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ORIGINAL ARTICLE

Prevalence of cancer history prior to renal transplantation

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Summary

Recurrent and *de novo* cancers contribute to morbidity and mortality post-transplantation. However, data on cancer prevalence in waiting list patients are lacking. The purpose of this study was to determine the prevalence of malignancy in patients considered for renal transplantation. Records of 382 potential renal transplant recipients were reviewed for the presence of malignant tumours. In 38 patients 45 tumours were detected. Forty-two malignancies were histologically confirmed, in three patients the evaluation was ongoing. Fourteen tumours were diagnosed before and 31 after initiation of dialysis. Overall cancer prevalence was 9.9%. For patients in the waiting list, the mean time from diagnosis of the malignancy was 2.2 years. Twenty of 45 (44%) tumours were located in the urinary system. The majority of malignancies was treated with a curative intention. Thus, 68% of patients with malignancies were listed as 'transplantable' or 'temporarily not transplantable'. From the waiting list, 13% were removed , 8% died and 11% had their evaluation halted because of their malignancy. Four patients received a transplant while eight patients died or were removed permanently from the list prior to transplantation. Death or removal from the list was as frequently related to tumour progression as to other causes (four patients each). A substantial number of waiting list patients had a history of malignancy. Future strategies have to identify patients at risk to assure intensive monitoring for recurrence, selection of patients who do not benefit from deferred transplantation and consideration of specific immunosuppressive protocols.

Introduction

Immunosuppressive therapy after renal transplantation has been associated with an increased incidence of *de novo* malignancies which also exhibit a more aggressive clinical course [1]. Therefore, at the time of transplantation, freedom from malignancy is essential. This directly raises the question as to whether potential transplant recipients should be screened for the presence of a malignoma. As with any other disease, the utility of a screening procedure rests on the fundamental prerequisites that the disease is prevalent in a considerable proportion of the cohort, screening detects the disease and detection leads to specific therapeutic consequences. Under these prerequisites, screening for malignomas in future recipients of allografts has not been evaluated. Transplant-specific therapeutic consequences of a diagnosis of cancer are obvious and include withdrawal from the list or deferral until the risk of recurrence is considered low. However, recurrence rates of pre-existing malignancies after transplantation vary, depending on tumour site, waiting period until transplantation and investigator, between 5% and 67% and are derived only from selected patients in registries [2,3]. While there seems to be a substantial prevalence of malignant tumours as registries report over 1200 patients with pre-existing malignancy who underwent transplantation, the actual incidence and prevalence of malignancies in transplant candidates is unclear [2]. Furthermore, these

registries did not state tumour stage, prevalence, if any specific screening protocol was used and how future transplant recipients would be selected. Dialysis patient registries also indicate a significantly increased standardized incidence rate for various malignancies but as acceptance of a patient on a waiting list represents a process of selection, the spectrum of pre-existing morbidity may greatly differ from unselected dialysis patients. Furthermore, during the waiting time, patients are removed from the waiting list because of various reasons which again alters the spectrum of comorbidity (Fig. 1). The purpose of this study was therefore to characterize the prevalence, organ involvement and stage of malignancies in future transplant recipients at a single centre.

Patients and methods

At a single centre, the records of all patients considered as transplant candidates were reviewed retrospectively for a diagnosis of malignancy. Patients having received a transplant were not included in this analysis. The time of diagnosis, organ involved, tumour classification according to TNM, intention of therapy (curative versus palliative), time of initiation of dialysis, outcome on the waiting list and status on the waiting list were recorded.

Results

A total of 382 records were available for analysis. Among these, in 38 patients 45 tumours were detected. Forty-two malignancies were histologically confirmed and in three patients the evaluation was still ongoing but highly likely because of noninvasive testing. The overall cancer prevalence was 9.9%. The demographic data for patients with and without malignancy are given in Table 1. When all patients with malignancies were analysed together, the time on dialysis was shorter compared with patients without malignancy. After exclusion of patients with a malignoma diagnosed prior to dialysis, no significant difference in time on dialysis was detected. Patients with and without malignancy were also not different with respect to age and previous transplantation. There was a trend towards male gender which did not reach statistical significance. Fourteen malignancies were diagnosed prior to uraemia with a median time of 4.4 years (0.7–8.8) from malignancy to uraemia. Thirty-one malignancies occurred after uraemia with a median time of 3.1 years (2.9–3.4) to malignancy.

The site of malignancy showed a preponderance for the urinary system where 20 of 45 tumours were located (44%) (Fig. 2). In the majority of patients the malignancies were treated with a curative intention. Thus 68% of

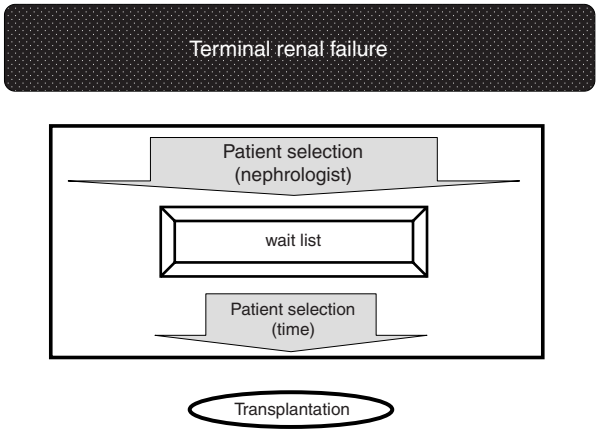

Figure 1 Selection bias during renal transplant evaluation. Current registries report on cancer prevalence in dialysis patients and after transplantation. The process of transplant evaluation (black box) which is crucial for the selection of appropriate candidates has not been studied for its effects on cancer prevalence.

Table 1. Cancer-free survival on the renal transplant waiting list. Demographic data for patients with and without a diagnosis of malignancy. After exclusion of patients with a malignoma diagnosed prior to dialysis, no significant difference in time on dialysis was detected.

	Malignancy	No malignancy	*P*-value
Male (%)	84.2	68.9	0.053
Age	51.1 (±17.3)	50.2 (±12.2)	NS
Previous transplants	1.7	1.3	NS
Dialysis (years)	1.3	3.0	<0.001
NPL prior	−4.4		
Dialysis prior	3.1		NS

NPL, neoplasia; NS, nonsignificant.

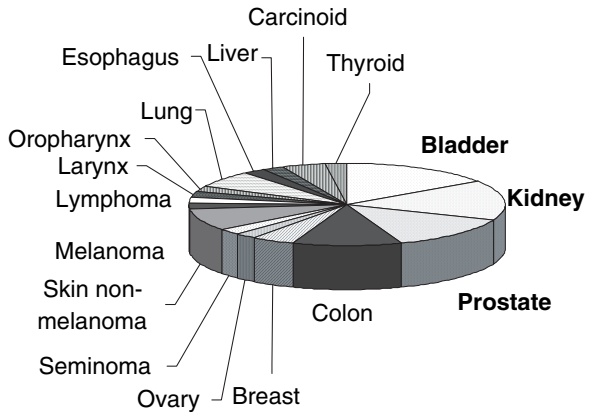

Figure 2 Organ involvement from cancers in waiting list patients.

patients with malignancies were listed as 'transplantable' or 'temporarily not transplantable'. From the waiting list 13% were removed, 8% died and 11% had their evaluation halted because of their malignancy. In patients on the waiting list, the mean time from diagnosis of the malignancy was 2.2 years. The corresponding cancer prevalence is 9.4% in all waiting list patients, 4.2% in patients transplantable, 21.2% in patients temporarily not transplantable and 8.8% in patients who died from *de novo* cancer while waiting for transplantation (Fig. 3).

After curative therapy of the malignancy, four patients of the entire cohort received a transplant while eight patients died or were removed permanently from the list prior to transplantation. Death or removal from the list was as frequently related to tumour progression as to other causes (four patients each). Among patients who received a transplant, no recurrence of the underlying malignancy was observed.

A more detailed description is given in Tables 2a and 2b. Sixteen patients with a nonurinary malignancy underwent curative therapy of the malignancy and were listed as transplantable or transplantation was deferred only because of the malignancy, i.e. patients were considered 'temporarily not transplantable'. Only three of these 16 patients received a renal transplant. Mean waiting time from the diagnosis of the malignancy to transplantation or the last follow-up was 61 months (Table 2a). In contrast, five of these

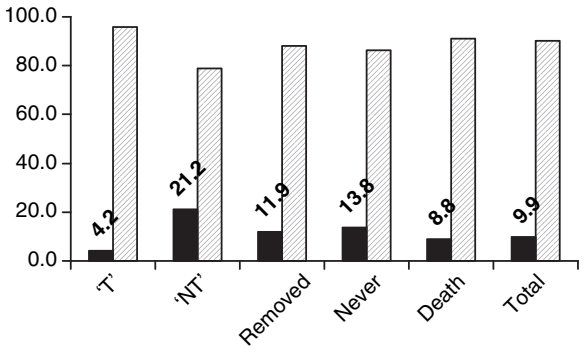

Figure 3 Cancer prevalence according to transplant status. The percentage of patients with (solid bars) and without a diagnosis of malignancy (shaded bars) is given for various patient categories. ('T' denotes patients listed transplantable, 'NT' for temporarily not transplantable, 'never' for patients with malignancy diagnosed during transplant evaluation).

Table 2a. TNM classification of tumours except the urinary system. For 21 patients with various tumours, age at diagnosis, sex, localization, TNM classification at diagnosis of the tumour, intention of the initial therapy, initial priority for transplantation, time in months from the diagnosis of the malignancy to the last follow-up, outcome data and cause of death or removal from the waiting list.

Pat. no.	Sex	Age	System	Malignancy	Stage (initial)	Therapy	List status (initial)	Time	Outcome	Reason
1	M	54	Endocrine	Carcinoid		Palliative	Removed			
2*	F	57	Endocrine	Carcinoid		Curative	Deferred	73	Waiting	
3	M	46	Endocrine	Thyroid		Curative	Deferred	26	Waiting	
4	F	41	Genital	Breast	pT2N1	Curative	Deferred	67	Deferred	
5*	F	64	Genital	Breast + ovary	pT1	Curative	Deferred	60	Death	Tumour
6	M	24	Genital	Seminoma		Curative	Transplantable	109	Waiting	
7	F	52	Blood	Lymphoma	Ie	Curative	Transplantable	60	Death	Cv
8*	M	77	Intestinal	Colon		Palliative	Removed			
9	M	62	Intestinal	Colon	Dukes C	Palliative	Evaluation		Removed	
10*	M	57	Intestinal	Colon	pT3N0M0	Curative	Deferred	56	Removed	Tumour
11	M	55	Intestinal	Colon	pT3N0M0	Curative	Transplantable	57	TX	
12	M	59	Intestinal	Colon	pT2N0M0	Curative	Transplantable	88	TX	
13	M	65	Intestinal	Oesophagus	pTx	Palliative	Evaluation		Removed	
14	M	59	Intestinal	Liver		Palliative	Death		Death	Tumour
15	M	58	Intestinal	Oropharynx	pT2N1M0	Palliative	Death		Death	Tumour
16	M	52	Respirat.	Larynx	pT4N0M0	Curative	Evaluation		Removed	Tumour
17	M	60	Respirat.	Lung		Palliative	Deferred		Death	Tumour
18	M	56	Respirat.	Lung		Palliative	Deferred		Death	Tumour
19	M	54	Respirat.	Lung		Curative	Deferred	8	Death	Tumour
20*	M	47	Skin	Basalioma		Curative	Transplantable		Waiting	
20*	M	53	Skin	Basalioma		Curative	Transplantable		Waiting	
20*	M	59	Skin	Basalioma		Curative	Transplantable	49	Waiting	
21	M	0	Skin	Melanoma		Curative	Transplantable	77	TX	
8*	M	79	Skin	Spinalioma		Curative	Removed			Second tumour

Pat. no., patient number; respirat., respiratory system; Cv, cardiovascular complication.
*Indicates multiple tumours.

Table 2b. TNM classification of tumours of the urinary system. For 20 patients with urinary tumours, age at diagnosis, sex, localization, TNM classification at diagnosis of the tumour, intention of the initial therapy, initial priority for transplantation, time in months from the diagnosis of the malignancy to the last follow-up, outcome data and cause of death or removal from the waiting list.

Pat. no.	Sex	Age	Malignancy	Stage (initial)	PSA	Therapy	List status (initial)	Time	Outcome	Reason
22	F	63	Bladder	pT3N2		Palliative	Death		Death	
23	M	43	Bladder	pT2a		Palliative	Removed		Death	
24	M	54	Bladder			Palliative	Evaluation		Removed	General
5*	F	63	Bladder	pTa		Curative	Deferred	50	Death	Second tumour
25	M	45	Bladder	pTa		Curative	Deferred	97	Waiting	
26	M	61	Bladder	pTa		Curative	Deferred	34	Deferred	
27	M	55	Bladder	pT1a,Nx		Curative	Transplantable	37	Death	Cv
10*	M	60	Kidney	pT1,N0		Curative	Deferred	21	Removed	Second tumour
2*	F	60	Kidney	pT1b,N0		Curative	Deferred	44	Waiting	
28	M	41	Kidney	pT1a,N0		Curative	Deferred	27	Waiting	
29	M	43	Kidney	pT1		Curative	Deferred	26	Waiting	
30	M	48	Kidney	pT1b		Curative	Deferred	22	Waiting	
31	F	47	Kidney	pT1		Curative	Deferred	41	Death	Sepsis
32	M	53	Kidney	pT3a,pNx		Curative	Transplantable	121	Waiting	
33	M	62	Prostate	pT2,Nx	3.7	Palliative	Evaluation		Removed	Vascular
34	M	60	Prostate	pT3,Nx	0.6	Palliative	Removed			
35	M	64	Prostate	T2a,Nx	<0.1	Curative	Deferred	39	Death	Cv
36	M	60	Prostate	pT2N0M0	1.18	Curative	Deferred	48	TX	
37	M	44	Prostate	pT2b, pNx	0	Curative	Deferred	31	Waiting	
38	M	65	Prostate	pT1a,Nx	0	Curative	Transplantable	30	Waiting	

Pat. no., patient number; PSA, prostate-specific antigen; Cv, cardiovascular complication.
*Indicates multiple tumours.

16 patients died or were removed from the waiting list for a transplant either from cardiovascular complications (one patient) or progressive malignancy (four patients). After curative therapy of a urinary tumour, 15 patients were listed as transplantable or transplantation was deferred strictly because of the tumour ('temporarily not transplantable'). Only one of these 15 patients received a renal transplant. Mean waiting time is 45 months after the diagnosis of the malignancy (Table 2b). In contrast, five of these 15 patients died or were removed from the waiting list for a transplant either because of cardiovascular complications (three patients) or a second primary tumour (two patients).

Discussion

At initiation of dialysis 9% of patients carry a diagnosis of malignancy. Thereafter, an increased incidence of malignancies in uraemic patients has been noted. A large study from registries including over 800 000 dialysis patients with over 21 000 malignomas reported significantly increased risks of genitourinary, endocrine and haematopoietic tumours after initiation of dialysis in Australia, Europe and USA. Furthermore, in Australia malignancies of the breast and respiratory system were also significantly increased while in USA malignancies of the digestive and respiratory system showed a significant increase [4]. However, patients on dialysis also exhibit a significantly increased cardiovascular morbidity and mortality which is reflected in the fact that malignancy accounts for only 6.3 of 179.3 deaths per 1000 patient years [5]. The evaluation of a patient for renal transplantation therefore reflects a process of selection where the cardiovascular risk for surgery and curative therapy of malignancies have to be taken into account. Not surprisingly, the comorbidity and life expectancy of prospective renal transplant recipients greatly differs from dialysis patients [6].

This is the first paper that investigates the prevalence of malignant tumours in patients on the waiting list for renal transplantation. In the cohort under investigation, an unexpected high number of 9.9% of all patients had a history of malignancy. Furthermore, malignancy was more often treated with a curative intention which resulted in only 29% of malignancies in withdrawal of the patient from the waiting list. The majority of malignancies led to deferral of transplantation, i.e. a classification of the patient as 'temporarily not transplantable', primarily because of the rather short interval from diagnosis of the malignancy. This rather high number of patients with a cancer history can be explained by a number of factors. Patients included were on average 2.8 years older compared with data from the United States Renal Data System [7]. In addition, the average duration of dialysis

Table 3. Current recommendations for selected cancer screening during transplant evaluation (adapted from [10]).

Cancer site	Method of screening	Patients
Prostate	Annual prostate exam + PSA	>50 years (>40 years)
Renal	Radiographic imaging urinalysis/urine cytology	High-risk patients (analgesic-, Balkan-, Chinese-herb nephropathy)
Bladder	Urinalysis/urine cytology cystoscopy	High-risk patients (toxic, infectious, obstructive nephropathies)
Breast	Breast exam	All women, annual
	Mammogram	Age 50–69 years (40–49 years), annual
Cervix/uterine	Pelvic and cytological exam	Women 20–65 years, every 1–3 years
Anogenital	History and physical exam	All patients
Testicular	Testicular exam	All men
Colorectal	FOBT sigmoidoscopy or colonoscopy	>50 years (>40 years), annual every 5 years every 10 years
Thyroid	Thyroid palpation	All patients
Skin	Skin examination	All patients

FOBT, faecal occult blood; PSA, prostate-specific antigen.

was longer than described from centres in the USA, which might enhance the chance of small cancers to progress to a size which facilitates diagnosis [8]. Finally, many patients were only recently diagnosed with cancer, which may reflect more intense screening of this population for cancer.

The follow-up data in these patients with a tumour emphasize another dilemma in dialysis patients. Although malignancy and mortality from malignancy are more prevalent than in the general population, there is an even greater increase in cardiovascular mortality. Thus, patients with a true cure of their malignancy are at substantial risk to die while being watched for tumour recurrence. In this cohort this is highlighted in patients with malignancies of the urinary system where all-cause mortality exceeds the rate of tumour recurrence. In contrast, patients with tumours of the genital, gastrointestinal and respiratory system are more likely to experience tumour recurrence, even despite early tumour stages and a curative approach.

The present recommendations for screening malignancies during a transplant evaluation have evolved gradually. While in 1995 screening was advocated but not further specified, the latest guidelines published by various societies provide detailed recommendations [9–12]. In brief, these guidelines reflect the recommendations for the general population with the addition of skin examination as well as renal imaging and bladder examination for high-risk patients (Table 3). This largely rests on the higher incidence of cancer in the urinary system for dialysis patients with toxic nephropathies [13]. The clinical benefit for these screening procedures is derived from studies in the general population. Thus, for breast and colon cancer screening there is evidence level A or B, whereas the recommendation for testicular, endocrine, prostate, renal and bladder examination rest on level C [10]. However, studies in prospective transplant recipients addressing their increased risk of cancer are lacking.

Moreover adherence to these recommendations is suboptimal. A recent survey showed that 69% transplant centres enforce 'routine cancer screening' [14], but a closer investigation of 154 European centres exhibited substantial differences in 28 of 45 diagnostic procedures, including ultrasound, urological or gynaecological consult, faecal occult blood and prostate-specific antigen [15]. The only significant determining factor for this variation was the geographical location, possibly reflecting also regional differences in cancer incidence [15]. The frequency with which these screening procedures should be performed also remains unclear. A periodic re-evaluation appears especially in the light of the extended waiting periods [9]. While current recommendations largely adopt recommendations for patients without uraemia, one has to be aware that this does not account for the increased risks in uraemic patients. Even with diligent examination of renal transplant recipients, the current strategies are far from optimal. In a series of 260 routine unilateral nephrectomies performed at the time of renal transplantation, 4.2% of patients were incidentally found to have renal carcinoma [8].

Currently missing are recommendations based on a higher evidence level for genitourinary malignancies, population-specific recommendations, which also address frequency and enforcement of screening procedures.

Conclusion

At transplantation, freedom from malignancy is essential, but renal failure is associated with an increased incidence of malignancy. Screening and appropriate therapy lead to approximately 9.9% of potential recipients with a history of malignancy, but regional differences should be considered. Despite current protocols, in 4.2% of patients, renal malignomas are not detected prior to transplantation. The present strategy of waiting time after a diagnosis of

malignancy is supported by low recurrence rates. However, it is clear from this cohort that while extended waiting time may reduce death from malignancy after renal transplantation, this occurs at the cost of death from cardiovascular causes on the waiting list. Trends towards improved cancer therapy, increased use of cytotoxic therapy, prolonged waiting time and screening programmes will likely result in increased cancer detection in potential transplant candidates. Future strategies have to identify patients at risk to assure intensive monitoring for recurrence and consideration of specific immunosuppressive protocols.

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