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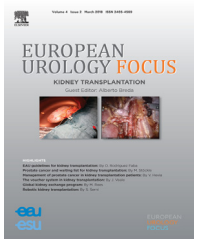

Review – Prostate Cancer

Management of Localised Prostate Cancer in Kidney Transplant Patients: A Systematic Review from the EAU Guidelines on Renal Transplantation Panel

Vital Hevia [a,*], *Romain Boissier* [b], *Óscar Rodríguez-Faba* [c], *Claire Fraser-Taylor* [d], *Rhana Hassan-Zakri* [e], *Enrique Lledo* [f], *Heinz Regele* [g], *Klemens Buddde* [h], *Arnaldo Figueiredo* [i], *Jonathon Olsburgh* [e], *Alberto Breda* [c]

[a] *Urology and Kidney Transplant Department, Hospital Universitario Ramón y Cajal, Alcalá University, Madrid, Spain;* [b] *Department of Urology & Renal Transplantation, La Conception University Hospital, Assistance-Publique Marseille, Aix-Marseille University, France;* [c] *Department of Urology, Fundacion Puigvert, University Autonoma of Barcelona, Barcelona, Spain;* [d] *Department of Urology and Transplant, St Georges NHS Trust Hospitals, London, UK;* [e] *Department of Transplant and Urology, Guy's & St Thomas' NHS Trust Hospitals, London, UK;* [f] *Department of Urology, Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [g] *Clinical Institute of Pathology, Medical University of Vienna, Vienna, Austria;* [h] *Department of Nephrology, Charité Medical University Berlin, Berlin, Germany;* [i] *Department of Urology and Renal Transplantation, Coimbra University Hospital, Coimbra, Portugal*

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Abstract

Context: Cancer development after kidney transplant (KT) has become a major problem, and currently, it is one of the primary causes of death in this population. Urological cancers after KT such as prostate cancer (PCa) have also increased, partly due to the increasing age of recipients and prolonged survival. PCa is the second most commonly diagnosed cancer in men, accounting for 15% of all cancers. Managing localised PCa after KT remains challenging because of treating an immunosuppressed patient with a kidney graft in the pelvic cavity. Several papers reporting PCa treatment after KT have been published. Merging all the available data and summarising most important evidence could be useful for scientific community involved in this issue.
Objective: To systematically review all the available evidence in literature regarding the management of localised PCa after KT.
Evidence acquisition: Computerised bibliographic search of Medline, Embase, and Cochrane databases was performed for all studies reporting outcomes of localised PCa diagnosed in KT patients undergoing curative treatments, including surgery, external beam radiotherapy (EBR) and brachytherapy.
Evidence synthesis: In total, 41?studies included 319?patients with localised PCa after KT. Their mean age was 61.8 (range, 47–79) yr and mean time from KT to PCa was 122 (range, 2–336) mo. Mean prostate-specific antigen was 8.5 (range, 0.3–82), most frequent biopsy Gleason score was 3 + 3 (50.5%), 62.1% were cT1-cT2, and 56.1% belonged to low-intermediate D'Amico-risk groups. Surgery was performed in 82.1%. After mean follow-up of 33 (range, 1–240) mo, cancer-specific survival at 5?yr was 97.5%, 87.5%, and 94.4% after surgery, EBR, and brachytherapy, respectively.
Conclusions: Radical prostatectomy is the preferred treatment of localised PCa after KT. Overall oncological outcomes do not seem to be worse than general population when performed in referral centres. Other curative treatments such as EBR or brachytherapy were less frequently used; however, brachytherapy showed promising results in a small number of patients. Further better-quality studies should help to clarify the optimal method of managing localised PCa after KT.
Patient summary: Localised PCa after KT seems to have similar oncological outcomes after curative treatments than in general population, with surgery being the most common option for treatment.

* Corresponding author. Department of Urology and Kidney Transplant, Hospital Universitario Ramón y Cajal, Ctra de Colmenar km 9,100, 28034 Madrid, Spain. Tel.: +34 913368760; Fax: +34 913368760.
E-mail address: vital.hevia@salud.madrid.org (V. Hevia).

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1. Introduction

Kidney transplant (KT) is the best treatment for patients with end-stage renal disease. Cancer development after KT has become a major concern as it is currently one of the main causes of death in this population. Urological cancers, such as prostate cancer (PCa), also have an increased incidence after KT, which is partly due to the increasing age of recipients and prolonged survival after transplantation. PCa remains the second most commonly diagnosed cancer in men, accounting for 15% of all cancers diagnosed, and the most frequent non-skin solid neoplasm in men who have undergone KT [1]. Majority of them are localised; therefore, they are suitable for undergoing curative treatments according to current clinical practice guidelines [2]. Given the progressive rise in the number of transplants performed and the higher life expectancy of recipients, urological surgeons involved in oncological and transplant surgery have to be familiar while dealing with this clinical situation.

Treatment of localised PCa after KT remains challenging, not only for treating urological cancer in an immunosuppressed patient but mainly due to the presence of the kidney graft in the pelvic cavity and very close to the prostate, which can play a negative role when treating the prostate with surgery or radiation, or even when subsequent kidney transplants need to be considered. In clinical studies, none of the immunosuppressant drugs have clearly demonstrated an increase or decrease in PCa risk; also, its incidence is not clearly increased in this particular population. Thus, several studies have reported a slightly increased incidence while others report a similar [3–5] but without the clear epidemiologic relation seen in other urological cancers such as renal cell carcinoma.

Several papers reporting PCa treatment have been published during last decades. Merging all the available data and summarising most important evidence found could help in providing some recommendations to urological and kidney transplant scientific community involved in treating these patients.

The aim of this study was to perform a systematic review (SR) to appraise all the available evidence regarding the management of localised PCa in renal transplant recipients.

2. Evidence acquisition

2.1. Data sources and searches

This SR was performed according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: the PRISMA Statement [6]. Databases searched were Embase, Medline, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. No language or year restrictions were applied. The database search was also complemented by screening the reference lists of the included studies.

2.2. Study selection

Studies eligible for inclusion were those reporting the oncological outcomes of patients who, having a previous KT, were diagnosed and treated for localised PCa with even RP, external beam radiotherapy (EBR), or brachytherapy. There was no language or year restriction. All study designs were eligible for inclusion except for reviews, editorials, or studies published as a conference abstract only. All identified abstracts were placed in a bibliography management software program (EndNote X7) and sorted according to inclusion and exclusion folders by drag and drop. Titles and abstracts of all identified studies were independently reviewed by two authors (VH, RB) and discrepancies resolved by a third reviewer (ORF).

2.3. Data extraction and risk of bias assessment

Data from eligible reports were extracted independently. A data-abstraction sheet was created a priori including year of publication, study type and its level of evidence, number of patients, age, follow-up, time from KT to PCa diagnosis, baseline immunosuppression, prostate-specific antigen (PSA) at diagnosis, biopsy Gleason score, clinical staging (cT), and EAU/D'Amico risk groups. Surgical data included approach, estimated blood loss (EBL), surgical time, and lymph node dissection (LND), whereas radiation data included total dose in Gy, usage or not of androgen deprivation (AD) and its duration. Pathology data included specimen Gleason score, specimen staging (pT, pN), and surgical margins (SM). Outcomes assessed were PCa recurrence, cancer-specific survival (CSS), overall survival (OS), and graft survival (GS) at 1-, 3-, and 5-yr time-points. PSA during follow-up was also collected as well as early (< 3mo) and late (>3 mo) complications according to Clavien-Dindo classification.

2.4. Data synthesis

A narrative synthesis of the data was performed. Primary outcomes (oncological) were PCa recurrence, CSS, and OS. Secondary outcomes (non-oncological) were GS, PSA levels, and complications according to Clavien-Dindo classification system.

3. Evidence synthesis

3.1. Search results

The search retrieved 1042 articles whose abstracts were screened; of this, 991 were excluded. A total of 51 full text articles went on for eligibility assessment. Of these, 16 were excluded. After the hand search of the reference lists of the included full-text papers, another six studies were included. Thus, a total of 41 studies were included in this SR (Fig. 1).

3.2. Characteristics of studies, population, and interventions

The 41 studies included a total of 319 patients with localised PCa after KT treated with radical surgery, EBR, or brachytherapy (Table 1).

All the studies were non-randomised, retrospective, and comparative studies or retrospective case series/reports recruiting patients between 1977 and 2017, all of them with

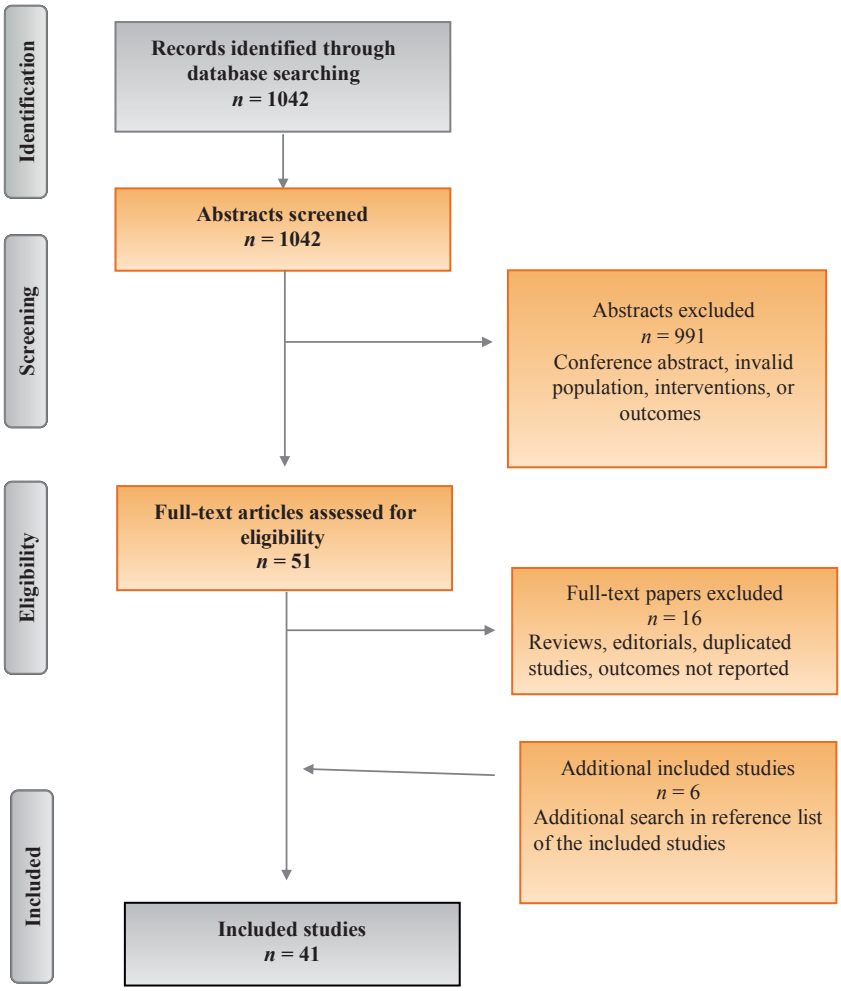


Fig. 1 – PRISMA flow chart.

low levels of evidence. The vast majority of them were focused only in PCa developed after KT, while other papers were institutional series reporting urological cancers after transplant, including PCa. Table 2 details characteristics of population treated and included in the SR.

Mean age was 61.8 (range, 47–79), mean time from KT to PCa was 122 (range, 2–336) mo, and mean time follow-up was 33 (range, 1–240) mo. Regarding baseline immunosuppression, calcineurin-inhibitor (tacrolimus/cyclosporine), and steroids were the most frequent drugs used. Mean PSA at diagnosis was 8.5 (range, 0.3–82) ng/ml, while 50.5% had a biopsy Gleason score 3 + 3, 62.1% were cT1-cT2, and 56.1% belonged to low and intermediate D'Amico-risk groups.

RP was performed in 262 patients (82.1%), EBR in 37 (11.6%), and brachytherapy in 20 (6.3%), each of them as single treatments except three patients who received RP followed by adjuvant or salvage EBR. Most common surgical technique was open retropubic (RRP), while laparoscopic (LRP) and robot-assisted (RARP) approach gained importance in the most recent studies. Complete distribution depending on surgical technique is detailed in Figure 2. LND was unilateral on the opposite side of the graft in 26.3% of the patients, bilateral in 6.1%, and not performed in 67.6%. Mean EBL was 404 cc, and mean surgical time was 180 min. Specimen pathology results after RP are detailed in Figure 2: specimen Gleason score was 3 + 3 in 49%, pathological T stage was pT2 in 71%, and SM were negative in 74% of the patients. Only 2.4% (2/84) of the patients who had LND were pN+.

EBR was performed as a single treatment in 37 patients; however, three additional patients who have had a previous RP also received salvage or adjuvant EBR. The mean dose used was 72.6 Gy, and only one patient received radiation to pelvic lymph nodes [7]. Furthermore, 75% patients received AD therapy concomitant to EBR during a mean time of 21 mo. High-dose-rate brachytherapy was used in 20 patients, with a mean dose of 144 Gy. Two patients (10%) received AD with a mean time of 12 mo, while seven patients did not receive it, and in the remaining 11, it was not reported.

Finally, regarding immunosuppression, 8.8% (28/319) patients were switched to mTOR inhibitor scheme after PCa treatment, while the remaining patients were not switched or not reported.

Table 1 – Summary of studies included with patients with a localised prostate cancer after kidney transplant treated with surgery, external beam radiotherapy, or brachytherapy.

Study	*n*	Study type	LOE	Country	Mean/median follow-up (mo)	Mean age (yr, range)
Narvaez 2018 [12]	29	Retrospective case series	3	Spain	61	66
Pettenati 2016 [19]	20	Retrospective case series	3	France	47	63,5
Carvalho 2016 [23]	18	Retrospective case series	3	Portugal	35	61,2
Moreno 2016 [24]	4	Retrospective case series	3	Spain	33	61,25
Jenjitranant 2016 [11]	1	Case Report	3	Thailand	1	73
Iizuka 2016 [25]	3	Case Report	3	Japan	18	62
Iizuka 2016 [26]	2	Case Report	3	Japan	45	62,5
Beyer 2016 [27]	20	Retrospective case series	3	Germany	25	64,5
Rosenfelder 2015 [7]	1	Case Report	3	UK	48	60,4
Le Clerc 2015 [28]	12	Retrospective case series	3	France	31	61,9
Heidenreich 2014 [13]	23	Retrospective case series	3	Germany	48	64
Beydoun 2014 [17]	4	Retrospective case series	3	Australia	44	64
Hevia 2014 [3]	6	Retrospective case series	3	Spain	31	59
Saema 2013 [29]	1	Case Report	3	Thailand	12	64
Wagener 2012 [30]	1	Case Report	3	Germany	12	71
Polcari 2012 [31]	7	Retrospective case series	3	USA	16	63,3
Coombs 2012 [16]	3	Retrospective case series	3	USA	61	64,8
Binsaleh 2012 [32]	8	Retrospective case series	3	Saudi Arabia	41	63,6
Karczewski 2012 [33]	4	Retrospective case series	3	Poland	120	57
Ghazi 2012 [34]	1	Case Report	3	USA	NA	68
Detti 2011 [20]	1	Case Report	3	Italy	NR	50
Smith 2011 [35]	3	Retrospective case series	3	USA	13	54
Melchior 2011 [4]	4	Retrospective case series	3	Germany	66	62,3
Di Capua 2010 [36]	11	Retrospective case series	3	Spain	82	66
Hoda 2010 [37]	16	Retrospective case series	3	Germany	25	61,8
Elkentaoui 2010 [38]	18	Retrospective case series	3	France	26	63
Alvarez 2010 [39]	2	Case Report	3	Spain	30	59,5
Robert 2009 [8]	9	Retrospective case series	3	France	12	62,4
Doerfler 2009 [40]	1	Case Report	3	France	18	63
Kleinclauss 2008 [41]	20	Retrospective case series	3	France	29	60,4
Thompson 2008 [42]	17	Retrospective case series	3	USA	60	59
Jhaveri 2008 [43]	1	Case Report	3	USA	2	54
Antonopoulos 2008 [44]	8	Retrospective case series	3	Brazil	12	59,6
Chabchoub 2005 [45]	6	Retrospective case series	3	France	23	61
Hafron 2005 [14]	7	Retrospective case series	3	USA	22	62,3
Mouzin 2004 [9]	8	Retrospective case series	3	France	28	65,2
Campagnari 2002 [46]	2	Case Report	3	Brazil	18	66
Yiou 1999 [15]	1	Case Report	3	France	10	56
Konety 1998 [47]	12	Retrospective case series	3	USA	32	62
Multanen 1998 [48]	1	Case Report	3	Finland	18	51
Kinahan 1991 [49]	3	Retrospective case series	3	Canada	12	60

LOE = level of evidence; *n* = number of patients; NA = not applicable (only 1-wk follow-up reported); NR = not reported;

3.3. *Primary (oncological) outcomes: recurrence and survival*

Figure 3 summarises oncological outcomes. After a mean follow-up of 33 (range, 1–240) mo, PCa recurrence at 1, 3, and 5 yr was 4%, 5.8%, and 12.3%, respectively, after surgery; 2%, 21.3% and 50%,respectively, after EBR; and 0% at all the time-points for brachytherapy. CSS at 1, 3, and 5 yr was 100%, 98.6%, and 97.5%, respectively, after surgery; 98.4%, 91.1%, and 87.5%, respectively, after EBR; and 100%, 100%, and 94.4%, respectively, for brachytherapy. Finally, OS at 1, 3, and 5 yr was 99.4%, 93.1%, and 85.3%, respectively, after surgery; 93.5%, 84.3%, and 75.9%, respectively, after EBR; and 100%, 100%, and 94.4%, respectively, for brachytherapy.

3.4. *Non-oncological outcomes*

Mean PSA levels reported at the end of follow-up period were 0.01, 5.01, and 0.15 ng/ml for surgery, EBR, and brachytherapy, respectively. GS at 1, 3 and 5 yr was 98.8%, 97.3%, and 96.0%, respectively, after surgery; 93.9%, 93.0%, and 85%, respectively, after EBR; and 100%, 100%, and 95%, respectively, for brachytherapy.

Complications according to Clavien-Dindo are summarised in Table 3. Early complications were present in 13% after surgery and 40% after brachytherapy. The majority of them were minor (Clavien I and II), particularly haematoma and need for transfusion after RP. One case of rectal fistula after surgery treated with colostomy (Clavien III), one case of ureteral injury, and one case of lymphocele requiring surgical drainage were the most outstanding, as well as one acute myocardial infarction after brachytherapy. Late complications were present in 3.1% after RP and 5.4% after EBR. Two cases of ureteral obstruction after EBR, as well as one case of deep venous thrombosis (DVT) involving the graft and two ureteral strictures after surgery were the most relevant.

Table 2 – Descriptive data of population with a localised prostate cancer after kidney transplant treated with surgery, external beam radiotherapy, or brachytherapy.

Study	All population of the included studies	
n	319	
Mean age at diagnosis (range, yr)	61.8 (47–79)	
Mean time from KT to PCa (mo)	122 (2–336)	
Baseline immunosuppression	• 216?CNI	
	• 132?MMF	
	• 206?steroids	
	• 10?imTOR	
Mean PSA at diagnosis (ng/ml)	8.45 (0.3–82)	
Biopsy Gleason score (*n*, %)	3 + 3	50.5 (161/319)
	3 + 4	21.0 (67/319)
	4 + 3	11.3 (36/319)
	4 + 4	3.8 (12/319)
	4 + 5	1.3 (4/319)
	5 + 4	0.3 (1/319)
	5 + 5	0.3 (1/319)
	Unknown	11.6 (35/319)
Clinical T stage	cT1	33.2 (106/319)
	cT2	28.9 (92/319)
	cT3a	1.6 (5/319)
	cT3b	0.3 (1/319)
	Unknown	36.1 (115/319)
D'Amico risk groups	Low	35.1 (112/319)
	Intermediate	21.0 (67/319)
	High	2.8 (9/319)
	Very high	2.2 (7/319)
	Unknown	38.9 (124/319)
imTOR switch after PCa treatment	• Yes: 8.8 (28/319)	
	• No: 18.2 (58/319)	
	• Unknown: 73.0 (233/319)	

CNI = calcineurin inhibitors; imTOR = mTOR inhibitor; KT = kidney transplant; MMF = mycophenolate mofetil; *n* = number of patients; PCa = prostate cancer; PSA = prostate-specific antigen.

Main intraoperative complication reported was rectal injury in two cases [8], which were repaired during surgery, one of them with no further complications and the other was the one with rectal fistula requiring colostomy in the early postoperative period.

4. Discussion

4.1. *Principal findings*

This SR has demonstrated that the majority of patients with localised PCa after KT are treated with RP (82%) instead of EBR (12%) or brachytherapy (6%). Moreover, although in the short- and mid-term (33 mo follow-up), oncological outcomes are comparable to non-transplanted population, with excellent rates of OS and CSS.

Population age at diagnosis was younger than the typical of PCa onset in non-transplant population. Although screening or diagnosis policy was not addressed or reported in the included studies, it is known that this population undergoes an active and strict follow-up usually including PSA, which could partly explain this fact. Worst biological behaviour and earlier development of PCa in this population does not seem to be a reason involved, given the mean time from KT to PCa diagnosis (>10 yr) and the overall oncological outcomes after treatment.

More than a half of the population included had a biopsy Gleason score 3 + 3 (50.5%), a clinical T1-T2 stage (62.1%), and belonged to low or intermediate D'Amico risk groups (56.1%). Additionally, mean PSA level at diagnosis was 8.45 ng/ml; however, the highest reported PSA reached 82 ng/ml, which could be in context of metastatic disease and explain relapse.

RRP has been the most frequently used surgical approach when treating a localised PCa after KT, as represented in Figure 2. However, minimally invasive surgical approaches such as LRP or RARP have gained importance in the last years as a result of the broad implementation of these techniques in urological practice at referral centres.

Presence of a functioning KT in the iliac fossa when planning to treat a PCa remains an important issue, which will play an important role in the work-up. Complications affecting the graft ureter or iliac vessels are infrequent but usually require surgical repair and even result in graft loss. EBR and brachytherapy are not free from these possible iatrogenic damages, particularly graft ureteral stricture [9] with subsequent or radiation nephropathy. Therefore, LND and pelvic lymph node radiation are usually avoided when managing this clinical setting.

mTOR inhibitors introduction have demonstrated an antitumor activity after kidney transplant, particularly in cutaneous squamous cell carcinoma [10] and renal cell carcinoma. Their effect within PCa still remains unknown,

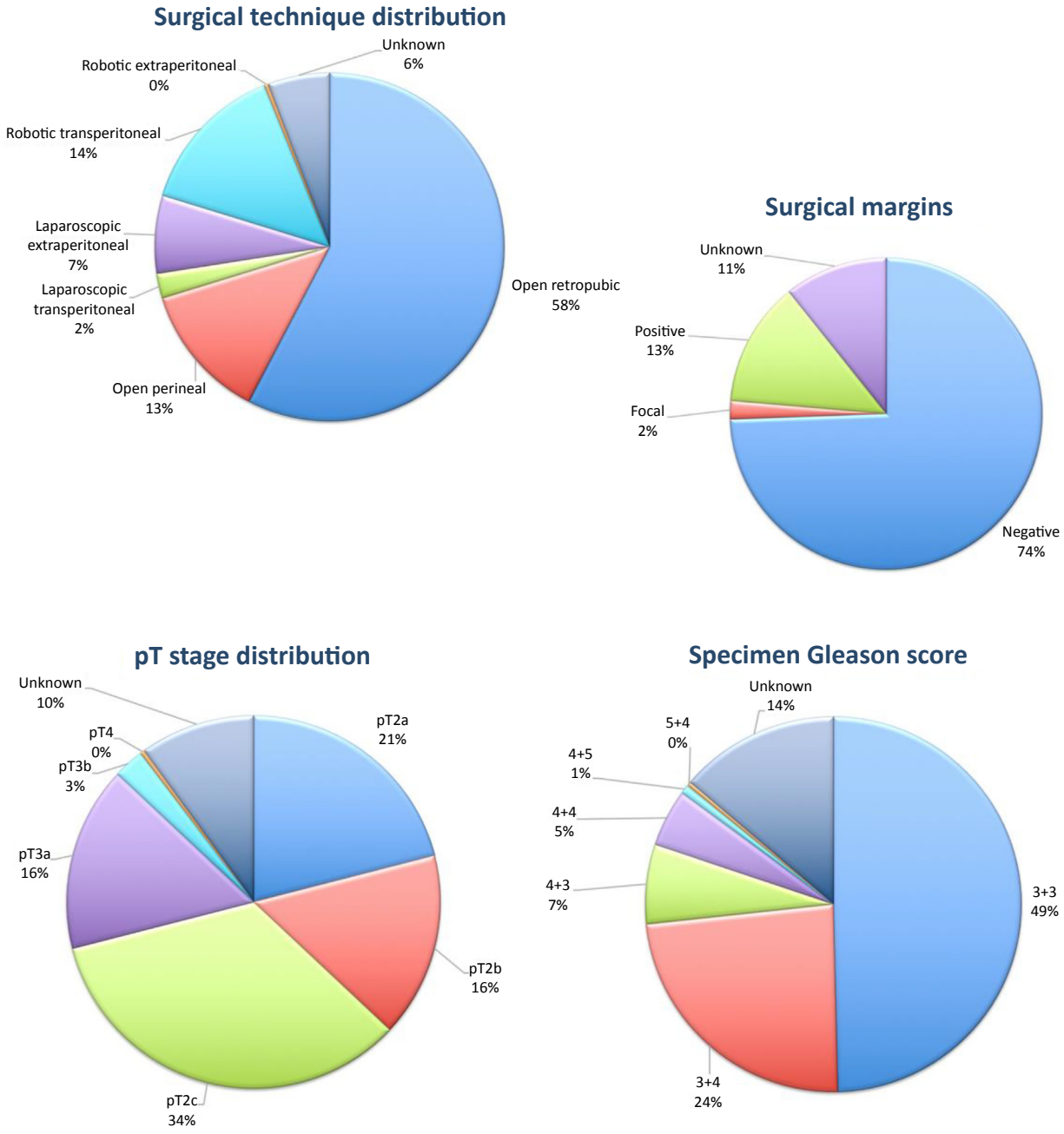


Fig. 2 – Surgical technique distribution and specimen pathology results after radical prostatectomy in patients with a localised prostate cancer after kidney transplant.

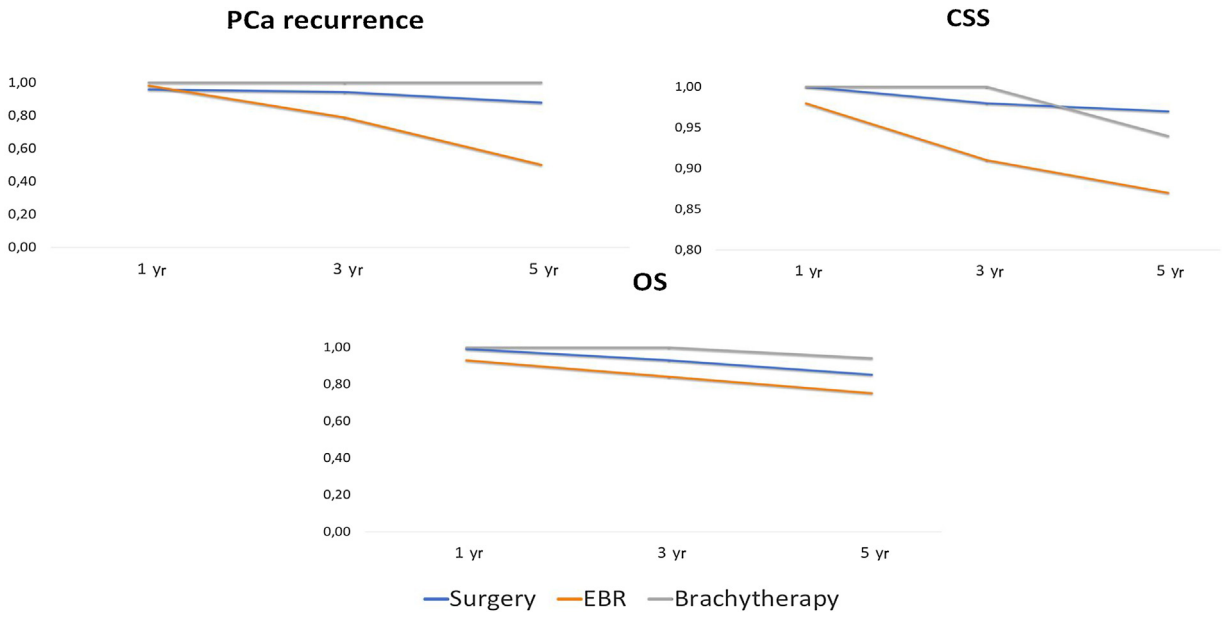
without strong clinical evidence. This explains why only 8.8% of the patients were switched to mTOR inhibitor scheme.

4.2. *Findings in the context of existing evidence*

Overall evidence quality still remains poor as all studies included are non-randomised, retrospective, comparative studies or retrospective case series/reports. Thus, although this SR gives quite clear ideas about how localised PCa after KT is managed around the world, it should be interpreted cautiously. Surgery is the preferred option when dealing with this clinical scenario and overall results seem to endorse it.

4.2.1. *Surgical approaches*

Surgical approach may be decided by the surgeon's experience, with the only limitation that perineal radical prostatectomy (PRP) should be logically avoided when LND is indicated. Regardless of the approach, RP in KT patients poses a number of important challenges. Presence of the graft in pelvis distorts normal anatomy and limits surgical exposure, particularly in the extraperitoneal-retropubic Retzius space. It usually requires some minor technical



Patients at risk table

	1 yr	3 yr	5 yr
Surgery	257	125	49
EBR	37	18	7
Brachytherapy	20	20	11

Fig. 3 – Oncological outcomes in patients with a localized PCa after kidney transplant stratified by type of treatment (surgery, EBR, or brachytherapy). CSS = cancer-specific survival; EBR = external beam radiotherapy; OS = overall survival; PCa = prostate cancer.

modifications of standard open or minimally invasive approaches in order to gain a proper access to prostate. Thus, some authors perform a Retzius-sparing RARP [11] or a PRP [12–15], moving far away from the graft in an attempt to avoid ureteral or vascular iatrogenic lesions. LND in these patients may be difficult and even dangerous, increasing the risk of an iliac or graft vessels trouble. This fact explains why LND was not performed in 67.6% and only unilateral over the graft opposite side in 26.3%. Furthermore, LND may have an impact if planning possible successive KT on the contralateral side, making that iliac fossa unfit for the future. Thus, it seems reasonable to perform it only if indicated according to current nomograms and clinical practice guidelines [2]. Whilst 58% of the surgeries were RRP, minimally invasive techniques were also present, with a growing number of reports in the last years; in fact, the second most frequent technique was RARP. Nevertheless, none of the surgical techniques demonstrated superiority above the others, except for the typical lower EBL linked to LRP and RARP. Despite challenges and peculiarities of surgery in these patients, evidence supports the safety and efficacy of RP in post-transplant population. CSS and OS after aggressive surgical therapy in transplant patients seem comparable to non-transplant population as well as SM, which were

Table 3 – Complications of prostate cancer after kidney transplant treated with surgery, external beam radiotherapy, or brachytherapy according to Clavien-Dindo classification.

Study	Surgery (n = 262)	Radiotherapy (n = 37)	Brachytherapy (n = 20)	Total
Early (<3 mo), n (%)				
• Clavien I	18 (6.9)	0	8 (40)	26 (62)
• Clavien II	11 (4.2)	0	0	11 (26)
• Clavien III	4 (1.5)	0	0	4 (10)
• Clavien IV	1 (0.4)	0	0	1 (2)
Late (>3 mo)				
• Clavien I	1 (0.4)	0	0	1 (10)
• Clavien II	3 (1.1)	2 (5.4)	0	5 (50)
• Clavien III	3 (1.1)	0	0	3 (30)
• Clavien IV	1 (0.4)	0	0	1 (10)
Total	42	2	8	52

negative in 83.3%. However, it is important to remark that all reports included were from high-volume and referral centres, with high experience in both transplant and uro-oncological surgery, which may have an impact in achieving such results obtained.

4.2.2. Oncological outcomes

Cancer-recurrence rates after EBR were the highest at all time-points. However, PCa after surgery relapsed in 12.3% and 0% after brachytherapy, whereas CSS at 5 yr was slightly better for surgery rather than for brachytherapy (97.5% vs 94.4%). Several aspects should be discussed at this point: the low number of patients receiving brachytherapy (only 6%) and their belonging to low-risk D'Amico group in the majority of cases could play a role creating bias, so these results should be interpreted cautiously. Anyway, it confirms that brachytherapy as well as surgery is a safe option for these patients [16]. Oncological outcomes after EBR were worse, and ideally, it should be reserved for patients with intermediate- or high-risk disease and a minimum but not very long-life expectancy. However, complications/functional outcomes were reported in only 24.3% receiving EBR [9] and 25% receiving brachytherapy [17], and the total number of patients treated was 18% between both.

EBR is a possible option in the treatment of localised PCa and can be used after KT [18]. Although the number of reported cases and the level of evidence are low, some conclusions can be drawn from this review. Patients were mainly treated according to the standards of the era of dose escalation with Biological Equivalent Dose $\geq$76 Gy and concomitant androgen deprivation therapy. The side effects seemed to be similar to those in general population. No graft loss and only two ureteral strictures without renal function impairment have been reported [9]. Several technical points could reduce the irradiation of the ureter and the transplant: intensity-modulated radiation therapy or even image-guided radiation therapy, which improves the precision of irradiation field, and performing the treatment with a full bladder in order to move the graft away and the ureteroneocystostomy [7,9,12,19]. At least one case of adjuvant radiotherapy was reported without any side effect [20].

4.2.3. Non-oncological outcomes

GS rates were excellent, and no cases of delayed graft function after treatment were reported. PSA level at the end of follow-up, as probably expected, was the lowest for patients treated with surgery, followed by those treated with brachytherapy and EBR, respectively. However, evidence was weak in terms of complication reports, and standardised classification systems (Clavien-Dindo) were rarely used.

Intraoperative rectal injury was reported in two cases of LRP [8], both repaired during surgery, one of them requiring colostomy in the early postoperative period due to persistent rectal fistula. It supposes an incidence of 0.76%, which is similar to the incidence in general population [21]. Demonstrated risk factors of rectal injury during RP are presence of previous pelvis radiation, local T stage, Gleason score, and surgical experience, but not surgical approach (open vs robot-assisted) [21].

Although there is a well-known relation between immunosuppressive drugs and wound healing problems, there was no significant increase in wound infection after surgery; however, data was lacking in several studies.

Early complications were present in 13% after surgery and 40% after brachytherapy, with 0% after EBR. However, complications and functional outcomes were reported in only 24.3% receiving EBR [9] and 25% receiving brachytherapy [17]. Furthermore, 88.1% (37/42) of early complications were minor (Clavien I and II), whereas the rate decreased to 60% when assessing late complications (>3 mo). Most common early complications were haematoma and need for transfusion. Regarding late complications, which usually have a major importance, the most frequent was ureteral stricture in four cases, both after surgery in two and after EBR in the other two. There was one case of late DVT affecting iliac vessels and subsequently the graft, leading to graft loss despite anticoagulation therapy [8]. Although this patient did not have LND during surgery, it highlights the importance of performing LND when indicated according to nomograms and clinical practice guidelines, given the known higher incidence of DVT after LND [22].

4.3. Implications for practice

The current best option considered for a localised PCa after KT seems to be surgery in highly experienced referral centres due to excellent oncological outcomes and acceptable complication rates comparable to general population. The technique should be ideally based on surgeon's experience and preferences, keeping in mind the additional goal of avoiding graft morbidity burden in addition to conventional PCa trifecta. In this sense, LND should be performed when indicated according to practice guidelines and whenever feasible during surgery, trying to limit it to graft contralateral pelvic side. In summary, according to this SR and as an expert advice, we conclude that PCa after KT should be treated following principles for general population. Considering the challenge to preserve the graft, any of the treatments detailed above should be performed in experienced referral centres managing KT.

4.4. Implications for research

Due to the included studies found in literature search, there is a lack of good-quality evidence. This should encourage urologists involved in KT to develop higher quality studies in order to confirm these promising results. If no significant differences from natural behaviour of PCa after KT are hypothesised, modern organ-preserving strategies included in guidelines such as active surveillance (AS) or focal therapy should also be addressed, as they are expected to reduce complication rates while maintaining oncological outcomes. However, the role of AS in this particular population should be cautiously managed, especially when dealing with young patients in whom a possible second transplant could be planned, as the presence of an active cancer remains an absolute contraindication for a transplant. Ideally, an international register of all localised PCa after KT supported and led by *European Association of Urology* appears an excellent route to clarify questions not answered in this SR.

4.5. *Limitations of the study*

Overall evidence quality still remains poor as all studies included are non-randomised, retrospective, comparative studies or retrospective case series/reports. Non-oncological outcomes and complications were poorly reported or lacking in the majority of the studies. Lastly, mean follow-up of 33 mo when dealing with localised PCa does not seem to be enough to draw strong conclusions. Thus, although this SR gives quite clear ideas about how localised PCa after KT is managed around the world, it should be interpreted cautiously.

5. Conclusions

RP is the most reported treatment of localised PCa after KT, accounting for 82% of the patients. Overall, oncological outcomes and complications does not seem to be worse compared to general population when performed in referral centres with experience in transplant and uro-oncologic surgery. Other curative treatments such as EBR or brachytherapy were less frequently used, but brachytherapy showed promising results although in a small number of patients. Further better-quality studies should help to clarify the optimal way of management of localised PCa after KT.

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Study concept and design: Hevia, Breda, Boissier, Rodríguez-Faba, Figueiredo, Lledo, Regele, Buddde, Figueiredo, Olsburgh.
Acquisition of data: Hevia, Boissier.
Analysis and interpretation of data: Hevia, Boissier, Rodríguez-Faba.
Drafting of the manuscript: Hevia, Boissier.
Critical revision of the manuscript for important intellectual content: Hevia, Breda, Boissier, Figueiredo, Olsburgh.
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