripled compared to recipients without a history of cancer. Whether overall mortality is also increased is debatable, with reports from Scandinavia finding no or only slightly increased relative risk of all-cause death (6-20%) [4, 5], whereas a review of UK and US cohorts reported a 53% increase in all-cause death. A similar long term all-cause mortality risk (HR 1.88) can be found for patients with pretransplant cardiac events, [6] Waitlisting of patients with a prior cardiovascular event has become less debated and is common practice. Active listing of patients with pre-existing malignancies however, is often postponed, because of a fear of cancer recurrence and/or the effects of post-transplant immunosuppression which is often incriminated of reactivating and aggravating the malignant disease.

Of note, the absolute long-term risk of mortality due to cancer recurrence seems to be relatively modest at about 10-15% [4, 5], and tumour recurrence rate was reported to be 2.4 per 100 person-years [7] These figures need to be interpreted in the context of a dialysis-related mortality of 5% per year.

(https://www.eurotransplant.org/cms/mediaobject.php?file=Eurotransplant+JV+PDF.pdf)

The rationale for malignancy screening in transplant candidates

Malignancies are a leading cause of morbidity and mortality after transplantation [8-13] and reviewed in [14]. Transplant candidates are at increased risk for a variety of cancers compared to the general population [15-18] and prognosis for several common cancers may be worse in transplant patients than in the general population [19, 20]

Transplant candidates need to undergo a thorough evaluation process before the operation. The presence of an active malignancy is a contraindication for renal transplantation. Patients must be in tumour remission for some time (the time span may vary depending on the type of malignancy) before being considered for transplantation. Previous recommendations for transplant candidates were typically compiled without involvement of oncologists or screening specialists and were not well validated. According to guidelines, screening in ESRD patients is usually performed following the same protocols suggested for the general population. [21-23]

Malignancy risks in dialysis and transplant patients

Malignancy risk is usually expressed as the standardized incidence ratio (SIR) which compares the respective incidence of a malignancy with the rate found in the general population. Transplant recipients are known to have increased SIRs for many types of malignancies. [17, 24, 25] It has to be appreciated, however, that dialysis patients also have increased tumour rates, [26-28] that for many malignancies do not differ significantly from rates in transplant recipients [25] (Table 1). Some, but not all types of cancer occur more often after transplantation. Cancers with particularly higher frequencies after transplantation include Kaposi sarcomas, lymphomas, lip, vulvovaginal , penile- and anal carcinomas, and non-melanoma skin cancers [17, 24, 25, 29]

Table 1

Relative risk of cancer among first-time recipients of deceased or living donor kidney transplantation (compared with cancer while on the waiting list in 1995–2001 (n = 35 765) ; adapted from [25]

Tumors with RR (relative risk) >1

Type of cancer	**RR**	**(95% CI)**	**p-value**
Kaposi sarcoma	9.03	(2.58-31.6)	0.0005
Non-Hodgkin's lymphoma	3.29	(2.40-4.51)	<0.0001
Esophagus	2.76	(1.03-7.37)	0.0428
Hodgkin's lymphoma	2.60	(1.01-6.68)	0.0471
Skin	2.55	(2.26-2.88)	<0.0001
Melanoma	2.19	(1.31-3.65)	0.0028
Mouth	2.19	(1.33-3.61)	0.0022
Vulvovaginal	2.19	(0.67-7.12)	0.1936
Any hematopoietic	2.04	(1.64-2.53)	<0.0001
Breast in men	1.88	(0.32-10.9)	0.4834
Leukemia	1.59	(1.03-2.45)	0.0355
Kidney	1.39	(1.10-1.76)	0.0058
Cervix	1.28	(0.48-3.36)	0.6230
Central nervous system	1.27	(0.78-2.06)	0.3304
Any non-skin	1.17	(1.07-1.28)	0.0004
Any genitourinary in women	1.16	(0.86-1.56)	0.3425
Bladder	1.12	(0.73-1.70)	0.6098
Lung	1.05	(0.79-1.40)	0.7241
Any genitourinary in men	1.02	(0.86-1.21)	0.8592

Tumors with RR (relative risk) < 1

Breast in women, Uterus, Ovary, Prostate, Testis, Endocrinologic
Stomach, Hepatobiliary, Pancreas, Small intestine, Colon
Myeloma, Bone, Larynx,

CI = confidence interval

Comparing malignancy risks post-transplantation with those while remaining on dialysis (i.e. relative risk between the ESRD modalities, rather than absolute risk compared to the general population without renal disease) is more relevant for an ESRD patient (Table 1). From a transplant patient´s or transplant candidate´s perspective SIRs, which express the risk compared to the general population are of limited value as dialysis is the transplant patient´s sole alternative survival option. Therefore, the relevant risk of cancer development post-transplantation should be the risk compared to cancers developing whilst on dialysis. A high SIR after transplantation should not be the sole reason for withholding a kidney transplant, especially if the SIR for a respective tumour is equally high in a dialysis patient. This may be particularily true in the case of living donation where both the donor and recipient can be adaequately informed and would have a good understanding of the risks involved.
An argument that is often used against transplanting patients with a history of cancer is that kidneys from deceased donors are scarce and should perhaps be allocated to lower risk individuals. Whether this argument, that could be equally used for other high risk situation such as diabetes or heart disease is ethically justifiable, remains open for discussion. Transplants in patients with pre-existing malignancies may be regarded more favourably in countries with a high deceased donor transplant acitivity and shorter waiting times than in regions where the waiting times are exceptionally long due to a low number of donor organs.

It can be expected that the overall health status of a patient with ESRD will considerably improve after receiving a functioning kidney transplant. Nevertheless, a potential increase in malignancy-risk and its associated impact on quality and length of life post transplantation has to be balanced against the expected overall health benefit. (Figure 1 and Table 1) [26-28]
In a recent review Acuna reported a recurrence rate of 2.4 per 100 person-years in kidney transplant recipients and concluded that the risk of cancer recurrence in recipients with pretransplant malignancies is considerably lower than in historic reports that formed the basis for current waiting time recommendations [7]

The fear of a potential cancer recurrence can lead to a delay of transplantation. The competing malignancy-independent mortality risk inherent to remaining on long-term dialysis, i.e. 5% per year [30], however, needs to be taken into account. Patients should be informed about these different competing risks and be given the opportunity to consent for earlier or later wait-listing and transplantation.

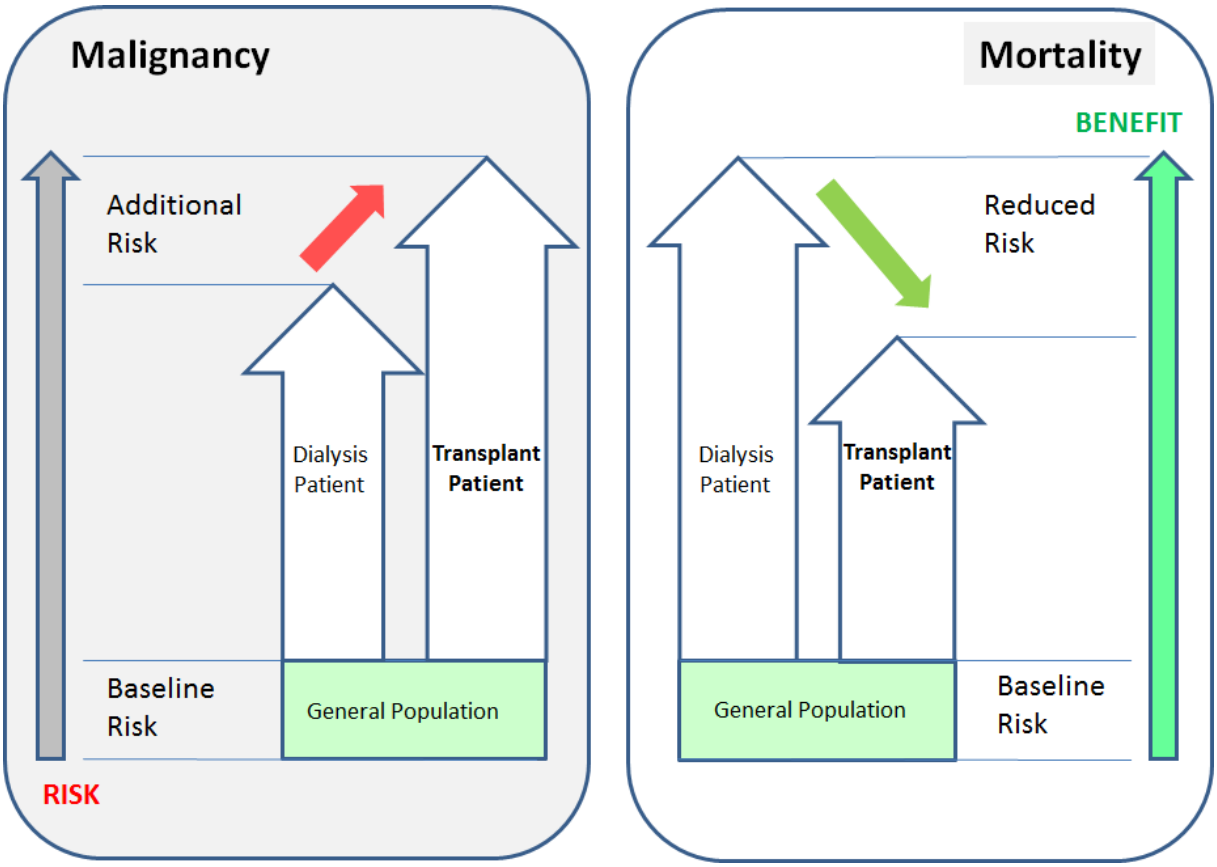


Figure 1

Risks for Malignancy and Mortality are elevated in dialysis patients as well as in transplant recipients when compared to the general population. Renal transplantation may increase the risk for malignancies, but the potential survival benefit in transplant recipients compared to patients remaining on dialysis should be taken into account when waiting times are defined in transplant candidates.

Dialysis time as a determinant for reduced survival

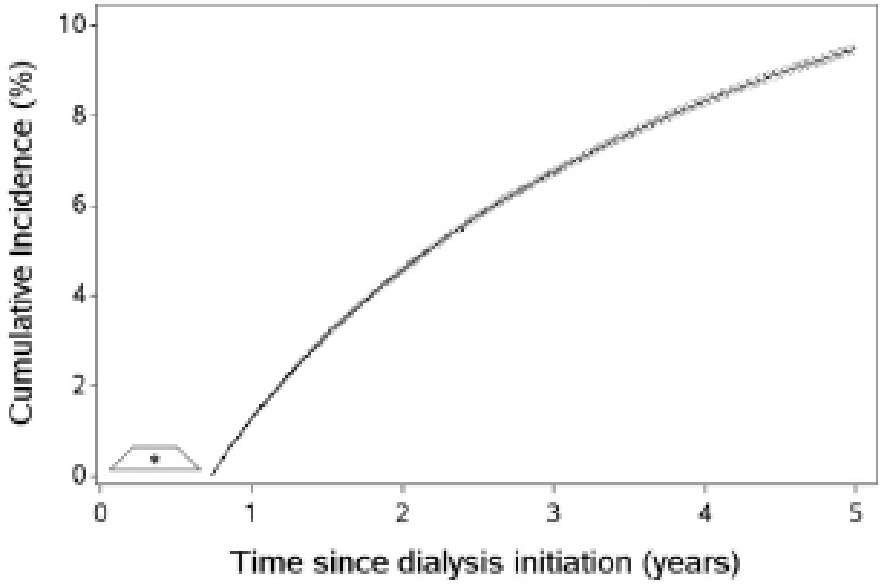
Dialysis duration constitutes a potentially modifiable factor for the survival of ESRD patients [31]. Patients undergoing pre-emptive transplantation have a -survival benefit compared to those who already initiated haemodialysis [32, 33]. Similarly, early transplantation as soon as possible after the start of dialysis leads to improved long term survival as compared to transplantation after a prolonged period of dialysis [34-37]. Remaining on dialysis has consistently been associated with a 5% yearly mortality (https://www.eurotransplant.org/cms/mediaobject.php?file=Eurotransplant+JV+PDF.pdf)

These observations make it clear that any uncritical decision to delay a transplant should be avoided, as it may negatively influence the patient´s long

term survival. Even if a potentially higher risk of cancer or of a recurrence of a pre-existing malignancy may have a negative impact on patient survival, a restrictive transplantation policy leading to an inappropriately long cancer-free waiting time may ultimately be disadvantageous for the overall survival of the patient.

Dialysis time as a determinant for increased risk of malignancy

Incidence ratios (SIR) for malignancies are increased in dialysis patients. [30, 38, 39] SIR´s in patients dialyzed in the 1980s in USA, Europe, Australia, or New Zealand were 1.18, with higher rates for cancers of the kidney (SIR, 3.60), bladder (SIR, 1.50), thyroid and other endocrine organs (SIR, 2.28). [26] Between 1996 and 2009 the SIR was 1.42 in an unselected dialysis cohort included in the US Medicare's ESRD programme with the highest risk for cancers of the kidney/renal pelvis (SIR, 4.03) and bladder (SIR, 1.57). [30]
With an increase of dialysis duration, the 5-year cumulative incidence of any cancer rises to almost 10% (Figure 2a). [30] In an Italian single centre study in wait-listed dialysis patients (the most appropriate control group for transplanted patients), the cancer risk also rose over time and cumulated to almost 5% after 5 years. The overall risk (SIR, 1.4) was within the published range for dialysis patients and less than in transplant recipients (SIR, 2.1). [40] The increase of cancers after transplantations was in accordance with the observations by Vajdic et al., mainly attributable to cancers associated with viral infections.[17, 40]
These data show that remaining on dialysis (instead of being transplanted) does not alleviate the risk for developing cancer, but that the cancer risk is likely to cumulate with increasing time on dialysis. The increasing age of dialysis patients and transplant candidates may further aggravate the problem.
The 5% cumulative incidence after 5 years in the wait-listed Italian dialysis patients corresponds well with the cumulative incidence of all cancers (excluding non-melanoma skin cancer and independent of mTOR Inhibitor use) in first deceased-donor kidney transplants (1999–2013) reported from the Collaborative Transplant Study [41] (Figure 2b), demonstrating that ESRD patients are at a significant malignancy risk, independent of the treatment modality.
Figure 2 a



No. at risk	482,510	431,525	291,956	197,524	131,318	84,890
No. of cancer cases	0	6,061	20,477	28,656	33,854	37,128
No. of deaths	0	27,313	103,527	155,709	192,605	217,773

Figure 2aCancer Incidence increases with time on dialysis

In hemodialysis patients the 5-year cumulative incidence of any cancer is 9.48%. (Results accounting for death as a competing event) (with permission from [30])

Figure 2 b

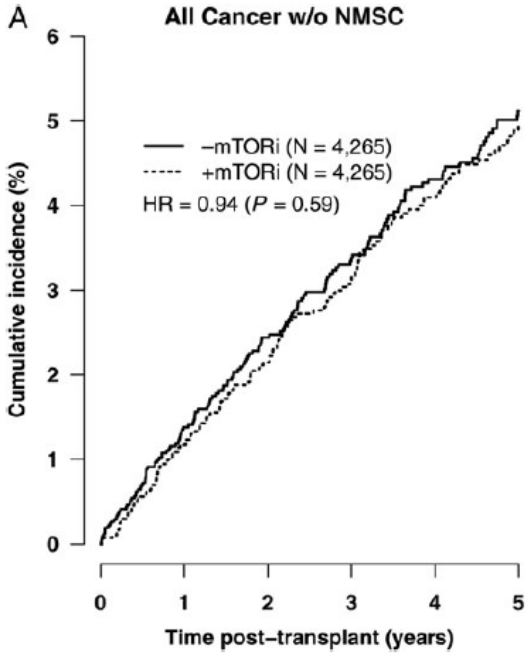


Figure 2 b

Cancer Incidence increases with time after transplant

Cumulative incidence of all cancers (excluding non-melanoma skin cancer) in propensity score matched first deceased-donor kidney transplants (1999–2013) reported from the Collaborative Transplant Study treated with or without mTOR Inhibitors (with permission from [41])

Post-transplant immunosuppression as a risk factor for malignancy

The increased risk for certain malignancies after transplantation is probably due to an immunosuppression-induced loss of normal immune surveillance mechanisms in combination with an increased prevalence of viral infections involved in the pathogenesis of cancer. [25, 42]
Well known examples of virally induced malignancies are Kaposi sarcoma (Human Herpesvirus 6), non-Hodgkin-lymphoma (EBV), and cervical, anogenital, oral cavity, and oropharyngeal cancers (Human Papillomavirus).
The link between immunosurveillance and virally-induced cancers is further underlined by the possibility of tumour reversal through reduction of immunosuppression in cancers with a confirmed infectious cause, such as EBV-related post-transplant lymphoproliferative disease. In contrast, reduction of immunosuppression does not significantly alter the course of other cancers, especially those related to end stage kidney disease. [43]
The role of immunosupressants for facilitating tumour development was recently reviewed by Acuna and de Fijter [14, 44]
mTOR Inhibitors seem to be advantageous for Kaposi sarcoma, mantle cell lymphoma and non-melanoma skin cancers, whereas for most other cancers equal benefits could not be shown. [44]. With regard to other drug classes the cumulative dose of the individual drug (e.g. T-cell depleting agents and non-Hodgkin lymphomas) and/or the cumulative total immunosuppression plays a relevant role. Il-2 receptor antibodies used as induction therapy do not confer an additional malignancy risk. [14] Whether new protocols (e.g. steroid sparing regimes or the use of belatacept) will have a longterm beneficial effect on tumor recurrence can hopefully be answered in the future.

In contrast, other types of cancer do not differ significantly between dialysis and transplant patients. [45] The risk for non-virally related solid cancers observed in dialysis patients, increased by 19% after transplantation (age standardized rate ratio (ASRR) = 1.19) in Italian patients as compared to a ASRR of 1.85 for all de novo cancers. [40] Mechanisms, such as sun light, may exert a negative impact on non-virally triggered tumorgenesis and may explain a higher frequency of skin cancers in transplant recipients. [46]
In addition direct, non immune mediated effects of immunosuppressives (e.g cyclosporine, azathioprine) may contribute to skin cancer development. [47]

In a large transplant cohort (1970-2008), recipients with a cancer history before transplantation had a 30% increased mortality risk after transplantation. This risk was moderately elevated for recipients of a kidney (HR 1.2 95%: 1.0-1.4) but clearly higher in recipients of other organs (HR 1.8), indicating that the type of transplanted organ and the corresponding intensity of immunosuppression also influences the cancer risk. [4] Additional factors playing a contributory role for malignancies after kidney transplantation are summarized in Table 2.

Table 2
Factors contributing to increased rates of malignancies after kidney transplantation

- Older Age
- Male Gender
- Longer time on dialysis
- Smoking
- Sun light exposure
- Prior malignancy
- Increased total immunosuppression
- Azathioprine
- T-cell depleting antibodies

Reasons to reconsider the traditional "2-or-5-year-waiting-time-rule" for patients with pre-existing malignancies

In his seminal paper in 1993, Penn reported that the time between pre-transplant cancer occurrence and transplantation impacts on the risk of cancer recurrence after the operation [48]. Penn suggested that disease free intervals should be observed before a transplant is undertaken. These suggestions were based on a very limited number of cancer cases (collected in Penn´s voluntary and by that nature incomplete Cincinnati registry). Nevertheless, being the best evidence at the time, Penn´s report was the major source for recommendations published in subsequent guidelines. (Reviewed in [49])

Most guidelines advised a cancer-free waiting time between 2 and 5 years for most cancers, depending on the cancer type. These recommendations were published more than 5 years ago and were summarized by Batabayal et al. in 2012. [49-52] More recently, the ERBP working group suggested (in an Ungraded Statement) that patients with current or previous cancer should be discussed with an oncologist and that waiting time should be considered on a case-by-case basis taking into account the following issues: " (a) the potential

for progression or recurrence of the cancer according to its type, staging and grade; (b) the age of the patient; (c) the existence of comorbidities."

Penn´s initial recommendations are cautious and based on concerns that patients may be deliberately exposed to cancer recurrence and an avoidable mortality risk, if they are transplanted too early. It should be appreciated, however, that a prolonged waiting time on dialysis may reduce the likelihood of cancer recurrence but at the same time may not change the risk for de novo malignancies and even increase the risk of death from other causes. [4, 53] Unfortunately a decision model to determine at which time point the balance tips in favour of a transplant, is yet to be developed.

Studies on the risk of recurrence and on mortality in ESRD patients with a history of malignancy

Cancer recurrence rates in transplant recipients vary between 1 and 25% depending on the type of cancer. [51, 54-56] Existing studies focused on recurrences in transplant patients with pre-existing malignancies and compared the rates to initial tumour-naïve recipients.
It is less clear, if recurrence rates differ significantly in patients who remain on dialysis or who receive a kidney transplant. This information, however, would be most relevant for a dialysis patient who had suffered from a malignancy and who wants to get a qualified estimate of the change in his/her recurrence risk if transplanted. Respective data are still to be collected.

A recent UK Study (median follow-up 4.4 yrs of 19103 kidney transplants performed between 2001 and 2012), in which only 0.4% of the study population (n= 74) had a history of malignancy at the time of transplantation, found a higher risk (17.6%) in cancer-specific mortality in transplant recipients with previous cancer compared to recipients without previous cancer (1.9%). The study did not distinguish between recurrent or de novo malignancies and did not compare the results to risks of patients who remained on dialysis. [57] In a large population based cohort in Sweden, kidney recipients with a history (versus no history) of malignancy had a slightly elevated risk (HR 1,2) of death after the transplant, which was primarily driven by cancer recurrence.
[4] Acuna et al. demonstrated in their meta-analysis in transplant patients with pre-existing malignancies in remission, that all-cause mortality risk was similar for kidney (HR 1.53) and non-kidney (HR 1.61) recipients, when compared to patients without pre-transplant malignancy. In general, pre-transplant malignancy (vs. none) was associated with increased risk of all cause-mortality,

cancer-specific mortality and development of de novo malignancies after solid organ transplantation (including kidneys). [53]

Using competing risk analysis in a population based study in patients from Ontario, Canada, Acuna et al., demonstrated that patients with pretransplant malignancy had an increased risk of both cancer-specific (HR, 1.85) and noncancer death (HR, 1.29), compared to recipients without pretransplant malignancies. In addition, patients who waited more than 5 years from malignancy diagnosis to transplantation had an increased risk of noncancer death. Only patients with high-risk malignancies were at increased risk for cancer-specific mortality (HR, 3.16). Patients with low risk malignancies (as defined by the authors: thyroid, prostate, bladder, kidney, oropharynx, or testis) did not have an adverse outcome if transplanted within 5 years of cancer diagnosis, but had an increased risk of death (HR, 1.76) similar to high risk patients if they were transplanted more than 5 years after cancer diagnosis. [58, 59]

A recent Norwegian study in a cohort of 5867 kidney transplant recipients reported results of a generally shortened 1-year recurrence-free waiting time after cancer occurrence. In this cohort, 6.4% of the transplant population had a pre-transplant cancer. Despite an increased cancer mortality particularly during the first 5 years after transplantation, ”recipients with a pretransplant cancer had a similar overall patient and graft survival as recipients without such cancer. A short waiting period was not associated with recurrent cancer mortality or all-cause mortality.” [60]
In an analysis of the Australian and New Zealand Dialysis and Transplant Registry, the survival in patients with a cancer recurrence was not different from patients who developed a first cancer after the transplant or a second primary cancer. Altogether recurrent cancers were infrequent events in this patient series, which was certainly carefully and conservatively selected with respect to the waiting time. Only three percent of transplant recipients between 1965 and 2012; n=651 of 21,415) had a previous cancer history and only 23 (0.8%) of them experienced a cancer recurrence. [20] In Norway the proportion of transplant recipients with a history of cancer was equally low (2,6%) in the early era (1963-1882). The significant increase to 8,9% in the period from year 2000 to 2010 indicates that pre-existing malignancy is now increasingly frequent and needs to be adequately addressed as an important clinical challenge in the future. [60]

Lack of studies reporting detailed information on cancers

In contrast to immunological issues (type of immunosuppression, rejection rates etc.) information on malignancies and related outcomes were hardly ever central to structured data collections in the field of transplantation. Thus the malignancy data in renal transplantation is still scarce and incomplete. The most recent comprehensive review on outcomes of urological cancers in patients, who either remained on dialysis or received a transplant exemplifies this fact. Despite all efforts, the study reports on only 439 transplant patients with renal cancers, 161 cases of prostate cancer and 137 urothelial cancer cases. [61] Equally low or even lower numbers of cases are reported for other tumours in recent reviews [17, 62-65]

Previous reports on cancers in transplantation were usually limited to the type of tumour and the time between its treatment and kidney transplantation. [52] Typically, more granular or elaborate clinical information was not available. These studies no longer reflect the epidemiology of patients seen during the transplant evaluation process today. Over the last decade, more detailed staging algorithms including histological and molecular sub-classification have been developed. With the availability of genetic testing, cancers can often be divided into many different biological subtypes. These refined classifications have led to a more precise selection of anti-tumour therapies and facilitated better therapy outcomes or even cure from malignancies.

Renal cell carcinoma is a good example in this respect. The histological subtype has been identified as one indicator impacting the recurrence risk in addition to stage and grade (reviewed in [61]). Leibovich et al. showed in a non-transplant population that clear cell carcinomas of the kidney have a significantly worse outcome than papillary or chromophobe subtypes with regard to recurrence. Taking histology into account and combining it with grade and stage, a respective scoring system identifies low, intermediate and high risk patients. [66]. This classification could be of value to individualize and potentially reduce waiting times in patients on the waiting list for a kidney transplant. Findings from a recent French study suggest that histological type clear cell RCC (13% vs 0% in papillary RCC), Tumor stage pT2 and Fuhrman grade IV are factors associated with a higher risk of cancer recurrence. However, there is no correlation between post-transplant recurrence and the interval before transplantation [67]

The issue of kidney cancer in polycystic kidney disease (PKD) patients is a matter of debate. While cancers in PKD are more prevalent when comared to the general population, they seem to be less common after transplantation in PKD patients than in unaffected individuals. Patients with acquired cystic kidney disease, however seem to carry a higher risk after transplantation [14]

A subset of renal cell carcinomas may be relatively benign, as suggested by a series of asymptomatic patients that underwent native nephrectomy at the time of transplantation. In this cohort, RCCs were found in 4,2 % of cases without having an effect on graft function or patient survival post-transplant.[68] It is thus tempting to speculate that patients with undetected small RCC may have been transplanted in the past without significant problems thereafter.
In patients with a low risk for the development of metastasis or recurrence, a short waiting time for a transplant would therefore seem to be justifiable. A longer waiting time may not be advantageous, as the risk of renal cancers also increases with a prolonged time on dialysis. [69] In addition, the overall mortality risk on dialysis may even exceed the tumour recurrence risk. On the contrary, symptomatic or large renal cell carcinomas, with recurrence rates of greater than 25% may warrant a longer interval between successful treatment and transplantation. [48, 70, 71] In children with Wilms tumor the 2-year waiting time period has recently been challenged for patients with low risk disease. [72]

Likewise, in prostate cancer a beneficial histological grade may allow a shortened waiting period [61]. For some tumours, a lack of recurrence after one or two years virtually suggests a complete cure of the tumour. Following a cautious approach it could make sense to wait for this respective period. For other cancers (like breast cancer) the risk of recurrence does not clearly subside over time, thus one could argue that there is no rational cut-off value for waiting time in these cases.
For certain PTLD cases it was recently suggested that after treatment re-transplantation is feasible, but that a waiting time of at least 1 year may be reasonable[73]

In the future the assessment of an individual's genetic profile may also be helpful for deciding on the appropriate waiting time. Two patients with ESRD and breast cancer were identified as low risk individuals by genomic profiling assays, leading to a decision to transplant way before the suggested waiting period was over. In one, transplantation was performed 1 year, in the other subject 1,5 years after breast cancer diagnosis. The patients remain tumour free six and five years after the operation, respectively. [74]
With rapid developments in the field of oncology case-by-case discussions with an oncologist in patients with current or previous cancer, as already suggested by the ERBP Guidelines will become even more relevant for the benefit of the patients in the future. [75]

Conclusions

With the aging population of transplant-candidates and transplanted patients, malignancies pre and post kidney transplantation are becoming increasingly important. As a transplant community we should start to focus on the emerging problem of malignancies and collect additional and more detailed information in a prospective manner. This will allow making well-informed decisions for our patients in the future.
Previously suggested waiting times, which were mainly based on a very limited numbers of cases seem to be disputable in the light of novel tumour stratifications and the advent of various new anti-tumour therapies. It is important to realize that withholding transplantation does not necessarily preclude cancer occurrence in renal patients and that the likelihood of tumour recurrence also rises with increasing time on dialysis. On top of the tumour risk, remaining on dialysis carries an additional mortality risk when compared to being successfully transplanted. Balancing the risk of malignancy with other dialysis-associated risks is warranted.

Transplant decisions in pre-transplant patients with malignancies should be made together with oncologists on an individual basis. This additional effort, even though increasing the workload for the specialists involved, may result in a significant benefit for the patient if waiting time can be shortened by a refined and individualized, yet critical decision. The risk of cancer recurrence seems to be mainly influenced by tumour type rather than the length of waiting time. A detailed histological subclassification and the use of genetic markers will be helpful for future identification of subgroups of patients at heightened risk of malignancy or recurrence (see Websites such as lifemath.net/cancer of the Laboratory for Quantitative Medicine of the Harvard Medical School and Massachusetts General Hospital for useful information) and to guide waiting time taking into account tumor heterogeneity.

A collective effort in prospectively collecting detailed malignancy data (compared to the crude information available to Penn 25 years ago) is necessary (Table3). This process should involve transplant physicians and oncologists specialized in respective tumour entities and should ultimately result in better defined risk benefit ratios and new treatment strategies and recommendations for transplant patients with malignant disease. These would allow a full and frank discussion with prospective transplant recipients,

enabling them to make the optimal treatment choice relevant to their condition and their threshold of risk-taking, in particular in living, but also in deceased donor transplantation

It is the aim of this statement to acknowledge new thoughts on pre-exsiting malignancy and transplantation. Earlier recommendations of waiting times for a transplant were based on a paucity of data and the fields of oncology, transplantation and genomic profiling have significantly improved in recent years. We hope to stimulate discussions for individual patient evaluations whenever applicable that may lead to shorter waiting times for some patients using new oncological diagnostic measures and experience.

Table 3 Areas where more research is urgently required

- Comprehensive prospective collection of malignancy data in kidney transplant data bases
- Comparative analysis of cancer recurrence in waitlisted and transplanted ESRD patients
- Prospective collection of granular data on tumour biology including genomic profiling in transplant candidates and patients
- Evaluation of tumour frequencies and characteristics under different immunosuppressive protocols (CNI free, steroid free etc.)

Key points

- Malignancies represent an emerging problem in the ageing population of transplant candidates.

- Remaining on dialysis is associated with an increasing cancer and mortality risk.

- Current recommendations for waiting times need to be reconsidered and may be shortened for a variety of malignancies.

- Waiting times should be defined together with an oncologist on an individual basis.

- Additional and more detailed information on malignancies should be collected in a prospective manner.

Conflict of interest statement: the results presented in this paper have not been published previously in whole or part

References

1. Laupacis, A., et al., *A study of the quality of life and cost-utility of renal transplantation.* Kidney Int, 1996. **50**(1): p. 235-42.
2. Wolfe, R.A., 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**(23): p. 1725-30.
3. Kalble, T., et al., *EAU guidelines on renal transplantation.* Eur Urol, 2005. **47**(2): p. 156-66.
4. Brattstrom, C., et al., *Overall and cause-specific mortality in transplant recipients with a pretransplantation cancer history.* Transplantation, 2013. **96**(3): p. 297-305.
5. Dahle, D.O., et al., *Association Between Pretransplant Cancer and Survival in Kidney Transplant Recipients.* Transplantation, 2017.
6. Aalten, J., et al., *Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death.* Transpl Int, 2008. **21**(10): p. 985-91.
7. Acuna, S.A., et al., *Cancer recurrence after solid organ transplantation: A systematic review and meta-analysis.* Transplant Rev (Orlando), 2017. **31**(4): p. 240-248.
8. Ajithkumar, T.V., et al., *Management of solid tumours in organ-transplant recipients.* Lancet Oncol, 2007. **8**(10): p. 921-32.
9. Buell, J.F., T.G. Gross, and E.S. Woodle, *Malignancy after transplantation.* Transplantation, 2005. **80**(2 Suppl): p. S254-64.
10. Chandok, N. and K.D. Watt, *Burden of de novo malignancy in the liver transplant recipient.* Liver Transpl, 2012. **18**(11): p. 1277-89.
11. Chapman, J.R., A.C. Webster, and G. Wong, *Cancer in the transplant recipient.* Cold Spring Harb Perspect Med, 2013. **3**(7).
12. Christie, J.D., et al., *Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report--2008.* J Heart Lung Transplant, 2008. **27**(9): p. 957-69.
13. Jiang, Y., et al., *Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study.* Liver Transpl, 2008. **14**(11): p. 1588-97.
14. Au, E., G. Wong, and J.R. Chapman, *Cancer in kidney transplant recipients.* Nat Rev Nephrol, 2018. **14**(8): p. 508-520.
15. Grulich, A.E., et al., *Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.* Lancet, 2007. **370**(9581): p. 59-67.
16. Heemann, U., et al., *Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement.* Nephrol Dial Transplant, 2011. **26**(7): p. 2099-106.
17. Vajdic, C.M., et al., *Cancer incidence before and after kidney transplantation.* JAMA, 2006. **296**(23): p. 2823-31.
18. Villeneuve, P.J., et al., *Cancer incidence among Canadian kidney transplant recipients.* Am J Transplant, 2007. **7**(4): p. 941-8.
19. Miao, Y., et al., *De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population.* Transplantation, 2009. **87**(9): p. 1347-59.

20. Viecelli, A.K., et al., *Cancer-Specific and All-Cause Mortality in Kidney Transplant Recipients With and Without Previous Cancer.* Transplantation, 2015. **99**(12): p. 2586-92.
21. Acuna, S.A., et al., *Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines.* Am J Transplant, 2017. **17**(1): p. 103-114.
22. *ERBP Guideline on the Management and Evaluation of the Kidney Donor and Recipient.* Nephrol Dial Transplant, 2013. **28 Suppl 2**: p. ii1-71.
23. Acuna, S.A., et al., *Cancer evaluation in the assessment of solid organ transplant candidates: A systematic review of clinical practice guidelines.* Transplant Rev (Orlando), 2018. **32**(1): p. 29-35.
24. Engels, E.A., et al., *Spectrum of cancer risk among US solid organ transplant recipients.* JAMA, 2011. **306**(17): p. 1891-901.
25. Kasiske, B.L., et al., *Cancer after kidney transplantation in the United States.* Am J Transplant, 2004. **4**(6): p. 905-13.
26. Maisonneuve, P., et al., *Cancer in patients on dialysis for end-stage renal disease: an international collaborative study.* Lancet, 1999. **354**(9173): p. 93-9.
27. Shang, W., et al., *Cancer risk in patients receiving renal replacement therapy: A meta-analysis of cohort studies.* Mol Clin Oncol, 2016. **5**(3): p. 315-325.
28. Wong, G., et al., *Chronic kidney disease and the risk of cancer: an individual patient data meta-analysis of 32,057 participants from six prospective studies.* BMC Cancer, 2016. **16**: p. 488.
29. Yanik, E.L., et al., *Variation in Cancer Incidence among Patients with ESRD during Kidney Function and Nonfunction Intervals.* J Am Soc Nephrol, 2016. **27**(5): p. 1495-504.
30. Butler, A.M., et al., *Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009.* Am J Kidney Dis, 2015. **65**(5): p. 763-72.
31. Meier-Kriesche, H.U. and B. Kaplan, *Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis.* Transplantation, 2002. **74**(10): p. 1377-81.
32. Mange, K.C., M.M. Joffe, and H.I. Feldman, *Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors.* N Engl J Med, 2001. **344**(10): p. 726-31.
33. Meier-Kriesche, H.U. and J.D. Schold, *The impact of pretransplant dialysis on outcomes in renal transplantation.* Semin Dial, 2005. **18**(6): p. 499-504.
34. Haller, M.C., et al., *Dialysis Vintage and Outcomes after Kidney Transplantation: A Retrospective Cohort Study.* Clin J Am Soc Nephrol, 2017. **12**(1): p. 122-130.
35. Meier-Kriesche, H., et al., *Deleterious effect of waiting time on renal transplant outcome.* Transplant Proc, 2001. **33**(1-2): p. 1204-6.
36. Meier-Kriesche, H.U., et al., *Effect of waiting time on renal transplant outcome.* Kidney Int, 2000. **58**(3): p. 1311-7.
37. Abramowicz, D., et al., *Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP.* Nephrol Dial Transplant, 2016. **31**(5): p. 691-7.
38. Birkeland, S.A., H. Lokkegaard, and H.H. Storm, *Cancer risk in patients on dialysis and after renal transplantation.* Lancet, 2000. **355**(9218): p. 1886-7.

39. Lin, H.F., et al., *Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan.* Nephrol Dial Transplant, 2012. **27**(4): p. 1585-90.
40. Mazzucotelli, V., et al., *De novo cancer in patients on dialysis and after renal transplantation: north-western Italy, 1997-2012.* J Nephrol, 2017. **30**(6): p. 851-857.
41. Opelz, G., et al., *Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients.* Nephrol Dial Transplant, 2016. **31**(8): p. 1360-7.
42. Hinten, F., et al., *Reactivation of Latent HPV Infections After Renal Transplantation.* Am J Transplant, 2017. **17**(6): p. 1563-1573.
43. van Leeuwen, M.T., et al., *Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study.* BMJ, 2010. **340**: p. c570.
44. de Fijter, J.W., *Cancer and mTOR Inhibitors in Transplant Recipients.* Transplantation, 2017. **101**(1): p. 45-55.
45. Stewart, J.H., et al., *The pattern of excess cancer in dialysis and transplantation.* Nephrol Dial Transplant, 2009. **24**(10): p. 3225-31.
46. Leiter, U., T. Eigentler, and C. Garbe, *Epidemiology of skin cancer.* Adv Exp Med Biol, 2014. **810**: p. 120-40.
47. Mittal, A. and O.R. Colegio, *Skin Cancers in Organ Transplant Recipients.* Am J Transplant, 2017. **17**(10): p. 2509-2530.
48. Penn, I., *Effect of immunosuppression on preexisting cancers.* Transplant Proc, 1993. **25**(1 Pt 2): p. 1380-2.
49. Batabyal, P., et al., *Clinical practice guidelines on wait-listing for kidney transplantation: consistent and equitable?* Transplantation, 2012. **94**(7): p. 703-13.
50. Girndt, M. and H. Kohler, *Waiting time for patients with history of malignant disease before listing for organ transplantation.* Transplantation, 2005. **80**(1 Suppl): p. S167-70.
51. Penn, I., *The effect of immunosuppression on pre-existing cancers.* Transplantation, 1993. **55**(4): p. 742-7.
52. Penn, I., *Evaluation of transplant candidates with pre-existing malignancies.* Ann Transplant, 1997. **2**(4): p. 14-7.
53. Acuna, S.A., et al., *Outcomes of Solid Organ Transplant Recipients With Preexisting Malignancies in Remission: A Systematic Review and Meta-Analysis.* Transplantation, 2017. **101**(3): p. 471-481.
54. Chapman, J.R., A.G. Sheil, and A.P. Disney, *Recurrence of cancer after renal transplantation.* Transplant Proc, 2001. **33**(1-2): p. 1830-1.
55. Hanaway, M.J., et al., *Risk for recurrence and death from preexisting cancers after transplantation.* Transplantation Reviews, 2005. **19**(3): p. 151-163.
56. Kauffman, H.M., et al., *Transplant recipients with a history of a malignancy: risk of recurrent and de novo cancers.* Transplantation Reviews, 2005. **19**(1): p. 55-64.
57. Farrugia, D., et al., *Malignancy-related mortality following kidney transplantation is common.* Kidney Int, 2014. **85**(6): p. 1395-403.
58. Acuna, S.A., et al., *Solid Organ Transplantation in Patients With Preexisting Malignancies in Remission: A Propensity Score Matched Cohort Study.* Transplantation, 2018. **102**(7): p. 1156-1164.
59. Knoll, G.A. and S.J. Chadban, *Preexisting Cancer in Transplant Candidates: Time for a Change in Practice?* Transplantation, 2018. **102**(7): p. 1037-1038.

60. Dahle, D.O., et al., *Association Between Pretransplant Cancer and Survival in Kidney Transplant Recipients.* Transplantation, 2017. **101**(10): p. 2599-2605.
61. Boissier, R., et al., *The Risk of Tumour Recurrence in Patients Undergoing Renal Transplantation for End-stage Renal Disease after Previous Treatment for a Urological Cancer: A Systematic Review.* Eur Urol, 2018. **73**(1): p. 94-108.
62. Hickman, L.A., et al., *Urologic malignancies in kidney transplantation.* Am J Transplant, 2018. **18**(1): p. 13-22.
63. Wong, G., et al., *Breast Cancer and Transplantation.* Am J Transplant, 2017. **17**(9): p. 2243-2253.
64. Prenner, S. and J. Levitsky, *Comprehensive Review on Colorectal Cancer and Transplant.* Am J Transplant, 2017. **17**(11): p. 2761-2774.
65. Kitahara, C.M., et al., *Risk of Thyroid Cancer Among Solid Organ Transplant Recipients.* Am J Transplant, 2017. **17**(11): p. 2911-2921.
66. Leibovich, B.C., et al., *Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials.* Cancer, 2003. **97**(7): p. 1663-71.
67. Cognard, N., et al., *Recurrence of Renal Cell Cancer After Renal Transplantation in a Multicenter French Cohort.* Transplantation, 2018. **102**(5): p. 860-867.
68. Denton, M.D., et al., *Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis.* Kidney Int, 2002. **61**(6): p. 2201-9.
69. Stewart, J.H., 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**(1): p. 197-207.
70. Cohen, H.T. and F.J. McGovern, *Renal-cell carcinoma.* N Engl J Med, 2005. **353**(23): p. 2477-90.
71. Knoll, G., et al., *Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation.* CMAJ, 2005. **173**(10): p. 1181-4.
72. Grigoriev, Y., et al., *Treatments and outcomes for end-stage renal disease following Wilms tumor.* Pediatr Nephrol, 2012. **27**(8): p. 1325-33.
73. Dierickx, D. and T.M. Habermann, *Post-Transplantation Lymphoproliferative Disorders in Adults.* N Engl J Med, 2018. **378**(6): p. 549-562.
74. Mukhtar, R.A., et al., *The Novel Application of Genomic Profiling Assays to Shorten Inactive Status for Potential Kidney Transplant Recipients With Breast Cancer.* Am J Transplant, 2017. **17**(1): p. 292-295.
75. Abramowicz, D., et al., *European Renal Best Practice Guideline on kidney donor and recipient evaluation and perioperative care.* Nephrol Dial Transplant, 2015. **30**(11): p. 1790-7.