

Malignancy

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Guidelines

1. We suggest that patients with active untreated malignancy not be transplanted. (Ungraded)
2. We suggest that screening for malignancy prior to transplantation be conducted in accordance with usual age and sex appropriate cancer screening policies for the general population. (Ungraded) [Comment: This could be a recommendation if it is felt to be an obvious clinical decision i.e. there would be no reason not to do it from a risk/benefit even though it is ungraded.]
3. We suggest that consideration be given to the following minimum waiting periods from successful treatment of malignancy to transplantation.
Nil:
 - a. Superficial Bladder Cancer (2D)
 - b. In situ Cancer of the Cervix (2D)
 - c. Non-metastatic Non-Melanoma Skin Cancers (2D)
 - d. Prostatic Cancer microscopic (2D)
 - e. Renal Cell Carcinoma Asymptomatic Stage 1 (non-invasive/non-metastatic <7cm) (2D)2 years:
 - a. Invasive Bladder Cancer (2D)
 - b. In situ Breast Cancer (2D)
 - c. Stage A and B Colorectal Cancer (2D)
 - d. Lymphoma (2D)
 - e. In situ Melanoma (2D)
 - f. Prostatic Cancer (2D)
 - g. Testicular Cancer (2D)
 - h. Thyroid Cancer (2D)
 - i. Wilm's Tumour (2D)5 years:
 - a. Stage II Breast Cancer (2D)
 - b. Extensive Cervical Cancer (2D)
 - c. Colorectal Cancer stage C (2D)
 - d. Melanoma (2D)
 - e. Symptomatic Renal Cell Carcinoma (2D)Not Recommended:
 - a. Uncontrolled or untreated malignancies (Ungraded)
 - b. Multiple Myeloma (2D)
 - c. Advanced Breast Cancer (stage III) (2D)
 - d. Colorectal Cancer (stage D) (Ungraded)
4. We suggest advising patients with a prior malignancy that they are at increased risk of de novo malignancy post-transplantation compared with those with no prior history of malignancy undergoing transplantation (2B)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

None provided.

IMPLEMENTATION AND AUDIT

Ideally all patients commencing renal replacement therapy (dialysis or transplantation) should have all information about previous malignancies recorded for ongoing analysis. Parameters recorded should include:

- Site of malignancy
- Stage and grade of malignancy
- Date of onset and date of completion of successful therapy.
- Therapy undertaken
- Date of renal replacement therapy and type
- Recurrence of malignancy and death from malignancy recurrence
- Other causes of death.

A comparison of outcomes could then be made between outcomes in patients remaining on dialysis compared with transplant recipients after controlling for other confounders.

Many of the above parameters are already measured by ANZDATA but with insufficient detail to allow a precise analysis. Sample size is also a major limitation in achieving meaningful results therefore an international registry is in order.

BACKGROUND

Prior malignancy in a potential renal transplant recipient is increasingly commonly encountered. This is likely to be due to the increasing age of patients accepted as suitable for renal transplantation. There are limited data available to guide decision making as to the suitability of transplanting patients with a prior malignancy with most information drawn from the work of a single US based database. This guideline seeks to provide some suggestions for Nephrologists involved in advising patients with a prior malignancy on waiting times from successful treatment of malignancy to transplantation.

SEARCH STRATEGY

Databases searched: Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for neoplasms, carcinoma and tumour and then combined with MeSH terms and text words for recurrence. The search was carried out in Medline (1950 – November Week 1, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 18 November 2009.

WHAT IS THE EVIDENCE?

The issue of prior malignancy in potential renal transplant recipients (RTRs) is increasingly commonly encountered likely due to the increasing mean age of RTRs [1]. Unfortunately the evidence base available to guide Nephrologists is somewhat thin. Most international guidelines draw their data from the seminal, 1993 publication of Israel Penn as well as several updates from Penn and his colleagues [2-4]. These articles summarise the outcomes of RTRs with a prior malignancy undergoing transplantation whose data was submitted voluntarily to the Cincinnati

Tumour Transplant Registry. It therefore does not include all patients undergoing transplantation with a history of prior malignancy. Despite its imperfections it remains the most informative and essentially the only, published series of any substance in the literature.

Malignancies are heterogeneous within the same organ as well as between organs and as such have different natural histories and recurrence rates. Therefore a blanket recommendation for malignancy overall would not be valid but even for a single type of malignancy such as breast cancer, recommendations would ideally be based on the tumour stage, grade and more detailed information such as receptor positivity or other molecular analysis. This level of information is simply not available at the present time. The guidelines are based on a small number of studies primarily of registry data with a consequent high risk of bias and hence presented as suggestions rather than recommendations.

Given the lack of high level evidence and the complexity of risk/benefit analyses in deciding on the suitability of patients for transplantation it is likely that transplantation will be offered to patients outside the above suggestions which were formulated for cadaveric transplantation with a view to an 80% likelihood of 5 year patient survival. Patients with a live donor who are cognizant of the risks involved but retain a firm desire to proceed may be considered in the pursuit of a better quality of life. These decisions clearly require close discussions between recipient, donor, the treating transplant team and an oncologist.

Screening

There is no evidence to support intensive screening of potential RTRs above that suggested for the general population. Whilst guidelines for the general population are based on the premise that screening will enable early detection and treatment of malignancy that improves survival, there are insufficient data in patients with chronic kidney disease to determine the utility of increased or reduced cancer screening [5]. It is apparent that patients with CKD are at an increased risk of malignancy [6] and as such it would seem prudent to screen at least as intensively for malignancy in CKD patients with the caveat that the benefit of early discovery of malignancy in CKD patients may not be equivalent to that in non-CKD patients given that patients with CKD and malignancy have poorer survival than patients with malignancy but not CKD [7].

Some guidelines have recommended targeting those at increased risk of cancer for more intensive screening [8, 9]. Pertinent screening modalities for patients with CKD would include cystoscopic surveillance for those with analgesic nephropathy and those who have received cyclophosphamide therapy; renal imaging for renal malignancies for patients with acquired cystic diseases; as well as appropriate screening for those with CKD and genetic disorders known to be associated with higher rates of malignancy.

Suggested waiting periods for prior malignancies

The concept of waiting times post successful treatment of a malignancy and transplantation is based on the observation that cancer recurrence becomes less likely the longer the disease free interval post-treatment. Penn reported that of the 185 cancer recurrences observed in his series 87% had waited less than 5 years post-treatment [3]. This would suggest that if a blanket 5 year waiting period was observed only 13% of patients who reached transplantation might be expected to have a cancer recurrence. There was however considerable variability between malignancies in terms not only of recurrence rates but more importantly mortality rates from the recurrences. It is important therefore to apply perspective to waiting periods such that unduly long waits are not applied to cancers with high recurrence rates but low lethality such as superficial bladder tumours. In addition, consideration should be given to the excessive mortality associated with remaining on dialysis compared with receiving a transplant.

A waiting period of 2 years is suggested for those with invasive bladder cancer. This is based on 7 of the 11 recurrences reported by Penn having been in patients treated <2 years prior [3]. Those

with recurrences had a mortality rate 36% (4 of 11). The overall recurrence rate was 26% (11 of 42) however there were 11 superficial or non-invasive lesions included. No patient with a superficial lesion developed an invasive recurrence despite a reportedly high incidence of superficial recurrences. If those with a superficial lesion are excluded the recurrence rate of invasive bladder cancer increases in the reported series to 35%. The corollary is that patients with superficial lesions may not require any waiting period but should be subject to regular cystoscopic surveillance. Based on an ANZDATA analysis by Merrifield and colleagues those transplanted with a history of bladder malignancy had a median survival from transplantation of 9.5 years compared to 16.0 years for those with no prior malignancy [10].

A waiting period of 5 years is suggested for most patients with a past history of breast cancer as 62.5% of recurrences were seen in patients with shorter wait times, in the Penn series [3]. The overall recurrence rate was 25% (16 of 64) the median wait time and disease stages were not given other than to state that 6 patients had lymph node involvement and 2 had bilateral disease. Of patients with recurrence, 81.25% (13 of 16) died of the recurrence. A subsequent analysis has been provided by the same group in all organ transplant recipient (52 of 91 were RTRs) [11]. The median wait time was >5 years. Disease stage was provided and revealed that whilst there were low recurrence and death rates from recurrence in stage I and II disease; stage III disease was associated with a 64% recurrence rate with 5 of the 7 patients with a recurrence dying from it. An ANZDATA analysis suggest a much lower overall recurrence rate and this probably relates to the differences in the reporting to the 2 databases and may reflect differences in the disease stage and waiting times [12]. The reported median survival in RTRs with a past history of breast Ca in Australian and New Zealand post-transplant was 9.3 years compared with 16 years for those with no prior malignancy [10]. Given the lower risk of recurrence and mortality in patients with in situ breast cancer a shorter wait time could be considered, 2 years has been suggested by the Canadian Society of Transplantation [9].

Suggestions on waiting times for patients with a past history of cervical cancer are difficult to make. Reported recurrence rates range from 5% (3 of 59) to 10% (2 of 20) in 2 separate reports [3, 12]. In the Penn series 2 of 3 recurrences were seen in patients with previous invasive disease treated 54 and 69.5 months prior to transplantation whilst the third recurrence was in a patient treated 3 months prior to transplantation for carcinoma in situ. Chapman et al reported 2 recurrences but there were no details given on the stage of disease or the duration of wait [12]. The recent Canadian guidelines have suggested a 2 year wait for localised disease and a shorter wait for in situ disease based on the scant data described above, they state that no recommendation can be given for those with more extensive disease but suggest a minimum 5 year wait [9]. These views appear reasonable based on the overall low recurrence rates and that 2 of the 3 recurrences described by Penn et al were in patients with invasive disease [3].

A waiting period of 5 years is suggested for patients with a past history of advanced colorectal carcinoma (stage C), whilst a shorter waiting period of 2 years could be considered in patients with lower stage disease A and B. Patients with treated stage D disease probably should not undergo transplantation. Penn describe 38 RTRs who were transplanted post treatment for colorectal cancer with a recurrence in 8 (21%) [3]. Interestingly, 0 of 8 who had waited less than 2 years experienced a recurrence a finding also reported by Husted et al [13]. Whilst this could be interpreted as suggesting that patients with colorectal cancer should be transplanted immediately to prevent recurrence it has been reported that there is a significantly increased incidence of de novo colon cancer and a decreased survival from this disease in transplant recipients which goes some way to suggesting that immunosuppression is not protective against colorectal cancer [14]. Husted et al report recurrence rates are dependent on disease stage with a 42% recurrence rate in patients with stage C1 or D disease [13]. Chapman et al report no recurrences in 23 RTRs with previous colorectal cancer [12], with a follow-up analysis revealing this cohort had a median wait time from treatment of 7.2 years and their median survival from post-transplantation was 9.4 years compared to 16 years for those with no malignancy [10].

The recommended waiting period for patients with a past history of lymphoma defaults to 2 years due to a lack of data. Of 29 patients with lymphoma (21 Non-Hodgkin's Lymphoma (NHL) and 8 Hodgkin's Lymphoma) 3 developed a recurrence post-transplantation [3]. One patient with a recurrence had been treated 24 months prior whilst the other 2 were treated more remotely (48 and 126 months prior). Two of the 3 RTRs with a recurrence died from the recurrence. Twenty three of the 29 RTRs had waited 2 years or more from treatment to transplantation thus making recommendations of transplanting such patients earlier than this difficult to support. Buell et al report 32 patients undergoing re-transplantation (18 kidney, 9 liver, 4 heart and 1 lung) at a median time of 37 months after treatment of post-transplant lymphoproliferative disorder [15]. Recurrence was seen in one patient who had a heart transplant and in none of the RTRs. Five year patient survival was 75% for RTRs. Overall therefore; successfully treated lymphoma has a low recurrence rate and should not preclude transplantation.

A waiting period of 5 years from successful treatment to transplantation is suggested in patients with a past history of melanoma. A 2 year waiting period is suggested in patients with in situ lesions only. Twenty patients with melanoma of the skin who underwent transplantation were described by Penn [3]. The recurrence rate was 30% (n=6) with all those with a recurrence dying from the recurrence. Half the recurrences were in those that waited less than 2 years from treatment to transplantation, whilst another 2 had waited between 2 and 5 years. One RTR developed recurrent melanoma 10 years after transplantation. Chapman et al describe 4 patients with melanoma undergoing transplantation with no recurrences [12] but there are no details regarding waiting times whilst Merrifield et al expand on this ANZDATA analysis to include 43 patients [10]. The median wait time was 7.9 years with a median overall survival of 8.8 years compared with a median of 16 years for those with no history of malignancy. A recurrence rate is not stated. Given the high recurrence rate and the lethality of melanoma a 5 year wait has been suggested.

Transplantation for patients with a past history of Multiple Myeloma cannot currently be recommended. Seven of 8 patients with multiple myeloma who underwent transplantation in the Penn series developed a recurrence after transplant and this was universally fatal [3]. No information is given regarding the waiting period from treatment to transplantation. Chapman et al report 4 patients with multiple myeloma who underwent renal transplantation without a recurrence but again no detail is provided with regards to waiting periods or follow-up duration [12]. Other investigators have examined aggressive treatment regimens for myeloma including combination bone marrow transplantation [16] however insufficient data exists to allow this to be recommended at this time.

Patients with localised non-melanomatous skin cancers (SCC and BCC) generally do not require a waiting period prior to transplantation. Whilst there was a high recurrence rate observed by Penn et al, 49 of 79 (62%), there was only one fatality [3]. There were however 4 patients who developed other skin malignancies including 3 with a melanoma, one patient required an arm amputation and a further 2 developed regional lymph node metastases. It appeared that most recurrences were de novo lesions and it was unclear whether the metastatic lesions were related to the lesions removed pre-transplantation or the de novo lesions. Patients with a history of SCC or BCC are highly likely to encounter a recurrence during any specified waiting period which would end up precluding them from transplantation. Therefore unless an individual has evidence of metastatic spread or a very high recurrence rate, transplantation should not be unduly delayed. Primary prevention of skin cancers via avoidance of sun exposure should be encouraged in line with current recommendations.

A waiting period of 2 years is suggested from successful treatment to transplantation in patients with a past history of cancer of the prostate. Patients with low grade microscopic disease may not require any waiting period whilst those with advanced disease may require a longer waiting period or not be offered transplantation at all. The recurrence rate after transplantation is reported to be 18-24% [3, 12, 17]. The mortality rate in those who developed a recurrence is reported to be 20-44%. Forty percent of those who developed a recurrence had been treated less than 2 years prior

in the Penn series. Gupta et al report that recurrence appeared to be related to stage of disease at diagnosis rather than waiting time post-treatment with recurrence and death rates of 14.3% and 2.9% for stage I disease; 15.9% and 6.8% for stage II disease and 36.4% and 27.3% for stage III disease [17]. It might therefore be reasonable to observe no wait time for stage I or microscopic disease, a 2 year wait for stage II disease and recommend a 5 year wait or not proceed to transplantation in stage III disease. Given the average age at diagnosis of prostate cancer in the reported series was 61.3 +/- 6.3 years, a prolonged wait will effectively exclude many from proceeding to transplantation. In this instance in the presence of a suitable live donor a patient may wish to proceed to transplantation anyway.

In patients with a history of successfully treated renal cell carcinoma no waiting time is recommended for localised asymptomatic lesions whilst a 5 year wait is suggested for patients with symptomatically discovered lesions. Penn reports on 59 patients with asymptomatic RCC who have undergone renal transplantation without any recurrences noted [3]. Most patients had their RCC removed at the time of transplantation. However, patients with symptomatic RCCs (n=169) had a recurrence rate of 30% with 76% of those with a recurrence dying from the recurrence. [2] Most patients (94%) who developed a recurrence had waited less than 5 years from treatment to transplantation.

In patients with a history of successfully treated cancer of the testes a waiting period of 2 years is suggested prior to transplantation. This condition has an excellent 5 year survival rate in the non-transplant population [18] and Penn et al report a low recurrence rate post-transplantation in 34 RTRs [3]. Most patients in that series and that of Merchen et al had waited more than 2 years prior to transplantation [19]. Penn's cohort included 7 patients with metastatic disease. The one recurrence that was observed occurred in a patient who had an orchidectomy at the time of transplantation.

It is suggested that patients with a history of successfully treated cancer of the thyroid wait 2 years prior to transplantation. Penn reports an 8% recurrence rate in his 39 patient series with 1 patient dying from recurrence [3]. Nearly half the patients had waited less than 2 years prior to transplantation. The author states that having 6 incidentally discovered lesions (during parathyroidectomy) and many low grade papillary lesions may led to the low recurrence rate, a shorter waiting period could be considered in such patients. Gupta et al contribute outcomes in 27 transplant recipients (23 RTRs), one patient developed a fatal recurrence and there were 2 recurrences in total (7.4%) [20]. The median wait time was 40 months.

A waiting period of 2 years is suggested from successful treatment to transplantation in patients with a previous history of Wilms tumour. Penn reports on the outcomes of 61 RTRs with previous Wilms with a recurrence rate of 16% [3]. Eighty percent (80%) of patients with a recurrence died from recurrence and 90% of recurrences occurred in patients who had waited less than 2 years prior to transplantation.

SUMMARY OF EVIDENCE

Recommendations are difficult in this area given the lack of sufficient evidence. Most data is from reports on outcomes in less than 100 patients (see evidence table in appendices). These reports do not described the malignancies sufficiently in terms of staging or the range of waiting times observed from successful treatment until transplantation to be able to offer a stage by stage suggestion as to waiting times. Therefore this guideline along with other international guidelines has grouped malignancies together in offering suggestions for waiting times. These should be read in that light as it is likely that a lower grade/stage malignancy may require a shorter duration of waiting than a more aggressive/advanced malignancy.

Overall the suggestions are that in situ or pre-malignant conditions require minimal or no waiting time whilst for other cancers a 2 or 5 year wait has been suggested on the basis of the reported

recurrence rates and associated mortality risks. The suggestions made are based on cadaveric transplant listing with the aim of achieving an 80% chance of 5 year survival although the data does not allow that degree of precision. In patients with a live donor a decision to proceed earlier may be made if all parties are agreeable after understanding the likely risks involved.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: Guideline 2.7 – Tx : Evaluation and selection of the renal transplant recipient. We recommend that renal transplantation should only be considered in potential recipients with previous malignancy (excluding non-melanoma skin cancer) if there is no evidence of persistent cancer. It is recommended that the waiting time between successful tumour treatment/remission and transplantation be at least 2 years. For certain malignancies the waiting time may need to be extended to more than 5 years. The Israel Penn International Transplant Tumor Registry should be consulted for tumour specific advice (www.ipittr.uc.edu/Home.cfm) [21].

Canadian Society of Nephrology: Very similar suggestions [9]

European Best Practice Guidelines: No recommendation.

International Guidelines: The American Society of Transplantation: Very similar suggestions [8]

SUGGESTIONS FOR FUTURE RESEARCH

1. More data is required on outcomes in transplant recipients compared with waiting list controls
2. More specific data on stage specific outcomes for individual cancers would be beneficial

CONFLICT OF INTEREST

William Mulley has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

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DRAFT

APPENDICES

Table 1. Characteristics of included studies – any cancer

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with any prev Ca	Recurrence Rate	Deaths from Recurrence	Comments
Merrifield, ICB abstract 2009 [10]	17168	Retro Registry analysis	ANZDATA 1963-2007	RTRs with cancer ptx, all-sites N=397 RTR no cancer ptx N=16771		Median (IQR) Time from Rx to Tx 5.7 (2.9-11) Time from ESKD to Tx i v c 2.5 v 1.2 yrs p<0.0001 Median pt survival from Tx 14.4 v 18.1 yrs p=0.01 Median graft survival 5.1 vs 5.5 y p=0.02	
Penn, 1993 [3]	823	Retro registry analysis	Cincinnati Tumour transplant registry	185 had recurrences Rx ptx >5 yrs 243, 24 had recurrence (10%)	22% Rx ptx 0-2y 98/185 (53%) 2-5y 63/185 (34%) >5y 24/185 (13%)		
Chapman, 2001 TProc [12]	210	Retro registry analysis	ANZDATA 1963-1999	Any non-skin	11 (5%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	Not enough data on time from Rx ptx, subtype of Ca to be of much use

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Birkeland, 1982 [22]	18	Retro registry analysis	Scandanavia 1956-1978	11 urinary tract 3 BCC 2 colorectal 1 breast 1 Bone	9 (50%)	6 (33%) All received Tx <12mths post diagnosis of Ca 5 RCC 1 rectal	1mth-7 yrs fu post diagnosis 1mth-2yrs fu post Tx
Matas, 1975 [23]	11	Retro	Uni of Minnesota Pre-1975	11 in toto 1 seminoma 3 breast 1 in situ cervix 1 Wilms 1 Thyroid 3 RCC (1 with breast as well) 1 insulinoma	1 (9%) Wilms pt 1 recurrent in situ cervix	1 (9%) Wilms treated 4 months prior	Many with long waits post diagnosis
Kauffman Tran Revs 2005 [18]	1358	OPTN/UNOS	1994-2002		31 (2.3%) De novo malig 106 (7.8%) with prev malig vs 1430/50291 (2.8%) with no prev malig	Pts with PHx of Ca have sig worse 5 yrs survival in those with NO recurrence or denovo vs those without Hx of prev Ca (?about 4%) AND With de novo malig (more dubious)	

Table 2. Characteristics of included studies- Bladder tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev bladder Ca	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	42	Retro registry analysis	Cincinnati Tumour transplant registry	10 incidentals 11 insitu/non-invasive 21 must have been invasive	11 (26%) time post Rx 7 at <24 mths, 2 2-5 y ptx 2 >5y ptx	4 (9.5%)	

The CARI Guidelines – Caring for Australasians with Renal Impairment

					2/10 incidentally discovered recurred (1 death) 11 insitu/non-invasive, no recurrences		
Merrifield, ICB abstract 2009 [10]	40	Retro registry analysis	ANZDATA (1963-2007)	Median wait from Rx to Tx 4.1 yrs (2.3-7.5) IQR	Not stated	Not stated Median time from Tx to death 9.5 yrs (7.1-22.9) 95% CI No cancer 16.0 yrs (15.7-16.5) 95% CI	
Chapman, 2001 TProc [12]	24	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	1 (4%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	

Table 3. Characteristics of included studies- Breast tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev breast Ca	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	64	Retro registry analysis	Cincinnati Tumour transplant registry	6 LN +ve 2 Bilat dis	16 (25%) time post Rx 3 at <24 mths, 7 2-5 y ptx 6 >5y ptx In the no recurrence group 7 (33%) 2-5y ptx	13 (20%)	
Buell, 2003 Abstract [11]	91 52 renal	Retro registry analysis	Cincinnati Tumour transplant registry	10 <2 yrs ptx 30 2-5y ptx 51 >5y ptx Renal break down	Overall 13 (14%) 11 (21%) renal Stage I 5.4% Stage II 8% Stage III 63.6%	8 (9%) median Stage I 3.6% Stage II 4% Stage III 45%	Recurrence and death appears related to stage I, II, III

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				unclear	Recurrence 20% <2 yrs ptx 20% 2-5y ptx 9.8% >5y ptx		
Merrifield, ICB abstract 2009 [10]	36	Retro registry analysis	ANZDATA (1963-2007)	Median wait ptx 7yrs (5-12) IQR	Not stated	Median survival 9.3 (7.4-NC) 95% CI Cf No cancer 16 (15.7-16.5)	
Chapman, 2001 TProc [12]	24	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	0 (0%)	Not stated This report identifies timing of initial Ca diagnosis in relation to dialysis start as the important prognostic factor	

Table 4. Characteristics of included studies- cervical tumours

Study ID (author, year)	N	Study Design	Setting	Interest group – RTRs with prev cervical Ca	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	59	Retros registry analysis	Cincinatti Tumour transplant registry	Prev Cx Ca 34 (58%) had in situ lesions 25 (42%) invasive lesions 24 (43%) <2 yrs ptx 6 (10%) 2-5 yrs 29 (47%) 72-360mths ptx	3 (5%) 2 had invasive Ca (54 and 69.5 mths prior) 1 in situ (3 months prior)	2 (3%)	3 other pts developed vulval ca after Rx for in situ cx ca
Chapman, 2001 TProc [12]	20	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	2 (10%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	

Table 5. Characteristics of included studies- Colorectal tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev colorectal Ca)	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	38	Retro registry analysis	Cincinatti Tumour transplant registry	No recurrence 6 in situ 2 Dukes A 1 Dukes B 4 Dukes C	8 pt (21%) Rx 1 at 24 mths, 7 from 33-74 mths ptx No cancer recurrence seen 8 (21%) <2y ptx 8 (21%) 2-5y ptx 14 (37%) >5y ptx	5 (13%)	
Husted, 2003 [13] Abstract	56 34 renal	Retro registry analysis	Cincinatti Tumour transplant registry	9 <2 yrs ptx 20 2-5y ptx 23 >5y ptx nos don't add up	Renal 4 of 34 (12%) No recurrence in those Tx <2yrs (all organs)	2 (6%) at 5 yr follow-up	Recurrence related to stage A,B,C
Merrifield, ICB abstract 2009 [10]	44	Retro registry analysis	ANZDATA (1963-2007)	Median wait ptx post Rx 7.2 (3-10.2) IQR	Not stated	Median pt survival post Tx 9.4yrs (6.5-30.4) 95% CI cf No cancer 16 (15.7-16.5)	
Chapman, 2001 TProc [12]	23	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	0 (0%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	

Table 6. Characteristics of included studies- lymphoma

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev lymphoma Ca)	Treatment Time before Transplant	Recurrence Rate	Death from Recurrence	Comments
Penn, 1993 [3]	29	Retrospective registry analysis	Cincinnati Tumour transplant registry	Prior lymphoma 21 NHL 8 Hodgkins	6 (21%) <2 yrs ptx 2 (7%) 2-5yrs ptx 21 (72%) >5y ptx	3 pt (10%) Rx 20, 48 and 126 months prior	2 (7%)	
Buell, 2003 [15] Abstract	32	Retrospective registry analysis	Cincinnati Tumour transplant registry	Re-transplants after treatment of PTLD 18 kidney Tx 9 liver 4 heart 1 lung	Median time from Rx 37 months (1-111)	1 (3%) overall 0/18 for renal tx	1 (3%) overall	

Table 7. Characteristics of included studies- Melanoma

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev melanoma	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	21	Retro registry analysis	Cincinnati Tumour transplant registry	20 skin, 1 of the eye	6 (30%) time post Rx 3 at <24 mths, 2 2-5 y ptx 1 >5y ptx	6 (30%)	
Merrifield, ICB abstract 2009 [10]	43	Retro registry analysis	ANZDATA (1963-2007)	Median wait ptx post Rx 7.9 (3.5-13.6) IQR	not stated	Median pt survival post Tx 8.8yrs (5.7-15.4) 95% CI cf No cancer 16 (15.7-16.5)	

Chapman, 2001 TProc [12]	4	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	0 (0%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	
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Table 8. Characteristics of included studies- Myeloma

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev myeloma	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	8	Retro registry analysis	Cincinatti Tumour transplant registry		7 (88%)	7 (88%)	
Chapman, 2001 TProc [12]	4	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated Timing not stated	0 (0%)	Not stated This report identifies timing of initial Ca diagnosis (in relation to dialysis start) as the important prognostic factor	

Table 9. Characteristics of included studies- Non-Melanoma Skin Cancers

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev Non-Melanoma Skin Ca)	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	79	Retrospective registry analysis	Cincinatti Tumour transplant registry	79 Numbers of SCC, BCC etc. not.	49 (62%) time post Rx 30 (61%) at <24 mths, 17 (35%) 2-5 y ptx 2 (4%) >5y ptx	1 (1.2%)	

Table 10. Characteristics of included studies- Prostate tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev Prostate Ca)	Treatment Time before Transplant	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	38	Retrospective registry analysis	Cincinatti Tumour transplant registry	Prior prostate Ca 21	No cancer recurrence seen in 7 (33%) treated 2-5y ptx	5 pt (24%) Rx 2 at <24 mths, 3 from 37-50 mths ptx	1 (5%)	?Not related to wait
Gupta, 2003 Abstract [17]	90 77 renal	Retrospective registry analysis	Cincinatti Tumour transplant registry	Prior prostate Ca 77 kidney	54 <2 yrs ptx 24 2-5y ptx 12 >5y ptx	Overall 16 (18%)	7 (7.8%) median f/u 20.5 mths	Recurrence appears related to stage I, II, III not related to wait?
Chapman, 2001 TProc [12]	5	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	1 (20%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor		

Table 11. Characteristics of included studies- renal tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev Renal Cancer	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	59	Retro registry analysis	Cincinatti Tumour transplant registry	Incidentally discovered RCC 21 removed at Tx 30 removed <2yrs pre-Tx 8 removed 26-56 months pre-Tx	0 (0%)	0 (0%)	

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Penn, 1993 [3]	169	Retro registry analysis	Cincinatti Tumour transplant registry	Symptomatic renal tumours 152 RCCs 1 oncocytoma 16 renal pelvis – 10 TCCs, 1 SCC, 5 unknown 63 (37%) had bilat lesions – 12 had von Hippel-Lindau	51 (30%) 31 (61%) Rx <2y 17 (33%) Rx 2-5y 3 (6%) Rx >5y 31 (61%) had bilat lesions pre-Tx	39 (23%) or 76% of those with a recurrence	
Merrifield, ICB abstract 2009 [10]	99	Retro registry analysis	ANZDATA (1963-2007)	Median wait ptx post Rx 5.1 (2.6-10.5) IQR	Not stated	Median pt survival post Tx 12.4yrs (9.1-18.9) 95% CI cf No cancer 16 (15.7-16.5)	
Chapman, 2001 TProc [12]	37	Retro registry analysis	ANZDATA 1963-1999	Subtype not stated	2 (5.4%)	Not stated This report identifies timing of initial Ca diagnosis as the important prognostic factor	
Birkeland, 1982 [22]	10	Retro registry analysis	Scandinavia 1956-1978	10 in toto 6 Unilateral renal 3 Renal pelvis 1 bilateral	5 (50%) At least five but no more than 8 i.e. not stated but they did say 2 had not recurrence during fu period	5 (50%) All received Tx <12mths post diagnosis of Ca	1mth-7 yrs fu post diagnosis 1mth-2yrs fu post Tx

Table 12. Characteristics of included studies- Sarcoma

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with Sarcomar prev	Treatment Time before Transplant	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	16	Retrospective registry analysis	Cincinatti Tumour transplant registry	5 Osteosarcoma 3 Ewing's 3 fibrosarcoma 2 Kaposi's 2 leiomyosarcoma	2 of 16 treated post-transplantation Regarding 4 recurrences of 14	4 (29%)	2 (14%)	

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				1 angiomyo-liposarcoma	2 at <24 mths, ptx 1 2-5 y ptx 1 >5y ptx Of the 10 with no recurrence 0 at <24 mths, ptx 4 2-5 y ptx 6 >5y ptx			
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Table 13. Characteristics of included studies- testicular tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev testicular Ca	Treatment Time before Transplant	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	34	Retrospective registry analysis	Cincinatti Tumour transplant registry	Prior testicular tumour 2 bilat 16 seminomas 9 teratomas 7 embryomas 2 unclassified 1 choriocarcinoma 7 with mets	7 (21%) <2 yrs ptx 9 (26%) 2-5yrs ptx 18 (53%) >5y ptx	1pt (3%) Pt had orchiectomy at time of tp, recurrence in other testis	0 (0%)	
Merchen, 2003 [19] Abstract	26	Retrospective registry analysis	Cincinatti Tumour transplant registry	12 seminomas 9 nonseminomas 5 unknown	Mean time from Rx 151.3 months	3 (11.5%) overall 2pt (17%) with seminomas 1 (11%)pt with nonseminoma	2 (8%) overall 1seminoma, 1 nonseminoma	

Table 14. Characteristics of included studies- thyroid tumours

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev thyroid tumours	Treatment Time before Transplant	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	39	Retrospective registry analysis	Cincinatti Tumour transplant registry	Prior thyroid tumour 23 papillary 7 follicular 6 unclassified 6 incidentally found with parathyroidectomy.	18 (46%) <2 yrs ptx 7 (18%) 2-5yrs ptx 14 (36%) >5y ptx	3 pt (8%) Rx 1 week, 26 months and 96.5 months prior	1 (3%)	
Gupta, 2003 Abstract [20]	27	Retrospective registry analysis	Cincinatti Tumour transplant registry	15 papillary 3 follicular 9 unknown Nodes +ve in 4 (2 papillary, 2 follicular)	Median time from Rx 40.1 months (0.8-415.3)	2 (7.4%) overall	1 (3.2%) overall	Mainly (20) caucasian

Table 15. Characteristics of included studies- Uterus

Study ID (author, year)	N	Study Design	Setting	Interest group RTRs with prev cancer of the uterus	Treatment Time before Transplant	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	19	Retrospective registry analysis	Cincinatti Tumour transplant registry	Prior uterine Ca	8 (42%) <2 yrs ptx 5 (26%) 2-5yrs ptx 6 (30%) >5y ptx	2 pt (11%) Rx 36 and 60 months ptx	2 (11%)	

Table 16. Characteristics of included studies- Wilms tumour

Study ID (author, year)	N	Study Design	Setting	Interest group – RTRs with prev Wilms	Recurrence Rate	Deaths from Recurrence	Comments
Penn, 1993 [3]	61	Retros registry analysis	Cincinnati Tumour transplant registry	57% bilateral 41 (67%) <6y ptx 20 (33%) >6y ptx	10 pt (16%) Rx <24 mths except one at 28 mths	8 (13%)	
Belzer, TP 1972 [24]	5	Single Centre	Case studies. University of California.	3 simultaneous Tx with nephrectomy The other 2 >8 months	1 (20%) at 16 months		Follow-up 5-42 mths