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Radical retropubic and perineal prostatectomy for clinically localised prostate cancer in renal transplant recipients

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KEYWORDS

Immunosuppression;
Radical prostatectomy;
Renal transplantation;
Prostate cancer;
Robot assisted prostatectomy

ABBREVIATIONS

RTR, renal-transplant recipient;
RP, radical prostatectomy;
RRP, retropubic RP;
RPP, perineal RP;

Abstract ***Objective:*** To analyse the functional and oncological outcome of consecutive renal-transplant recipients (RTRs) with clinically localised prostate cancer who underwent radical retropubic (RRP) or perineal (RPP) prostatectomy.

Patients and methods: Between January 2000 and July 2011 16 patients underwent RRP (group 1) and seven RPP (group 2). In all, 200 consecutive non-RTRs served as the control group, of whom 100 each underwent RRP and RPP, respectively. The mean (range) interval between renal transplantation and RP was 95 (24–206) months, the PSA at the time of diagnosis was 4.5 (3.0–17.5) ng/mL, and the mean patient age was 64 (59–67) years.

Results: The mean follow-up was 39 (RRP) and 48 months (RPP). There was no deterioration in graft function. In group 1, 13 and three patients had pT2a-cpN0 and pT3a-bpN0 prostate cancer, respectively, with a Gleason score of 6, 7 and 8 in 11, three and one patients, respectively. In group 2, three and four patients had pT2a-c and pT3a-b disease, respectively, with a Gleason score of 6 and 7 in two and five, respectively. In both groups one patient had a positive surgical margin and was followed expectantly, and all patients have no evidence of disease. Wound infections

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PLND, pelvic lymph-node dissection; RT, renal transplantation

developed more often in the RPP group (29% vs. 7%), but there were no Clavien grade III–V complications. All patients achieved good continence, and two need one pad/day.

Conclusions: RRP and RPP are suitable surgical treatments for prostate cancer in RTRs. RRP might be preferable, as it has the advantage of simultaneous pelvic lymphadenectomy and a lower risk of infectious complications.

Introduction

With the extension of the upper age limit for renal transplantation (RT) more patients aged $\geqslant 50$ years are candidates for this option [1–3]. Currently, ≈40% of all renal-transplant recipients (RTRs) in the USA are >50 years old and they have a mean graft survival of 21.6 years [4]. Both the increasing age of RTRs and the long-term survival with functional renal grafts might result in an increasing number of RTRs with prostate cancer.

With the routine use of PSA testing and increased public awareness, the incidence of prostate cancer as an early diagnosis has significantly increased during the last decade [5,6]. However, there is some controversy about the true incidence of prostate cancer in RTRs, as there are few data available from transplant registries that routinely record serial PSA measurements for the early detection of prostate cancer [7–10]. When screened for prostate cancer, the prevalence in RTRs appears to be identical or lower than in the general population [7–10].

With regard to local treatment for cancer, immunosuppression and the presence of the renal allograft in the iliac fossa must be considered. Together with the serum PSA level, the clinical stage and the histopathological data derived from the prostate biopsy, a risk-adapted therapeutic approach to the individual patient must be chosen [6]. In general, the same therapeutic interventions, i.e., active surveillance, radical prostatectomy (RP), radiotherapy and androgen deprivation, as in the general population, should be considered. Currently, 133 RTRs with prostate cancer who had a RP have been described, and only 11 have been treated with external beam radiotherapy or brachytherapy, due to the suboptimal functional and oncological outcome [7,11–30]. Recently the first reports on laparoscopic and robot-assisted retropubic RP (RRP) in RTRs were described in 16 and four patients, respectively, with apparently equal functional results to those from open RRP or perineal RP (RPP) [12,23–28].

Here we report one of the largest series of open RP for clinically localised prostate cancer in 23 consecutive RTRs. We compared RRP and RPP in terms of functional and oncological outcome, and surgery-related complications. The potential pitfalls of surgical and non-surgical approaches are discussed, and previous reports on the management of prostate cancer in RTRs are reviewed.

Patients and methods

We retrospectively analysed the prostate cancer database of our institution to identify all RTRs who had undergone RP for clinically localised prostate cancer. The retrospective data analysis was approved by the local ethics committee.

Between January 2000 and July 2011, 23 RTRs were diagnosed with clinically localised prostate cancer. The surgical approach was chosen according to the surgeon's preference, so 16 (70%) and seven (30%) patients had an open RRP with pelvic lymphadenectomy (PLND) and RPP, respectively. PLND was always done using an anatomically extended approach on the contralateral side of the renal allograft, as described previously [31], using a limited technique on the unilateral side of the renal allograft.

In all patients the increase in serum PSA levels during the routine follow-up after RT, with a mean of 1.1 (0.7–2.3) ng/mL, led to the suspicion of cancer, verified by TRUS-guided transrectal biopsy of the prostate with 8–14 cores. The biopsy Gleason score was $\leqslant 6$ in 17 (74%) patients, 7 in five (22%; 7a in three, 7b in two) and 8 in one (4%) patient. The PSA serum level was $\leqslant 10$ ng/mL in 20 (87%) patients and 10.1–20 ng/mL in three (13%).

Radionuclide bone scintigraphy and CT of the abdomen and the pelvis were reserved for patients with intermediate (five) and high risk (one) cancer, according to the European Association of Urology guidelines on prostate cancer [6]. None of the patients received neoadjuvant androgen deprivation or preoperative radiotherapy.

RRP and RPP were performed according to standardised surgical techniques used in non-RTRs, with two exceptions in the RRP group: (1) to prevent pressure damage to the transplanted kidney, the retractor blades of a self-retaining retractor system were placed just above the rectus abdominis muscle on the ipsilateral side of the renal allograft (if necessary, a hand-held retractor was introduced); and (2), to prevent injury to the ureter of the renal graft, the bladder was displaced

cephalad by a surgical towel and the assistant's hand, not using a retractor blade. The RP was performed as a nerve-sparing procedure in 10 patients with preoperatively preserved erectile function, applying the standard technique, and later using a high lateral incision [32].

PLND was performed in all patients with intermediate- and high-risk disease, and in 12 low-risk patients. It was omitted in five patients with a very low risk of lymph-node involvement [33]. In all patients silicone drains were placed after PLND and the drains remained *in situ* until the total volume discharged was < 50 mL/24 h.

In brief, the cranial border of LND was defined by the ureteric crossing of the common iliac artery, and laterally all lymphatic tissue overlying the external iliac artery, but not the pelvic side wall, was removed. Inferiorly, the femoral canal was the caudal margin of dissection and posteromedially all lymphatic tissue surrounding the obturator nerve, obturator vessels and the internal iliac artery was removed completely. Lymphatic vessels were either clipped or ligated, but no electrocautery was used, to completely occlude the lymphatics and to prevent lymphoceles. The dissected lymph nodes were submitted for histopathological analysis in separate packages, fixed in neutral buffered 4% formaldehyde for 24 h.

As with routine RP, a cystogram was taken at 5–7 days after surgery. Once the cystogram showed no or only minimal extravasation, the transurethral 20 F silicone bladder catheter was removed.

Unlike in routine RP, all RTRs received perioperative antibiotic prophylaxis with oral quinolones as long as the bladder catheter was in place. The anti-rejection medication was maintained peri-operatively with no changes, as discussed with the consulting nephrologists. Sixteen patients had been treated with a cyclosporin-A-based regimen and seven had been treated with a tacrolimus-based regimen.

Complications, and the functional and oncological outcomes, were compared to those in a group of 100 non-RTRs who had undergone RRP and RPP, respectively, by the same surgeons. Complications were defined as early or late if they developed within the first 30 days after surgery or later, respectively. Perioperative complications were graded as described recently [34], i.e., I = oral medication, II = intravenous medication, III = interventional endoscopy, transurethral manipulations or reoperation, IV = major organ resection, and V = death.

Patients were classified as continent if they required $\leqslant$1 pad/day in the absence of medical or surgical treatment. Erectile function was assessed according to the possibility of achieving erections sufficient for intercourse with and without 5-phosphodiesterase inhibitors.

The follow-up assessment comprised a physical examination by a DRE, and serial PSA measurement at 3-month intervals. Disease progression was defined as a PSA level of > 0.2 ng/mL followed by two confirmatory rises [6]. Patients with disease progression were evaluated for metastatic disease, and androgen-deprivation therapy was initiated at the discretion of the treating physician.

Results

The characteristics of the RTRs and the control group are shown in Table 1. The mean (range) patient age at the time of surgery was 64 (59–67) years, and the mean interval between RT and a diagnosis of prostate cancer was 95 (24–206) months. The mean (range) serum PSA level at the time of diagnosis was 4.5 (3.0–17.5) ng/mL.

RRP and RPP were technically feasible in all patients with no significant problems or complications (Table 1). The operative duration, blood loss and postoperative recovery did not differ significantly among the four groups, except that the RRP group always had a PLND, which resulted in an additional mean 25 min operative duration. There were two statistically significant differences in postoperative complications, in that impaired wound healing and perioperative wound infections developed more often in the RPP group (29% vs. 7%, $P < 0.05$). All complications were managed conservatively, with none of the patients requiring revisional surgery. Two additional patients in the RPP group reported the new onset of rectal symptoms, such as faecal incontinence and perineal pain. None of the patients developed Clavien grade III–V complications after surgery.

The mean (range) number of dissected lymph nodes was 15 (11–26) in the group of RTRs who had RRP, compared to 21 (12–32) lymph nodes in the control group.

The histopathological evaluation of the RRP specimens showed stage pT2a-cpN0 in 13 patients and stage pT3a-bpN0 in three patients. The Gleason score of the specimen was 6 (3 + 3) in 11, and 7a and 8 in three and one patient, respectively. In one patient a unifocal positive urethral margin was associated with a pT2cpN0 cancer and a Gleason score of 6 (3 + 3) was identified; currently, this patient is actively monitored but there was no evidence of biochemical recurrence at 18 months after RP. The histopathology of the RPP specimens showed organ-confined stage pT2a-c and locally advanced pT3a/b in three and four patients, respectively. The RP Gleason score was 6 (3 + 3) in two patients, and 7a and 7b in three and two patients, respectively. One patient had a bilateral positive surgical margin of 4 mm long at the apex, with a Gleason score of 6 (3 + 3). He is being monitored and his PSA level is < 0.1 ng/mL at 6 years after surgery.

Postoperative cystography at 5 days after RP showed no urinary extravasation at the urethrovesical anastomosis in 19 patients (83), but in four patients the

Table 1 The characteristics of RTRs undergoing RRP or RPP compared to a contemporary series of non-RTRs with clinically localised prostate cancer treated with RRP or RPP by the same surgeon. There were no significant differences between the groups.

Variable	RTRs		Controls	
	RRP	RPP	RRP	RPP
Number of patients	16	7	100	100
Mean (range):				
Age (years)	64 (59–67)	64 (52–69)	62.6 (49–72)	63.8 (42–74)
Preop. PSA level (ng/mL)	4.5 (3.0–17.5)	4.3 (3.6–10.5)	13.4 (1.6–39)	9.5 (2.5–15.6)
Biopsy Gleason score	6.4 (6–8)	6.3 (4–8)	6.2 (4–8)	6.1 (4–8)
Operative duration (min)	125 (105–215)	154 (132–215)	112 (85–150)	165 (124–256)
Blood loss (mL)	390 (100–1500)	520 (250–1500)	320 (150–1800)	650 (450–1500)
Hospital stay (days)	7.9 (5–13)	9.0 (5–14)	6.5 (3–14)	9.0 (8–17)
Duration of transurethral Catheterisation (days)	5.9 (5–12)	8.5 (7–13)	5.6 (4–19)	8.0 (7–12)

transurethral catheter was left in place until 12 days after RP, for minor leakage.

Ultrasonography of the small pelvis at 2 days after RP and at hospital discharge showed no lymphoceles. There was no prolonged lymphorrhoea and the mean (range) time of drainage was 3.4 (3–6) days. The mean (range) hospital stay was 7.9 (5–13) days.

Urinary continence was evaluated every 3 months after RP, using mailed questionnaires asking for the need and the number of pads/day. All patients responded to the questionnaire. The final evaluation for this report was at 1 year after surgery. The continence was excellent, with most patients being continent and requiring no pads, and two needing one safety pad/day. Erectile function with and without 5-phosphodiesterase inhibitors was preserved in six of the 10 patients in whom a nerve-sparing approach was used.

The mean (range) follow-up was 48 (45–141) months and 39 (10–85) months in the RRP and RPP groups, respectively. Currently, all patients have no evidence of disease, as shown by undetectable serum PSA levels.

Renal transplant function was well maintained in all patients, as documented by stable postoperative creatinine and urea nitrogen serum levels, at 1.4 (0.9–2.0) mg/dL and 45 (40–54) mg/dL, which did not differ significantly from the preoperative serum values of 1.3 (0.8–2.0) mg/dL and 48 (40–58) mg/dL. Ultrasonography of the renal graft at discharge showed no hydronephrosis in any patient.

Discussion

As the age limits for RT are extended to patients even in their sixties and seventies [1–4] it can be anticipated that significantly many of these men will have prostate cancer at time of RT. It was shown in recent studies of RT registries that the prevalence of prostate cancer in RTRs is equivalent to that in the general population [7–10]. It was concluded by various groups that the true risk of prostate cancer among RTRs remains underestimated, due to the lack of systematic screening by an annual DRE and serum PSA measurements [9,10]. In this context, it was shown that neither haemodialysis, immunosuppression or RT has a profound effect on serum PSA levels [21,22]. However, there is substantial evidence that free PSA is eliminated from the blood circulation by glomerular filtration, so that a decrease of up to 30% in serum free PSA levels can be expected after RT in patients with previous chronic renal insufficiency [35,36].

The early detection of prostate cancer appears to be even more crucial in RTRs, as it was suggested that immunosuppression might increase the biological aggressiveness of malignancies [9,37]. As there are so few patients, the natural history of prostate cancer in RTRs remains unknown, but there is some evidence that immunosuppression might depress T-cell responsiveness, thereby enhancing disease progression. The type of immunosuppression is thought to have a profound effect on the development of cancer after RT [9,37,38]. Cyclosporin might be associated with an increased risk of malignancies, whereas other agents such as mycophenolic-acid base agents and sirolimus are associated with a lower risk of cancer [9]. However, the prognosis of early-detected and adequately treated cancers of the genitourinary tract does not differ significantly from non-RTRs [38]. Kleinclauss et al. [9] evaluated 62 RTRs with prostate cancer who were treated at different transplant centres in France. The authors concluded that the type of immunosuppressive maintenance regimen was the only independent risk factor associated with the presence of locally advanced and metastatic prostate cancer. Patients with a combined protocol of calcineurin inhibitors and azathioprine had a nine times higher risk of developing locally advanced prostate cancer (odds ratio 8.7, 95% CI 1.8–42, $P = 0.007$) than those only receiving azathioprine. The risk of having locally advance disease and/or metastasis was 44% and the risk of dying from prostate cancer was 24% after a mean follow-up of only 25 months, which is significantly higher than in the group of non-RTRs. In the present group

of 23 RTRs, none of the patients developed biochemical recurrence or died from cancer after a mean follow-up of 39 months. Based on these data, active treatment instead of active surveillance might be the most appropriate treatment to be offered to RTRs with biopsy-confirmed prostate cancer, dependent on stage, grade and the age of the patient.

With regard to the treatment of prostate cancer there is a general consensus that the same therapeutic interventions should be used as in the general population, and that aggressive approaches should not be withheld from RTRs [1,7]. This recommendation is based on data from recent retrospective studies that compared the long-term outcome of the renal graft among RTRs aged >60 years with those of younger patients [1–5]. None of the studies showed significant differences in patient and graft survival at 1, 5 and 10 years.

As to the method of treatment, RRP and RPP, three-dimensional conformal radiotherapy and interstitial brachytherapy are available options for managing clinically localised disease [6]. In the present study, radiotherapy was not considered as the most appropriate method as it has had poor oncological and functional outcomes [30]. Clinical experiences with radiotherapy are limited to external-beam radiotherapy in eight RTRs and brachytherapy in three [29,30]. After a mean follow-up of 28 months, a quarter had a biochemical relapse, a quarter developed significant obstruction of the terminal ureter, resulting in the need for surgical reimplantation, and one patient had a significantly decreased function of the renal graft.

RRP and RPP with or without PLND were regarded as the preferred method in the present 23 patients. Several challenges might be associated with any type of cancer surgery in RTRs, such as a greater risk of impaired wound healing and perioperative complications, and more difficult surgery due to perivesical and intrapelvic scar tissue. Several proponents of RP are in favour of the perineal approach, as it might not subject the renal allograft and its ureter to a potential risk, and as it might not interfere with a subsequent repeat RT if the graft fails in future due to the lack of a PLND [11,13,17]. On the contrary, RPP is associated with a lack of important histopathological information of the lymph nodes, an increased frequency of wound infections, and increased frequency of functional rectal impairments. According to the most recent guidelines, an extended PLND should always be used in patients with intermediate- and high-risk prostate cancer, due to the increased frequency of microscopic lymph-node involvement, whereas a PLND can be omitted in patients with low-risk disease [33]. The principles of cancer surgery should not be neglected for the sake of an anatomically easier approach. However, wound infections might be significantly more common after RPP, as was shown in a recent direct comparison with RPP [39]. Wound infections developed in 20% and none of the men undergoing RPP and RRP, respectively, with the

Table 2 Previous reports of RP in RTRs.

References	*n* patients	RP	PLND	bNED	Follow-up (months)	Graft injury
[16]	1	RRP	1	1		0
[15]	3	RRP	3	3		0
[18]	2	RRP	?	No data		0
[14]	1	RRP	1	1		0
[8]	9	RRP		8		0
[19]	2	RRP	0	No data		0
[7]	9	RRP	6	6		0
[20]	16	RRP	0	16	25	0
[21]	9	RRP	0	9	13	0
[11]	20	RRP	0	–		2[†]
[22]	9	RRP	0	8	58	0
Present	16	RRP	16	16	48	0
	7	RPP	0	7	39	0
[17]	2	RPP	1	No data		0
[13]	7	RPP	0	6	22	0
[23]	9	Laparoscopic	0	9		0[*]
[24]	2	Laparoscopic	0	2	24 & 36	0
[25]	3	Laparoscopic	0	3		
[26]	1	Laparoscopic	0	1		0
[12]	1	laparoscopic	0	1		0
[27]	3	RALP	0	3	13	0
[28]	1	RALP	0	1	11	0
Total, n (%)	133	–	27 (20)	94%		2 (1.5)

[*] Significantly greater frequency of rectal injury vs. non-RTR (22% vs. 1.8%, $P = 0.022$); RALP, robot-assisted laparoscopic radical prostatectomy; bNED, no evidence of biological recurrence.

[†] Two ureteric injuries, significantly greater rate of systemic bacterial infections vs. non-RTR (15% vs. 2.5%, $P = 0.01$);

need for surgical therapy in 4% of men. Also, in the present series, wound infections were significantly more common in the RPP than in the RRP group. As RTRs are immunosuppressed, the surgical approach with the lowest probability of infectious complications should be chosen.

In the present study, there were no significant differences in functional and oncological outcomes when comparing RTRs to a series of controls who also had RRP and RPP. The follow-up of the patients was uneventful, continence rates were similar to controls, and surgical cancer control was excellent, with all patients having undetectable serum PSA levels and no evidence of disease [29]. Including the result of the present retrospective series, data on 110 and 23 RTRs with prostate cancer who had RRP or RPP, respectively (Table 2) [7,8,11–28] have been reported [8,11–18]. In all cases, RP was safe, with no significant complications, and with the maintenance of a well-functioning graft. We, in accordance with others, had found no significant disadvantages for the RRP compared with RPP. In our experience bladder descent was never impaired because of a fixed allograft or the transplant ureter, and in all cases a tension-free vesicourethral anastomosis was made. Especially for patients with intermediate- and high-risk disease, the RRP offers the possibility to use a staging PLND in these men who are at a greater risk of microscopic lymph-node involvement [6]. In men with low-risk disease and $< 50\%$ of prostate biopsies involved, we agree that PLND is not mandatory, and both RPP and RRP will result in the same high oncological efficacy [33].

As noted above, the first laparoscopic and robot-assisted RRP in RTRs were reported in 16 and four patients, respectively, with apparently equal functional results to those from open RRP or RPP [12,23–28]. Therefore, a minimally invasive approach might be considered in experienced centres.

In conclusion, we propose a surgical approach to RTRs with clinically localised prostate cancer. Compared to other treatment options, RP offers optimal cancer control with low morbidity, an extremely low risk of renal-graft injury, and a long-term cure of prostate cancer. In our opinion, both the RRP and RPP are equally effective, and the selection of the surgical technique should be based on the surgeon's experience, the oncological need for a PLND, the lowest likelihood of harming the renal graft, and the lowest probability of even minor complications to the RTR.

Conflict of interest

None.

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None.

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