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Platinum Priority – Review – Renal Disease

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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

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Abstract

Context: Renal transplantation is the gold standard renal replacement therapy in end-stage renal disease owing to its superior survival and quality of life compared with dialysis. When the potential recipient has a history of cancer, the waiting period before renal transplantation is usually based on the Cincinnati Registry.
Objective: To systematically review all available evidence on the risk of cancer recurrence in end-stage renal disease patients with a history of urological cancer.
Evidence acquisition: Medline, Embase, and the Cochrane Library were searched up to March 2017 for all relevant publications reporting oncologic outcomes of urological cancer in patients who subsequently received a transplantation or remained on dialysis. The primary outcome was time to tumour recurrence. Secondary outcomes included cancer-specific and overall survival. Data were narratively synthesised in light of methodological and clinical heterogeneity. The risk of bias of each included study was assessed.
Evidence synthesis: Thirty-two retrospective studies enrolling 2519 patients (1733 dialysed, 786 renal transplantation) were included. For renal cell carcinomas, the risks of recurrence, cancer-specific, and overall survival were similar between transplantation and dialysis. For prostate cancer, most of the tumours had favourable prognoses consistent with nomograms. Studies dealing with urothelial carcinomas (UCs) mainly included upper urinary tract UC in the context of aristolochic acid nephropathy, for which the risks of synchronous bilateral tumour and recurrence were high. Data on testicular cancer were scarce.
Conclusions: Immunosuppression after renal transplantation does not affect the outcomes and natural history of low-risk renal cell carcinomas and prostate cancer. Therefore, the waiting time from successful treatment for these cancers to

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transplantation could be reduced. Except in the particular situation of aristolochic acid nephropathy, more studies are needed to standardise the waiting period after UC owing to the paucity of data.

Patient summary: Renal transplantation does not appear to increase the risk of recurrence of renal carcinoma or the recurrence of low-risk prostate cancer compared with dialysis. More reliable evidence is required to recommend a standard waiting period especially for urothelial and testicular carcinomas.

1. Introduction

Renal transplantation is the gold standard renal replacement therapy in end-stage renal disease (ESRD) owing to its superior survival and quality of life compared with other replacement therapies [1,2].

The standard procedure for transplantation candidates includes systematic screening for the presence of any active/latent cancer or a history of cancer [3]. In transplantation candidates with a previous history of urological cancer, it can be challenging to decide if patients are suitable for transplantation and if so how long the waiting period prior to transplantation should be. So far, the clinical decision has been mainly based on the Cincinnati Registry, which essentially considers the type of tumour and the time between its treatment and kidney transplantation [4]. The waiting period varies from less than 2 yr to at least 5 yr according to the Registry. However, the Cincinnati Registry has several deficiencies: (1) the treatment and the staging of the disease are not defined, (2) the epidemiology of tumours, (3) the diagnostic and therapeutic procedures/tests have changed, and (4) the prognostic tools have improved.

The objective of this systematic review was to appraise all available evidence on the risk of cancer recurrence in ESRD patients who underwent transplantation after having been successfully treated for a urological cancer. The primary objectives were to determine in patients with chronic kidney disease (CKD) 4/5 and a history of urological cancer, the risk of tumour recurrence after transplantation compared with renal replacement therapy (peritoneal and haemodialysis). The secondary objectives were to report on the overall and cancer-specific survival of transplanted and nontransplanted patients with a history of malignancy and to determine for each urological cancer the minimum tumour-free waiting period prior to transplantation.

2. Evidence acquisition

2.1. Data sources and searches

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [5]. The systematic review protocol was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016046867). Studies (January 1, 1995, to March 1, 2016) were identified by highly sensitive searches of electronic databases (Medline, Embase, Cochrane library databases). The initial literature search was performed in February 2016 and an updated search performed in March 2017. The search was complimented by additional sources including the reference lists of included studies. The search strategy is described in detail in Supplementary data.

2.2. Study selection

There was no restriction on types of study design. All randomised control studies, nonrandomised comparative studies, and noncomparative studies (single-arm cohort studies, case reports), and meta-analyses published in the English language were included.

2.3. Types of participants

The study population was adults ($\geq$ 18 yr) with CKD 4/5 and previous urological cancer under renal replacement therapy or who subsequently underwent renal transplantation.

2.4. Data collection and data extraction

Following deduplication of abstracts, two reviewers (R.B. and V.H.) screened all abstracts and full-text articles independently. Disagreement was resolved by a third party (M.B.). References cited in all full-text articles were also assessed for additional relevant articles. A standardised data-extraction form was developed a priori to collect information on study design, patient characteristics (sex and age, type of urological cancer, baseline risk of tumour recurrence [based on stage, grade, histology, or risk stratification using nomograms or risk groups]), interventions (duration of dialysis before cancer treatment, type and duration of immunosuppressive regimens, duration of tumour-free period prior to transplantation), and outcome measures (cancer recurrence, cancer-specific, and overall survival).

2.5. Risk of bias assessment

Two reviewers (R.B. and V.H.) independently assessed the risk of bias (RoB) of each included study any discrepancies were revolved by a third reviewer (M.B.). The Cochrane RoB tool was used for RoB assessment. For nonrandomised studies, the tool was modified to include an additional domain to assess the risk of confounding bias. A list of five important potential confounders was developed a priori with clinical content experts (European Association of Urology Renal Transplantation Guidelines Panel) [6,7]. The confounders included were: (1) type of urological cancer, (2) baseline

risk of tumour recurrence, (3) means of diagnosis of tumour recurrence, (4) duration of free period prior to transplantation, and (5) tumour-free status prior to transplantation. For each study, it was assessed whether each confounder was considered and whether, if necessary, the confounder was controlled in analysis. The RoB was considered to be high if the confounder had not been considered, was imbalanced between patients or not corrected for during analysis. This approach is detailed in the study protocol (PROSPERO).

2.6. Data synthesis

Methodological and clinical heterogeneity of the included studies meant that meta-analysis was inappropriate, therefore, a narrative synthesis of the data was performed (https://www.york.ac.uk/crd/guidance/). The primary outcome was cancer recurrence at <1-yr, 1–5-yr, and >5-yr time points and is summarised in descriptive tables. Secondary outcomes were cancer-specific and the overall survival at <1-yr, 1–5-yr, and >5-yr time points. Possible reasons for heterogeneity were explored using the available information such as differences in the population studied, the treatment given, or the way in which the outcomes were assessed. Intended formal subgroup analysis was not possible due to the inclusion of nonrandomised comparative studies. Therefore, any subgroup differences were discussed narratively to explore potential effect size differences. A planned sensitivity analysis to assess the robustness of our review results by repeating the analysis only including studies with an overall medium to low RoB, was not possible.

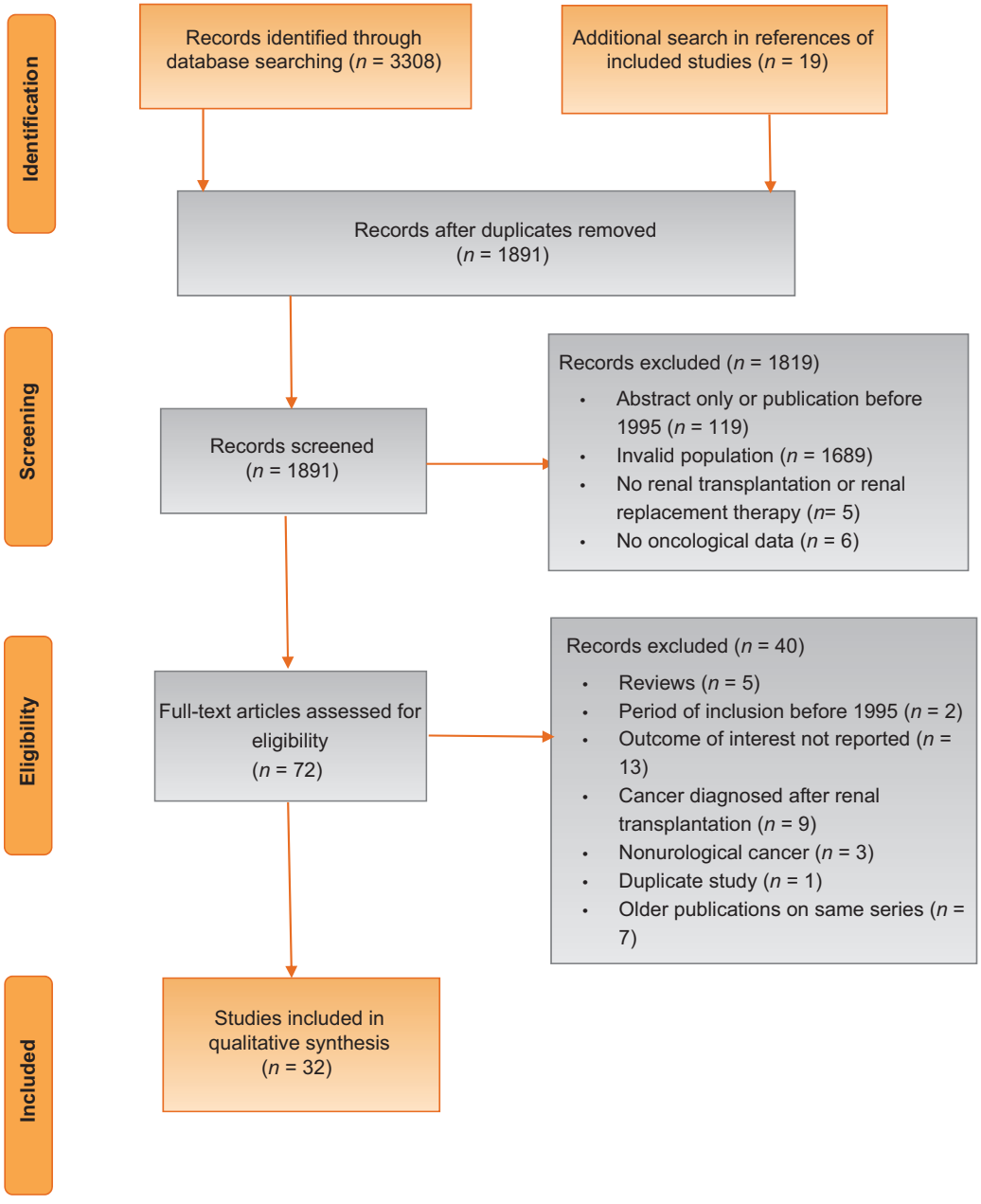

Fig. 1 – Preferred reporting items for systematic reviews and meta-analyses flow chart.

3. Evidence synthesis

3.1. Quality of the studies

A total of 1891 studies were identified by the literature search and two reviewers screened all study abstracts independently. Of these, 53 studies were selected for full-text screening and 20 studies were eligible for inclusion. After an additional search in the references of these 20 studies and the elimination of duplicates with the selection of the most up-to-date publication for each series, 32 studies (4 retrospective comparative studies, 21 retrospective noncomparative studies, and 7 case reports) were eligible for inclusion (Fig. 1). The quality of studies was assessed as described above. RoB is summarised in Figure 2. Overall, there was a low RoB across all studies. Study design was retrospective for all studies.

3.2. Characteristics of studies, population, and interventions (Tables 1–4)

In total, 2519 patients were included, suffering from: (1) renal cell carcinoma (RCC; $n = 1810$, 72%), prostate cancer (PC; $n = 213$, 8%), upper urinary tract carcinoma/bladder cancer (UUTUC; $n = 451$, 18%), and testicular cancer (TC; $n = 45$, 2%). The time on dialysis before cancer treatment ranged from 1 mo to 14 yr. Among these patients with a history of urological cancer, 1733 (69%) remained on dialysis, while 786 (31%) had a transplantation with a waiting period ranging from 0 yr to >5 yr. Tables 1–4

3.3. Oncological outcomes

3.3.1. Real cell carcinoma

Seventeen included studies evaluated patients suffering from RCC (Table 5). Mean age at diagnosis ranged from 37 yr

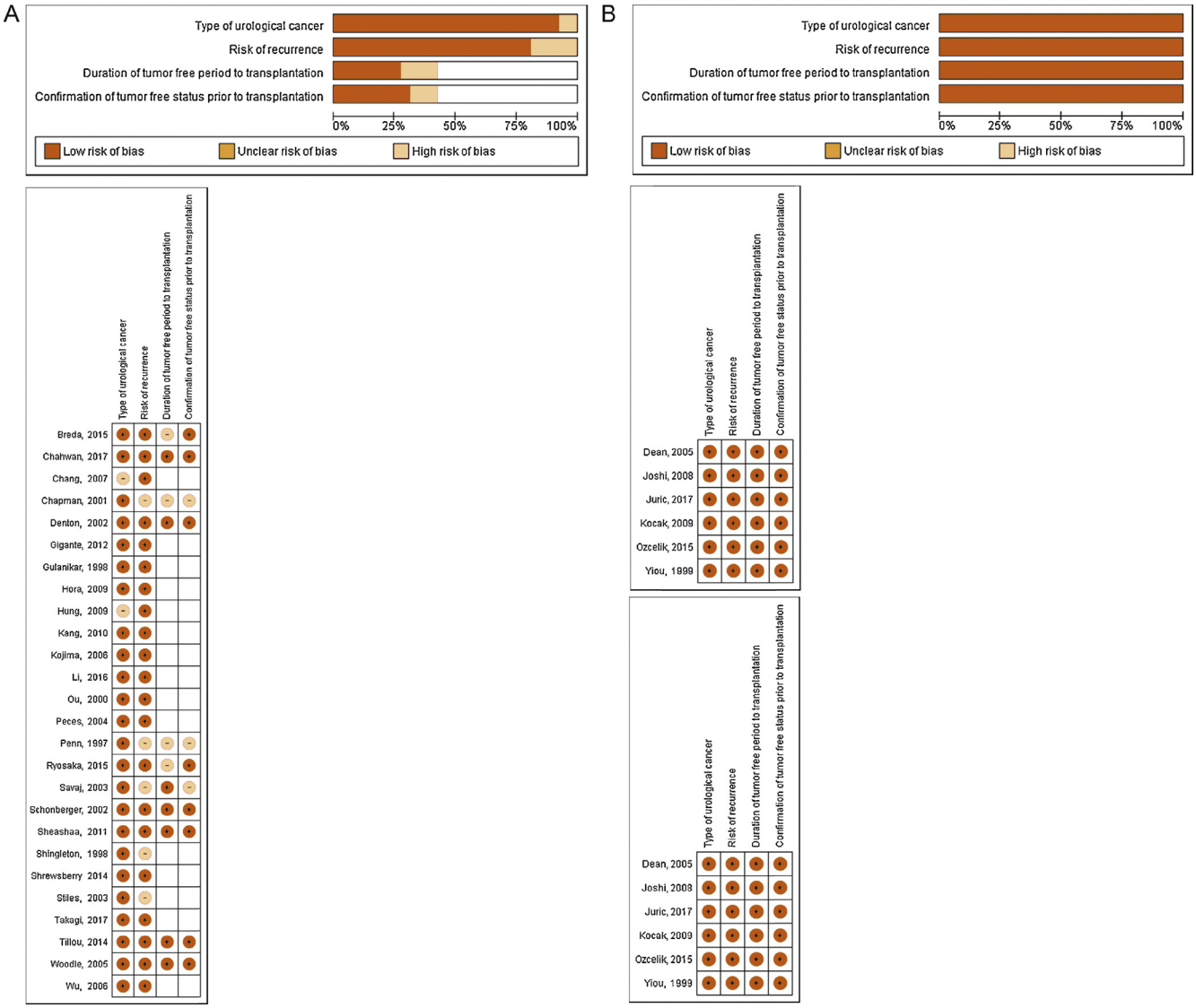

Fig. 2 – Evaluation of the risk of bias and confounders. (A) Bias and confounders for retrospective cohort studies. (B) Bias and confounders for case reports. Blank domains stand for "not relevant" and concerns studies with no intervention (transplantation) arm.

Table 1 – Characteristics of the included studies: kidney cancer

Study (1st author, yr)	Study type	Recruitment period	Mean age (yr)	Mean follow-up from cancer treatment, yr (range or SD)	No. of patients		Duration of dialysis before cancer treatment, yr (mean, range, or SD)
					Transplantation	Dialysis	
Ryosaka, 2015 [27]	Retrospective cohort study	2000–2013	56 ± 11	3.75 ± 3.5	44	158	14.2 ± 8
Chapman, 2001 [46]	Retrospective cohort study	1963–1999	NS	NS	37	73	NS
Savaj, 2003 [28]	Retrospective cohort study	1997–2002	52	NS	2	6	5.1
Penn, 1997[a] [4]	Retrospective cohort study	<1997	NS	>5	274	0	NS
Breda, 2015 [14]	Retrospective cohort study	NS	58 (37–66)	7.52 (7.02–7.99)	58	0	4.0
Sheashaa, 2011 [23]	Retrospective cohort study	1997–2008	56 ± 14	4.7	12	0	1.8 (0.4–5) Median (min–max)
Denton, 2002 [24]	Retrospective cohort study	1994–2000	53 ± 6	2.6 ± 1.9	11	0	3.36 (0–10)
Joshi, 2008 [29]	Case report	2008	37	9	1	0	0.5
Takagi, 2017 [30]	Retrospective cohort study	1982–2015	56 ± 11	4.8 ± 4.7	0	467	14.3 ± 9
Stiles, 2003 [35]	Retrospective cohort study	1995–1990	61	2.12	0	404	NS
Shrewsberry, 2014 [31]	Retrospective cohort study	1999–2001	56 ± 13	NS	0	95	4.5
Gigante, 2012 [16]	Retrospective cohort study	1985–2009	61 ± 14	NS	0	90	6.8 ± 6.6
Kojima, 2006 [33]	Retrospective cohort study	1993–2004	55 ± 11	3.9 (0.5–10)	0	44	11.2 ± 7.2
Hora, 2009 [32]	Retrospective cohort study	2002–2006	54 ± 10	1.6 (0.3–4.5)	0	14	6.5 (0–12.8)
Peces, 2004[b] [34]	Retrospective cohort study	1982–2001	60 ± 11	3.5 (0–20)	0	8	5.0 ± 3.9
Gulanikar, 1998 [36]	Retrospective cohort study	1995–1997	37	1.2 (0.4–2.75)	0	8	6
Shingleton, 1998 [37]	Retrospective cohort study	1984–1994	42.3	(1–9)	0	4	3

max = maximum; min = minimum; NS = not stated; SD = standard deviation.
[a] Update of Penn.
[b] 1995 update of Peces 2001.

Table 2 – Characteristics of the included studies: prostate cancer

Study (1st author, yr)	Study type	Recruitment period	Mean age (yr)	Mean follow-up from cancer treatment, yr (range or SD)	No. of patients		Duration of dialysis before cancer treatment, yr (mean, range, or SD)
					Transplantation	Dialysis	
Tillou, 2014 [25]	Retrospective cohort study	2003–2013	62	3.2 (0.5–6.5)	14	5	NS
Chapman, 2001 [46]	Retrospective cohort study	1963–1999	NS	NS	5	42	NS
Woodle, 2005[a] [9]	Retrospective cohort study	NS	61	3.32 (1.7–15.2)	90[b]	0	NS
Chahwan, 2017 [38]	Retrospective cohort study	1993–2015	59.8 (45.6–72.9)	3	52	0	NS
Schonberger, 2002 [39]	Case report	NS	62	4	1	1	NS
Ozcelik, 2015 [40]	Case report	2015	63	1.5	1	0	NS
Kocak, 2009 [41]	Case report	2009–2010	57	0.5	1	0	NS
Yiou, 1999 [26]	Case report	1999	69	4.5	1	0	NS

NS = not stated; SD = standard deviation.
[a] Woodle 2005 is the last update of the prostate cancer cancer cohort of Penn 1997.
[b] 77 renal, 10 heart, 3 liver transplantations.

Table 3 – Characteristics of the included studies: urothelial carcinoma

Study (1st author, yr)	Study type	Recruitment period	Mean age (yr)	Mean follow-up from cancer treatment, yr (range or SD)	No. of patients		Duration of dialysis before cancer treatment, yr (mean, range, or SD)
					Transplantation	Dialysis	
Chapman, 2001 [46]	Retrospective cohort study	1963–1999	NS	NS	24	93	NS
Penn, 1997[a] [4]	Retrospective cohort study	<1997	NS	>5	55	0	NS
Hung, 2009 [43]	Retrospective cohort study	1994–2006	67.6	12.6	46	0	NS
Chang, 2007 [42]	Retrospective cohort study	1993–2002	57.5	1.6	12	0	3.87 (0.25–9)
Kang, 2010[b] [21]	Retrospective cohort study	1992–2001	61	5 (2.6–10.2)	0	77	1.6 (0.08–14)
Li, 2016 [44]	Retrospective cohort study	2008–2010	66.4	5.25 (4–7)	0	72	NS
Wu, 2006[c] [20]	Retrospective cohort study	1996–2002	60	2.5	0	55	2.25 (0.5–11)
Ou, 2000 [45]	Retrospective cohort study	1987–1997	61.1	NS	0	17	3.2 (0.2–12)

NS = not stated; SD = standard deviation.
[a] Update of Penn, 1995.
[b] Update of Kang, 2004.
[c] Update of Wu, 2004.

Table 4 – Characteristics of the included studies: testis cancer

Study (1st author, yr)	Study type	Recruitment period	Mean age (yr)	Mean follow-up from cancer treatment, yr (range or SD)	No. of patients		Duration of dialysis before cancer treatment, yr (mean, range, or SD)
					Transplantation	Dialysis	
Penn, 1997[a] [4]	Retrospective cohort study	<1997	NS	>5	43	0	NS
Dean, 2005 [8]	Case report	2005	53	4.3	1	0	NS
Juric, 2017 [47]	Case report	1995	24	21.5	1	0	4

NS = not stated; SD = standard deviation.
[a] Update of Penn, 1995.

to 57 yr. The primary treatment was radical nephrectomy. Mean follow-up after nephrectomy was 3.6 yr (ranging from 1.2 yr to 10.0 yr). The mean waiting period before transplantation ranged from 0 yr to 10 yr. The recurrence rates for transplanted versus dialysed patients at <1 yr, 1–5 yr, and >5 yr were 0–8% versus 0%, 0–27% versus 0–9% and 0–41% versus 0–48%, respectively. The 5-yr cancer-specific survival rates for transplantation versus dialysed patients were 79–100% versus 77–100%, respectively. Overall 5-yr survival rates for transplantation versus dialysed patients were 80–100% versus 76–100%, respectively.

3.3.2. *Prostate cancer*

Eight included studies evaluated patients suffering from PC (Table 6). Mean age at diagnosis ranged from 57 yr to 69 yr. Treatments were prostatectomy alone (61%), prostatectomy + adjuvant radiotherapy (13%), external beam radiotherapy (10%), brachytherapy (1%), and androgen deprivation therapy (7%). The type of treatment was not specified in 8%. Average follow-up after treatment ranged from 0.5 yr to 4 yr. The mean interval between cancer treatment and transplantation ranged from 3 mo to 4 yr. Recurrence rates for transplantation patients at <1 yr and >5 yr were 0–9% and 4–20%, respectively. The 1–5-yr cancer-specific survival rates for transplantation patients ranged from 96% to 100%. Overall, 1–5-yr survival rates for transplantation patients ranged from 62% to 100%. No study reported results with a median follow-up beyond 5 yr.

3.3.3. *Urothelial carcinoma: bladder cancer and upper urinary tract urothelial carcinoma*

Nine studies evaluated patients suffering from urothelial carcinoma (Table 7). Mean age on diagnosis ranged from 37 yr to 66 yr. The treatments performed for UUTUC ranged from unilateral or bilateral nephroureterectomy to complete exenteration of the urinary tract. Bladder tumours were treated with endoscopic resection or cystectomy. Mean follow-up after treatment was 1.6 yr to 9 yr. The interval between cancer treatment and transplantation was specified in one case report: 6 yr.

Table 5 – Oncological outcomes of included patients with a history of renal carcinoma: renal transplantation (I) versus renal replacement therapy (C)

Study (1st author, yr)	No. of nephrectomies	Arms (Nb)	Oncological outcomes				Histological outcomes			Follow-up[a] (yr)	Free time to transplantation (yr)	Recommendations concerning waiting period & prognostic factors of recurrence, according to authors of the included studies
			Cancer recurrence		Cancer specific survival (time)	Overall survival (time)	Stage (%)	Grade (%)	Histologic subtype (%)			
			≤5 yr	>5 yr								
Ryosaka, 2015 [27]	70 Solid tumours	I (17)	24%	41%	79% (> 5 yr)	80% (> 5 yr)	pT1 84% pT2–3 16%	Low 87% High 13%	CRCC 77% PRCC 17% Others 6%	3.8 ± 3.6	2	- No waiting period if history of cystic RCC - Waiting period if history of solid RCC - Prognostic factors of recurrence: - Tumour stage - Fuhrman grade
		C (53)	0%	0%	100% (> 5 yr)	83% (> 5 yr)						
	132 Cystic tumours	I (27)	0%	0%	100% (> 5 yr)	100% (> 5 yr)	pT1 93% pT2–3 7%	Low 92% High 8%	CRCC 76% PRCC 22% Others 2%	5.7 ± 3.8	2	
		C (105)	2%	10%	96% (> 5 yr)	80% (> 5 yr)						
Savaj, 2003 [28]	8	I (2)	NS	NS	100% (1–5 yr)	100% (1–5 yr)	pT1 88% pT2 12%	NS	CRCC 63% PRCC 37%	10 ± 7.4	4.3	
		C (6)	NS	NS	100% (1 –5 yr)	83% (1–5 yr)						
Chapman, 2001 [46]	110	I (37)	NS	5.4%	NS	NS	NS	NS	NS	5	NS	- Prognostic factor of recurrence: - Diagnosis of cancer while on dialysis vs before dialysis - Waiting period: - >2 yr - >5 yr if cancer diagnosed while on dialysis
		C (73)	NS	18%	NS	NS						
Takagi, 2017 [30]	467	C (467)	NS	NS	84% (5 yr)	76% (5 yr)	pT1–2 88% pT3 5% pT4 6%	NS	CRCC 11% PRCC 77% Others 2%	4.8 ± 4.7	NR	- Prognostic factors of cancer specific survival: - Tumour stage - Fuhrman grade
Breda, 2015 [14]	58	I (58)	NS	NS	95% (> 5 yr)	NS	pT1 84% pT2-3 16%, N+ 1.7% M+ 1.7%	Low 77% High 23%	CRCC 79% PRCC 17% ChRCC 4%	7.5 (7–10)	NS	- Prognostic factors of cancer specific survival: - Tumour size (HR 1.10) - Tumour stage (HR 1.46) - Node invasion (HR 2.22) - Visceral metastases (HR 3.49) - Fuhrman grade (HR 1.48)
Penn, 1997 [4]	71 Incidental tumours	I (71)	1%	NS	100% (1–5 yr)	NS	NS	NS	NS	5.75 (0–19)	1.1	- Waiting period: - 5 yr for large (> 5 cm) symptomatic RCC - 2 yr for small (< 5 cm) symptomatic RCC - 0–2 yr for incidental RCC - Prognostic factor of recurrence: - Symptomatic vs incidental RCC - Tumour stage (size)
	203 Symptomatic tumours	I (203)	27%	NS	78% (1–5 yr)	NS	NS	NS	NS	3.83 (0–19)		
Joshi, 2008 [29]	1	I (1)	NS	NS	100% (> 5 yr)	100% (> 5 yr)	pT2b 100%	NS	NS	9	10	
Sheashaa, 2011 [23]	12	I (12)	25%	NS	NS	95% (> 5 yr)	pT1a 100%	Low 83% High 17%	CRCC 75% PRCC 17% ChRCC 8%	4.7	0	

Table 5 (*Continued*)

Study (1st author, yr)	No. of nephrectomies	Arms (Nb)	Oncological outcomes				Histological outcomes			Follow-up[a] (yr)	Free time to transplantation (yr)	Recommendations concerning waiting period & prognostic factors of recurrence, according to authors of the included studies
			Cancer recurrence		Cancer specific survival (time)	Overall survival (time)	Stage (%)	Grade (%)	Histologic subtype (%)			
			≤5 yr	>5 yr								
Denton, 2002 [24]	11	I (11)	0%	NS	100% (1–5 yr)	100% (1–5 yr)	pT1N0M0 100%	Low 63% High 37%	CRCC 60% PRCC 45% ChRCC 9%	2.6 ± 1.9	0	- Waiting period: - No waiting period for low T stage and low grade RCC - 36% of contralateral tumour on postoperative imagery
Shingleton, 1998 [37]	4	C (4)	0%	0%	100% (> 5 yr)	86% (1–5 yr)	pT1 100%	NS	CRCC 50% PRCC 50%	(1–9)	NS	
Kojima, 2006 [33]	44	C (44)	9%	NS	98% (1–5 yr)	98% (1–5 yr)	pT1 97.7% pT2 2.3% N1 2.3%	Low 100%	CRCC 84% PRCC 8% ChRCC 8%	3.9 (0.5–10)	NR	- Prognostic factor of recurrence: tumour stage - 9% of recurrence even with pT1–2 low grade
Shrewsberry, 2014 [31]	95	C (95)	3%	12%	88% (1-5 yr)	74% (1–5 yr)	pT1 82% pT2 4% pT3 9% N+ 6%	Low 51% High 49%	CRCC 65% PRCC 32% ChRCC 2% ColDRCC 1%	1.9	NR	- Prognostic factor of recurrence: - Clear cell subtype - Lymphovascular invasion
Gigante, 2012 [16]	303	C (90)	NS	48%	77% (> 5 yr)	NS	pT1-2 86% pT3–4 15% N1 6%	Low 66% High 34%	CRCC 77% PRCC 22% ChRCC 1%	3 (0.1–23)	NR	- Prognostic factor of cancer specific death: - T stage
Hora, 2009 [32]	19	C (14)	0%	NS	93% (1–5 yr)	86% (1–5 yr)	pT1 84% pT3a 11% pT3aN2 5%	NS	CRCC 68% PRCC 22% Liposarcoma 5%	1.6 (0.3–4.5)	NR	- 21% combination of CRCC and PRCC - Do not recommend systematic contralateral nephrectomy before transplantation
Peces, 2004 [34]	8	C (8)	0%	NS	75% (1–5 yr)	75% (1–5 yr)	pT1-2 75% pT3N0 12% pT3M1 12%	Low 88% High 12%	CRCC 63% PRCC 37%	3.5 (0–20)	NR	- Prognosis of time under dialysis on histological outcomes: - Multifocal tumour - PRCC
Stiles, 2003 [35]	404	C (404)	NS	NS	NS	12% (1-5years)	NS	NS	NS	2.1 ± 1.2	NR	- Patients with CKD/dialysis owing to nephrectomy for RCC had the same survival as patients under dialysis for other reason (diabetes)
Gulanikar, 1998 [36]	8	C (8)	0%	NS	100% (1-5years)	100% (1-5years)	pT1a 100%	NS	CRCC 14% PRCC 88%	1.2 (0.4–2.8)	NR	- 25% of bilateral RCC -Do not recommend systematic contralateral nephrectomy before transplantation

C = control (dialysis); ChRCC = chromophobe renal cell carcinoma; CKD = chronic kidney disease; CRCC = clear renal cell carcinoma; ColDRCC = collecting duct renal cell carcinoma; HR = hazard ratio; I = intervention (renal transplantation); N = not stated; NR = not relevant (for noncomparative studies with one control arm); PRCC = papillary renal cell carcinoma.

[a] From cancer treatment to last news.

Table 6 – Oncological outcomes of included patients with a history of prostate cancer: renal transplantation (I) versus renal replacement therapy (C)

Study (1st author, yr)	Primary management	Arms (no. of patients)	Oncological outcomes						Histological outcome and prognosis (pTNM and/or nomogram)	Follow-up[a] (yr)	Free time to transplantation (yr)	Recommendations concerning waiting period & prognostic factors of recurrence, according to authors of the included studies
			Cancer recurrence		Cancer-specific survival		Overall survival					
			≤5 years	>5 years	≤5 years	>5 years	≤5 years	>5 years				
Tillou, 2014 [25]	16 Prostatectomy 3 Prostatectomy + adjuvant EBRT	I (14)	0%	NS	100%	NS	100%	NS	D'Amico: Low risk 53%, intermediate 43% 10-yr progression without recurrence MSKCC 97% (mean)	3.2	2.7	Waiting period among D'Amico classification: - 1 yr for low risk - 2 yr for intermediate risk - 5 yr for high risk
		C (5)	0%	NS	100%	NS	100%	NS				
Schonberger, 2002 [39]	2 Prostatectomy	I (1)	0%	NS	100%	NS	100%	NS	pT2 R0	4.0	4	Prognostic factor of recurrence: stage T Waiting period: at least 2 yr for organ confined disease
		C (1)	0%	NS	100%	NS	100%	NS				
Woodle, 2005 [9]	55 Prostatectomy 13 Prostatectomy + Adjuvant EBRT 12 Hormonotherapy 14 Radiotherapy 10 Unknown Rx	I (90)	NS	NS	96%	NS	62%	NS	Stage I 38% Stage II 49% Stage III 12%	3.3	1.6	Prognostic factor of recurrence: - Stage - Initial PSA Waiting period: - 2 yr for stage I/II or low Gleason score - 5 yr for stage III or high Gleason score
Chahwan, 2017 [38]	35 Prostatectomy, 8 Prostatectomy + adjuvant EBRT (5 positive margins, 3 pT3a) 4 EBRT 2 brachytherapy	I (52)	0%	4%	100%	NS	100%	NS	D'Amico: Low risk 52% Intermediate 46% High 2%	3	2.1 for D'Amico low risk 3.6 for D'Amico intermediate/ high risk	Waiting period: - 1 yr for D'Amico low risk - 2 yr for D'Amico intermediate risk - 5 yr for D'Amico high risk
Chapman, 2001 [46]	NS	I (5)	NS	20%	NS	NS	NS	NS	NS	NS	NS	-Prognostic factor of recurrence: - Diagnosis of cancer while on dialysis vs before dialysis - Waiting period: - >2 yr - >5 yr if cancer diagnosed while on dialysis
Kocak, 2009 [41]	1 Prostatectomy (case report)	I (1)	NS	NS	100%	NS	100%	NS	D'Amico Low risk Partin OC 84%, EC15%, SV 1%, N0%	0.5	0.3	Waiting period: - No waiting period for low-risk cancer - Consider Kattan nomogram
Ozcelik, 2015 [40]	1 Prostatectomy (case report)	I (1)	0%	NS	100%	NS	100%	NS	D'Amico low risk Partin OC 90%, EP 5%, vs 1%, N 1%	1.5	0.3	Waiting period: - No waiting period for low-risk cancer
Yiou, 1999 [26]	1 Prostatectomy (case report)	I (1)	NS	NS	100%	NS	100%	NS	D'Amico high risk pT2G7 (3 + 4) N0R0	4.5	4.0	

C = control; EP = extraprostatic; I = intervention; N = node invasion; NS = not stated; OC = organ confined; SV = seminal vesicle.

[a] From cancer treatment to last news.

Table 7 – Oncological outcomes of included patients with a history of urothelial carcinoma: renal transplantation (I) versus renal replacement therapy (C)

Study (1st author, yr)	Primary management	Arms (no. of patients)	Oncological outcomes				Histological outcomes			Follow-up[a] (yr)	Recommendations concerning waiting period & prognostic factors of recurrence, according to authors of the included studies
			Cancer recurrence		Cancer specific survival	Overall survival	Location	Stage	Grade		
			≤5 yr	>5 yr							
Chapman, 2001 [46]	NS	I (24)	NS	4.2%	NS	NS	NS	NS	NS	NS	-Prognostic factor of recurrence: - Diagnosis of cancer while on dialysis vs before dialysis - Waiting period: - >2 yr - >5 yr if cancer diagnosed while on dialysis
		C (93)	NS	24%	NS	NS					
Penn, 1997 [4]	NS	I (55)	NS	29%	NS	NS	NS	NS	NS	>5	- Bladder cancer = high risk of recurrence - Waiting period: - 2 yr for low-grade bladder cancer - >5 yr for high-grade bladder cancer
Joshi, 2008 [29]	1 TURB	I (1)	0%	0%	100% (> 5 yr)	100% (> 5 yr)	Bladder 100%	T1 100%	G2 100%	9	
Chang, 2007 [42]	8 NUT 4 NUT + TURB	I (12)	NS	NS	96% (1–5 yr)	79% (1–5 yr)	Bladder 65% Ureter 42% Renal pelvis 15% Multifocal 27%	Ta 12% T1 69% T2 15% T4bN1M1 4%	G1 12% G2 73% G3 15%	1.6	- High rate of contralateral tumour - Do not recommend systematic contralateral NUT but close monitoring before transplantation
Hung, 2009 [43]	46 NUT	C (46)	NS	32%	98% (> 5 yr)	88% (> 5 yr)	Bladder 29% UUT 71% Multifocal 54%	T1–2 71% T3–4 29%	G1 9% G2–3 91%	12.6	
Kang, 2010 [21]	13 NUT 64 NUT + cystectomy	C (67)	NS	53%	96% (> 5 yr)	43% (> 5 yr)	UUT 100%	Ta/T1 56% T2 14% T3–4 30%	G1 17% G2 30% G3 53%	5 (5.6–10.2)	- Synchronous contralateral tumour 10% - Asynchronous bladder tumour 39% - Do not recommend systematic bilateral NUT before transplantation but close monitoring
Li, 2016 [44]	72 TURB + intravesical chemotherapy (BCG excluded)	C (72)	40%	57%	NS	60% (> 5 yr)	Bladder 100%	Ta 66% T1 34%	G1–2 31% G3–4 69%	5.2 (4–7)	
Ou, 2000 [45]	2 NUT 1 NUT + TURB 11 TURB	C (17)	50%	NS	92% (1–5 yr)	75% (1–5 yr)	Bladder + UUT	Stage 0/A 82% Stage B1 6% Unknown Stage 12%	NS	NS	
Wu, 2006 [20]	28 NUT unilateral 4 NUT bilateral 23 Urinary tract exenteration	C (55)	55%	NS	86% (> 5 yr)	86% (1–5 yr)	Bladder + UUT	Ta 46% T1 19% T2 12% T3 22% T4 1%	G1 5% G2 70% G3 25%	2.5	- Bilateral involvement 16% - Contralateral recurrence 31% - Propose: bilateral NUT for young patients and waiting period ≥ 2 yr before transplantation

C = control; I = intervention; NS = not stated; NUT = nephroureterectomy; TURB = transurethral bladder resection; UC = urothelial cancer; UUT = upper urinary tract.

[a] From cancer treatment to last news.

Table 8 – Oncological outcomes of included patients with a history of testicular cancer: renal transplantation (I) versus renal replacement therapy (C)

Study (1st author, yr)	Primary management	Arms (no. of patients)	Cancer recurrence		Cancer specific survival (time)	Overall survival (time)	Histological outcomes	Follow-up[a] (yr)	Free period to transplantation (yr)	Recommendations concerning waiting period & prognostic factors of recurrence, according to authors of the included studies
			≤5 yr	>5 yr						
Penn, 1997 [4]	NS	I (43)	NS	5%	NS	NS	NS	>5	NS	Low risk of recurrence Consider transplantation according to clinical, radiological, and biochemical criteria
Dean, 2005 [8]	1 Orchidectomy + adjuvant radiotherapy 20 Gy	I (1)	100%	NS	100% (1–5 yr)	100% (1–5 yr)	Seminoma stage I	4.3	2	Case-by-case discussion for waiting period before transplantation Transplantation did not interfere with chemotherapy for recurrence at 2.3 yr
Juric, 2017 [47]	1 Orchidectomy	I (1)	0%	100%	100% (> 5 yr)	100% (> 5 yr)	Teratoma	3.6	20	Retroperitoneal recurrence 8 × 4 cm (seminoma) treated by lymphadenectomy + adjuvant chemotherapy (cisplatine/etoposide). Free from recurrence with 2 yr of follow up.

C = control (dialysis); I = intervention; NR = not relevant; NS = not specified.
[a] From cancer treatment to last news.

Five-year recurrence rates for transplantation and dialysed patients were 4.2–29% versus 24–57%, respectively. Five-year cancer-specific survival rates and overall survival were 86–98% and 43–88%, respectively, for patients who remained on dialysis. Cancer-specific and overall survival rates were not reported for transplanted patients.

3.3.4. *Testicular cancer*

Three studies evaluated patients suffering from TC (Table 8) [4,8]. The 5-yr recurrence rate was 5%. The waiting period before transplantation was not defined. Histology and grade were specified only in two case reports: stage I seminoma and teratoma. Cancer-specific and overall survivals of 100% at 1–5 yr were reported in the two case reports.

3.4. *RoB and confounding*

The RoB and confounding was relevant, in particular in the light of the generally low level of evidence studies (Fig. 2). The type of urological malignancy and the risk of recurrence were taken into account in most of the studies. The duration of the tumour-free period to transplantation and the confirmation of a tumour-free status prior to transplantation were relevant only for the studies with an intervention arm (transplantation).2

4. Conclusions

4.1. *Principal findings*

For RCC, the risk of recurrence was similar between transplantation and dialysis. Stage, grade, histological subtype, and solid/cystic component of the tumour were the main prognostic factors for recurrence.

For PC, data were too scarce to reach a conclusion on the impact of transplantation on the risk of recurrence because the majority of the included studies were noncomparative and involved only transplanted patients. Except in the study of Woodle et al [9], which is the last update of the Cincinnati Registry, studies included mainly PC with favourable prognosis: low stage, low grade, and low recurrence rates consistent with nomograms (D'Amico, Partin, Kattan, Memorial Sloan Kettering Cancer Center) [9].

For urothelial carcinoma, the studies mainly included UUTUC in the context of aristolochic acid nephropathy. In this specific situation, the rate of synchronous bilateral tumour was 10–16% and the rate of contralateral recurrence was 31–39%. Data on bladder urothelial carcinoma and TC were scarce.

For TC, one case report highlighted the possibility of late recurrence (2.3 yr) even for a stage I seminoma.

4.2. *Findings in the context of existing evidence*

Organ transplantation is a risk factor of cancer recurrence especially for viral-induced cancers. However, this risk is modulated by the type of cancer and the type of transplant [10].

In a large cohort of solid organ transplant recipients (1970–2008), Brattström et al [11] reported a 30% increased mortality risk for recipients with a history of cancer. However, this risk was moderately increased for renal transplant recipients (hazard ratio:1.2%, 95%: 1.0–1.4, $p < 0.05$) and mainly concerned recipients of other organs (hazard ratio: 1.8).

An active cancer is a contraindication for transplantation and a patient with (except active surveillance for prostate cancer) a history of malignancy must be in remission before transplantation. Pretransplant evaluation includes a systematic search for subclinical active or latent tumours. For patients with a history of treated malignancy, the waiting period before transplantation varies from 2 yr to 5 yr after cancer treatment. These recommendations are based on the Israel Penn International Transplant Tumour Registry [4,9].

However, these studies from 10 yr ago now have several shortcomings and may no longer reflect the epidemiology of patients currently seen in pretransplantation evaluation. Several oncological data were missing: stage, histological subtype, grade, and type of treatment. For PC, the Penn [4] study essentially included T3 tumours diagnosed in the preprostate-specific antigen era. For RCC, the tumours were mainly large and symptomatic. For bladder tumours, the stage, grade, multifocality, type of adjuvant intravesical instillation, and the distinction between nonmuscle invasive and muscle invasive tumours were not reported.

4.2.1. Real cell carcinoma and chronic kidney disease

In this systematic review, the main histological subtype was clear cell RCC (53–79%), followed by tubulo-papillary RCC (17–50%). The tumours were mainly of low stage (78–100% of pT1), and/or low grade (51–92% grade I–II; Table 8).

RCC diagnosed in a context of CKD may have a better prognosis for several reasons. ESRD patients are often monitored more closely than the normal population, favouring early diagnosis with smaller size and lower grade. The main risk factor of RCC is acquired cystic kidney disease, which increases with the duration of dialysis [12]. RCC is more common for patients with CKD compared with the general population. The standardised incidence ratio of RCC in dialysis patients is 14–17 times higher than that in the general population [13]. The systematic review data were consistent with the current knowledge on RCC in CKD patients, reporting an increased prevalence of low-grade tumours (51–100%) and the papillary subtype (17–37%; Table 6) [14–16]. The duration of dialysis alters the histological spectrum of tumours: clear cell RCC is the predominant subtype for patients with short dialysis duration, papillary RCC being the predominant type in patients on dialysis for more than 4 yr [14].

4.2.2. Prostate cancer and chronic kidney disease

In this systematic review, the series included were mainly cohorts of patients who were transplanted after their PC treatment (111 transplanted patients vs 6 patients who remained on dialysis) with mainly localised PC of excellent prognosis (D'Amico low to intermediate risk or stage $\leq$ II). By contrast, in 2005 the report of Woodle et al [9] included 12% with stage III PC. In 2001, Chapman et al [46] did not report the histology and prognosis of the patients included (Table 7).

To date, there is no evidence of worse prognosis for PC in ESRDs. Although the increased prevalence of hypogonadism was suspected to induce PC of worse prognosis, there is no study validating this hypothesis [17]. It was not demonstrated that the prognostic performance of pretherapy (D'Amico, Partin) and post-therapy (Kahn, Kattan) nomograms is altered for CKD patients [18,19].

4.2.3. Urothelial carcinoma and chronic kidney disease

In this systematic review, the most common tumour site of UC was the upper urinary tract (57–100% of the case series). The prevalence of a synchronous bladder tumour was 42–81% and the prevalence of a bilateral tumour was 10–16% [20,21]. Concerning the stage, 72% (56–100%) of the patients were diagnosed with a nonmuscle invasive tumour. All publications followed the three-stage classification according to the 1973 World Health Organization classification with a high-grade distribution ranging from 15% to 69% (Table 7).

There were few studies on bladder cancer. Among them, tumour stage (tumour invading muscle or not) and use of adjuvant intravesical therapy were rarely mentioned.

Most studies dealing with UUTUC concerned patients with aristolochic nephropathy and seemed to have a higher risk of recurrence and multifocality than UUTUC induced by tobacco and toxic substances [22].

4.2.4. Testicular cancer

We found no comparative study concerning TC. TC had a low risk of recurrence according to Penn [4]. A single clinical case indicated the possibility of recurrence for stage I seminoma [8].

4.3. Implications for practice

Considering the rates of recurrence and the prognostic factors of recurrence reported in this systematic review of the literature, it seems possible to optimise the waiting period between treatment for cancer and transplantation.

4.3.1. Real cell carcinoma

The main prognostic factors of recurrence identified in this systematic review were: stage, tumour size, Fuhrman grade, tumour solid nature, symptomatic tumours on diagnosis, conventional renal cell carcinoma subtype, and lymph node involvement (Table 5).

This systematic review reported a significant risk of recurrence even for low-stage and low-grade tumours. In Sheashaa et al [23] and Denton et al [24], in particular, where ipsilateral nephrectomy was performed systematically during transplantation, there was a risk of recurrence of up to 25% at 5 yr, even though these were low-grade and low-stage infraradiological tumours. In these studies, contralateral involvement occurred in up to 36% of the cases. Recurrences were essentially recurrent/second contralateral RCC with an

early diagnosis. Cancer-specific and overall survival rates were similar between dialysed and transplanted patients (Table 5).

The conclusion of this systematic review highlights the requirement for regular annual monitoring of the native kidney in CKD patients and particularly those with a history of RCC. The reference treatment for a cancer of the native kidneys is radical nephrectomy.

4.3.2. Prostate cancer

In this systematic review, the main prognostic factors for recurrence were: stage, prostate-specific antigen, and Gleason score. Radical prostatectomy is the preferred treatment both for staging and curative purposes. Lymph node resection may be best limited to one side of the pelvis to preserve the iliac vessels for the transplantation on the other side [25]. Transperineal prostatectomy could also be an option to preserve the iliac vessels [26].

The studies reported low recurrence rates consistent with prognostic nomograms. In the Tillou et al [27] study, the risk of biochemical recurrence at 10 yr, calculated using the Memorial Sloan Kettering Cancer Center nomogram did not exceed 3% in the worst case and was 1–2% in all other cases. This nomogram has proven its reliability in other studies on large cohorts. The nomogram allowed registration of patients on the transplantation waiting list at an earlier stage, whilst radical prostatectomy made the decision to put the patient on the transplant list easier. The authors reported no recurrence with a mean follow-up of 3.2 yr, suggesting that there could be no waiting period for transplantation in cases of cured low-risk PC [25].

In their study, Woodle et al [9] (which was an update of the PC series published by Penn in 1995 and 1997 [4]) included a significant number of high-risk extraprostatic tumours. Despite its shortcomings, this study is still unequalled for the study of high-risk PC before transplantation [11].

4.3.3. Urothelial carcinoma (bladder and upper urinary tract urothelial carcinoma)

The included studies showed that UUTUC has a high risk of recurrence. The risk of synchronous bilateral involvement is 10–16% and the risk of contralateral recurrence is 31–39% (Table 7). For candidates for transplantation with a history of UUTUC, two strategies are justified:

1. Systematic treatment of the contralateral upper urinary tract and/or the bladder by nephroureterectomy and/or even cystectomy;
2. Close monitoring of the bladder and the contralateral upper urinary tract.

4.3.4. Testicular cancer

The level of evidence reported in this study did not allow us to conclude on the risk of testicular tumour recurrence after renal transplantation. The two case reports highlighted the risk of retroperitoneal recurrence after transplantation, even with a long waiting period (Table 8). A case-by-case discussion is needed to decide on a period of exclusion before transplantation.

4.4. Implications for research

Although the findings of this systematic review enabled us to identify the prognostic factors of recurrence and to conclude that immunosuppression did not modify the natural history of urological cancer for selected patients, the literature in this particular area differed according to the type of cancer. With the exception of Tillou et al [25] (19 patients), we found no comparative study for PC. There were few studies on bladder cancer, with no data concerning the stage (tumour invading the vesical muscle or not) and the use of adjuvant intravesical therapy.

In practice, it appears to be difficult to evaluate the excess risk of recurrence represented by the initiation of immunosuppressive therapy and thus the possible deleterious impact of transplantation on recurrence and cancer-specific survival. Randomised controlled trials will ethically and logistically be difficult to conduct. However, well-designed prospective cohort studies with homogenous type/stage of cancer and clear predefined oncological outcomes at different time points are needed to strongly support a reduction of the waiting period for low-risk RCC and PC, which was a tendency suggested in this systematic review.

4.5. Limitations of this study

This report is the first systematic review assessing and appraising all available evidence of the risk of cancer recurrence for CKD patients on dialysis or who have undergone transplantation. Limitations mainly consist in the low level of the references:

- The included studies are all retrospective and most of them are not comparative. As such, the RoB and/or confounding is high in most studies.
- Long-term follow-up is lacking. Several data were not systematically reported: prognostic score or monograms, duration, and type of immunosuppressive treatment, type of recurrence (local or systemic). For PC, the oncological results of nontransplanted patients were based on only six patients in two studies.
- For urothelial tumours, the majority of studies included UUTUC occurring in the particular field of aristolochic acid nephropathy.

4.6. Conclusions

Although this systematic review summarised all the available evidence on renal transplantation and history of cancer, it was limited by the level of evidence of the included studies, which mainly consisted of noncomparative retrospective cohort studies of preselected patients. Acknowledging that the comparison is not free from bias, this systematic review indicates that immunosuppression does not seem to alter the natural history of recurrence and mortality for low-risk renal and PC, and could lead to a shortening of the waiting period in this specific situation. For high-risk renal and PC, the historical Cincinnati registry

is still an unequalled source of data. Although this registry study suffers from many shortcomings, waiting period should not be modified for high-risk renal and PCs. Urothelial carcinomas are multifocal and highly recurrent tumours. For transplantation candidates, close follow-up or systematic bilateral nephroureterectomy are both possible strategies. For patients with a history of TC a case-by-case discussion is recommended.

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Appendix A. Supplementary data

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