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Original Article

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Management of localized prostate cancer by retropubic radical prostatectomy in patients after renal transplantation

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Abstract

Background. The study aimed to report our experience with retropubic radical prostatectomy (RRP) for treatment of localized prostate cancer in renal transplant recipients (RTR).

Methods. Data of 16 RTR who had an RRP between 2001 and 2007 were retrospectively analysed and compared to the data of 294 non-transplanted patients who were operated for RRP during the same period. Diagnostic work-up consisted of digital rectal examination, serum prostate specific antigene levels, as well as Transrectal Ultrasonography (TRUS)-guided prostate biopsy. Follow-up was obtained in all patients with a mean follow-up time of 2.1 years in RTR.

Results. Mean time distance to the renal transplantation at the time of RRP was 81.2 ± 19.1 months. RRP was successfully performed and tolerated in all RTR without pelvic lymph node dissection. No major complications occurred during or after the operation. There were two minor complications in transplant group (prolonged haematuria and urinary leakage). Mean operative time was 108.3 ± 3.9 min in transplant group, which was significantly longer as in non-transplanted group (89.1 ± 4.1, $P < 0.05$). Mean estimated intra-operative blood loss was significantly lower in transplant group ($P < 0.05$). In RTR, one case of positive surgical margins was present (R_1: 6.2 vs. 12.3% in non-transplanted group, $P < 0.05$). None of the RTR had impairment of graft function. At follow-up, no case of biochemical recurrence was observed in RTR.

Conclusions. RRP is safe and feasible for management of localized prostate cancer in patients with kidney allograft being under immunosuppression. However, concern about impairment of graft function, infection and wound healing remains important.

Keywords: kidney transplantation; prostate cancer; prostate specific antigene; radical prostatectomy

Introduction

The increased relative risk for cancer in renal transplant recipients (RTR) has been well established. The incidence of post-transplant cancer increases with time, recipients' age, duration and cumulative dose of immunosuppressive therapy and is associated with high morbidity and mortality [1]. With improved management and better outcomes of post-transplant infections and cardiovascular complications, it is plausible that in the future post-transplant cancer may become an increasingly important cause of death. The relative risk for cancer in transplant recipients is different among the various cancers. Some cancers like breast and colon occur at a 1 to 2-fold increased frequency, whereas skin cancers occur at greater than a 100-fold increased frequency compared with the general population [2]. Prostate cancer is the most common tumour and cause of cancer-related deaths in men. This statistic, combined with increasing numbers of older male transplant recipients, makes prostate cancer an increasing health risk in transplant recipients.

Immunosuppression, the presence of a pelvic renal graft and the potential for future transplants in the event of graft failure are all factors that must be considered when managing prostate cancer after renal transplantation. In the reported series of patients with prostate cancer after organ transplantation, more were found to have localized disease at the time of diagnosis than in the general population, and aggressive interventions were recommended [3,4]. Radical prostatectomy (RP) has been reported as a therapeutic option for the management of localized disease but it still carries some risk of injury to the renal graft, ureter or bladder in RTR [5,6]. Retropubic radical prostatectomy (RRP) has been used successfully in heart recipients without complication and likely transplant patients of non-pelvic organs would do well with surgery [7,8]. For patients with renal or pancreas transplants, inconclusive data are available regarding the risks and benefits of different approaches for RP [9]. For instance, perineal prostatectomy has been reported to lower the risk of graft injury as the perineal ap-

Table 1. Characteristics of the patient's population

Variable	KTx + RRP	RRP
Number of patients	16	294
Age (years)		
Mean ± SD	61.8 ± 8	64.4 ± 9.3
Range	51–66	49–77
Time since KTx (months)		
Mean ± SD	81.2 ± 19.1	
Range	28–219	
Mean PSA ± SD (ng/mL)	4.7 ± 1.4	6.32 ± 1.7
Gleason sum biopsy		
5–6	11/16	162/294
7	5/16	86/294
>7	0	46/294
Mean follow-up (years)	2.1	2.8

SD, standard deviation; KTx, kidney transplantation; RRP, retropubic radical prostatectomy.

proach avoids the need to disturb the area of transplanted organ [10]. However, most urologists are more familiar with RRP for treatment of localized prostate cancer. In addition, due to lack of the possibility of pelvine lymphadenectomy, the perineal approach might not be indicated in many patients. In this report, we present our experience with RRP for management of localized prostate cancer in RTR.

Materials and methods

This is a retrospective, single-centre analysis including 16 RTR who had an RRP between 2001 and 2007. In addition, data of 294 non-transplanted patients who were operated for RRP during the same period were collected. All available clinicopathological data were reviewed; all patients presented with an elevated serum prostate specific antigene (PSA) levels, three had abnormal digital rectal examination (DRE) findings. In all cases, the diagnosis was confirmed on TRUS-guided prostate biopsy. Clinical and pathological staging was assigned using the 2002 TNM guidelines. Radionuclide bone scintigraphy and cross-sectional imaging were reserved only for patients with a PSA level of >15 ng/mL, suspicion of locally advanced disease or the presence of poorly differentiated cancer on needle biopsy (Gleason score >7). None of the patients in the transplanted series received preoperative hormone or radiation therapy. Patients underwent a standard open RRP as described by Walsh [11]. After RRP, the patients received standard routine care, including immediate return to diet (as tolerated), ambulation and then on the evening after surgery, immediate resumption of their immunosuppressive regimen. The Penrose drain was removed 2 or 3 days after RP, depending on the volume of drainage, and the patients discharged home after the urinary catheter was removed 7 days after RP. The follow-up consisted of physical examination, including a DRE and serial serum PSA measurements every 3 months. PSA failures were defined as men with a PSA of >0.4 ng/mL and increasing after three consecutive measurements. Follow-up was obtained in all patients with a mean follow-up time of 2.1 years in transplant group (vs. 2.8 years in non-transplanted group; Table 1). Statistical analysis was performed using SigmaPlot® software version 11.0 (SPSS Inc., Chicago, IL, USA). Depending on the normal distribution of the variable, Mann–Whitney or ANOVA tests were applied. Data are expressed as mean ± standard deviation (SD), and statistical significance was accepted at $P < 0.05$.

Results

The preoperative patients' characteristics are listed in Table 1. The mean ± SD (range) age at surgery in transplanted group was 61 ± 8 (51–66) years, and the mean interval from renal transplant to RRP was 81.2 ± 19.1 months (range 28–219 months). All patients had a cadaveric transplant before the operation. The maintenance immunosuppression protocol was standardized in all recipients consisting of a triple combination (tacrolimus, methylprednisolone and mycofenolate mofetil). RRP was successfully performed and tolerated in all transplant patients without pelvic lymph node dissection. Peri- and post-operative clinical data for both groups are listed in Table 2. However, in transplant group, no major complications occurred during or after the operation. There were two minor complications in two transplant patients: prolonged haematuria in one patient (6.2%) with requirement for blood transfusion and urinary leakage at the site of vesico-urethral anastomosis (6.2%), which required prolonged catheterization. Mean operative time was 108.3 ± 3.9 min (88–188 min) in the transplant group, which was significantly longer as in non-transplanted group (89.1 ± 4.1, $P < 0.05$). Mean estimated intra-operative blood loss was significantly lower in the transplant group, 211.1 ± 87.1 mL (128–498 mL) versus 349 ± 102 mL (200–980 mL, $P < 0.05$). Mean duration of hospital stay was 10.1 ± 3.4 days (7–18 days) in the transplant group comparable to the non-transplant group (Table 2). Post-operative oncological outcomes are shown in Table 3. In transplant group, one case of positive surgical margins was present (R_1: 6.2%), with this significantly differing from 36 cases of positive surgical margins in non-transplanted group (12.3%, $P < 0.05$). As further shown in Table 3, all cases of carcinoma in transplanted group were organ-confined, compared to 34% of $pT_{3a/b}$ histological findings in non-transplanted group ($P < 0.05$). As far as graft function is concerned, none of the patients had impairment of their graft function by discharge, as shown by stable levels of serum creatinine as a measure of graft function (preoperative: 1.12 ± 0.12 mg/dL vs. post-operative: 1.18 ± 0.39 mg/dL). At follow-up, none of the patients had evidence of biochemical recurrence.

Table 2. Operative outcomes and complications

Variable	KTx + RRP (n = 16)	RRP (n = 294)
Surgery time (mean ± SD; min)	108 ± 3.988–188	89.1 ± 4.1*(65–182)
Estimated blood loss (mean ± SD; mL)	211.1 ± 87.1128–498	349 ± 102*(200–980)
Intra-operative transfusion	1/16 (6.2%)	3.7%
Hospital stay (mean ± SD; d)	10.1 ± 3.4	9.4 ± 1.8
Complications (%)		
Prolonged haematuria	6.2% (1/16)	3.7%
Rectal lesion	0%	1.4%
Lymphocele	0%	3.7%
Revision	0%	2.8%
Wound infection	0%	3.6%
Urinary leakage	6.2%	8.4%
Duration of catheterization (days)	12.4	10.3

SD, standard deviation; KTx, kidney transplantation; RRP, retropubic radical prostatectomy.*$P < 0.05$.

Table 3. Onco-pathological outcomes

Variable	KTx + RRP (n = 16)	RRP (n = 294)
Gleason sum after RRP		
6	87%	73%
7	13%	23%
8	0%	4%
Pathological state, %		
pT2a	14%	19%
pT2b	24%	22%
pT2c	62%	25%*
pT3a/b	0%	34%*
Surgical margins		
R_0	15/16	258/294
R_1	1/16 (6.2%)	36/294 (12.3%)*
Positive lymph nodes, %	NAV	2.1

KTx, kidney transplantation; RRP, retropubic radical prostatectomy. *$P < 0.05$.

Discussion

Malignancy is a well-recognized complication of transplantation. The increased incidence has been attributed to the decreased immuno-surveillance, activation of oncogenic viruses, chronic stimulation of the immune system and immunosuppression [12]. In 2003, the United States Renal Data System (USRDS) reported that genitourinary (GU) malignancies were the second most common tumours in transplant recipients after skin cancers [13]. GU tumours demonstrate a significant impact on graft survival and function, with a 3-fold increase of death with a functioning graft and an increased risk of death-censored graft failure [14]. Furthermore, the USRDS reported a 3-year cumulative incidence of 3.1% for prostate cancer, 2.2% for renal cell carcinoma, 0.7% for bladder cancer and 0.1% for testes [13]. Although it is clear that GU tumours can have an impact on transplant recipients, renal patients present with unique problems not seen with other organ recipients, namely that allograft dysfunction can occur due to the proximity of the organ to the treatment field. This can occur either directly with organ injury or indirectly with obstruction or bladder dysfunction.

In the present retrospective analysis, surgery was the preferred method of treatment of organ-confined prostate cancer in kidney transplant recipients, specifically using the retropubic approach. Data from this study reveal that the RRP is clinically and oncologically safe in patients after renal transplantation. Bladder descent was not impaired by the allograft or by the ureteric reimplantation and a tension-free vesico-urethral anastomosis was easily achieved. There was no significant increased blood loss, transfusion requirement or hospital stay in the present series, compared with a series of non-transplant patients undergoing RRP during the same period at our institution. All the present patients returned to their baseline creatinine before discharge, and only one required a blood transfusion. There were no major complications and only two minor complications, which resolved with conservative management. In this series, one patient had positive surgical margins, which was focal and located at the apex of the prostate. Large contemporary series comparing perineal and RRP have reported no significant differences in margin positivity rates [15,16]. Although there were few patients in the present series, the margin positivity rate (6.2%) is lower compared to our own series (12.3%, $P < 0.05$) and to other large RRP series in non-transplanted patients [16].

Surgical therapeutic options for localized prostate cancer in renal transplant patients being under immunosuppression include retropubic, perineal or laparoscopic radical prostatectomy (LRP) [5,18]. However, which one of the procedures constitutes the optimal clinical and oncological therapeutic strategy is still a matter of debate. Nevertheless, pitfalls in management of PCa in renal transplant patients include the presence of a pelvic renal graft, potential for future transplants in the event of graft failure and the possibility of pelvic lymph node dissection. The current consensus is that perineal RP offers a similar outcome for potency, continence and cancer control when compared with RRP [19]. However, perineal RP does not offer the possibility of pelvic lymph node dissection, while this is possible at the contralateral side when performing retropubic or laparoscopic retroperitoneal RP. For instance, Antonopoulos *et al.* reported on eight cases of RRP with contralateral pelvic lymphadenectomy in kidney transplant recipients [20]. While the operative time was similar to our series, the mean estimated blood loss was somewhat higher in their series (656 mL) with two patients requiring blood transfusion. Also, 2/8 (25%) patients in this study had positive surgical margins, which was clearly higher than in our study. For perineal RP after kidney transplantation, Hafron *et al.* reported on a series of seven patients [10]. In this series, mean operative time was 92.7 min, and mean estimates blood loss was 492 mL. However, also in this study, there were two cases of positive surgical margins. In the meantime, there are some few reports on LRP in RTR. Thomas *et al.* reported on transperitoneal LRP in three kidney transplant patients performed in a high-volume laparoscopic centre [17]. The average operative time in this small series was 237 min, and mean estimated blood loss was 425 mL. In this report, relatively short duration of hospital stay (mean 3.3 days) was noted. Recently, Robert *et al.* reported on nine cases of extraperitoneal LRP in RTR [18]. Lymph node dissection was performed in one patient. While they had no case of blood transfusion, the incidence of rectal injury was 22.2%. Furthermore, at follow-up after 6 months, one patient had thrombosis of the iliac vein with extension to the renal allograft vein resulting in loss of the function of transplant graft. External beam therapy, as a non-surgical option for management of localized PCa in kidney transplant recipients, has been shown to be feasible in one publication [21]. Mouzin *et al.* reported on the use of three-dimensional conformal radiotherapy (nine-field, 70 Gy in 2-Gy fractions) in eight RTR. After a mean follow-up of 28 months, two patients showed a biochemical recurrence (25%). Furthermore, a significant obstruction of the terminal ureter occurred in two patients [21]. However, given these results, the safety of this method is somewhat questionable, as the ureteral obstruction might enhance the risk of graft dysfunction and/or require an endoscopic or open surgical revision.

An important issue to consider when treating renal transplant patients is the risk of future graft failure, which

is a serious complication and associated with a high mortality rate. After graft failure, the patient survival at 5 years has been reported to be between 57 and 64% [22]. The lifetime risk of graft failure and need for subsequent repeat transplantation is up to 33% [23]. Thus, in transplant recipients operated for localized prostate cancer, the graft function should be monitored carefully after a radical procedure. However, in the present study, we did not observe any impairment of graft function in the early and late phase after the RRP. Except for one case of iliac vein thrombosis with subsequent renal vein thrombosis in the report by Robert *et al.*, no other case of graft loss related to the RP has been reported so far [18]. Thus, aggressive therapeutic interventions in the appropriate clinical setting should not be withheld in renal transplant patients with prostate cancer. Age, general state of health, clinical stage, serum PSA and Gleason sum remain critically important in determining the proper treatment for localized prostate cancer.

The natural history of prostate cancer in the immunosuppressed patient is unknown but there is mounting evidence to indicate that immunosuppression may enhance malignant cell growth; it increases the risk of neoplasia by three to five times that in age-matched controls in the general population [24]. In a retrospective review of 1297 renal transplant patients with pre-existing tumours, most recurrences were within 2 years, correlating with the initiation of immunosuppression [25]. Furthermore, 52% of the patients treated >5 years before transplantation died from metastatic disease within 2 years of the transplantation, raising the possibility that immunosuppression may have stimulated the growth of dormant metastases. In the present study, after 24 months of follow-up, none of the patients had evidence of biochemical recurrence. Nonetheless, there are very few comprehensive studies that have addressed the effect of long-term immunosuppression on prostate cancer, although in the early reported series (18 patients, 1998) those presenting with advanced or metastatic disease progressed more rapidly than the general population, and the therapy tended to fail earlier than in patients not immunosuppressed [3]. More recently, Kleinclauss *et al.* reported on a retrospective multi-centre study to determine the characteristics of prostate cancer in RTR and to analyse the relation with immunosuppressive maintenance therapies [4]. Using data of 62 patients from 19 French transplant centres, it showed that patients with more heavy maintenance immunosuppressive therapy (calcineurin inhibitors and azathioprine) presented more high-stage prostate cancer (T3 and T4) and had a non-significant increase in lymph node invasion [4]. Therefore, expectant management with a patient on immunosuppressive therapy has the potential for a poor outcome and is not recommended to any of the present patients. Until there is definite evidence that immunosuppression has no adverse effects on prostate cancer, we consider that watchful waiting should be reserved for highly selected patients. More recently, interest has grown in the anti-tumoural effect of rapamycin, a mammalian target of rapamycin inhibitor, which functions also as an immunosupressant. Experimental data have shown that sirolimus may inhibit tumour cell growth, enhance the apoptosis and prevent disease progression in prostate cancer cell lines and in a Pten-deficient mouse model of prostate cancer [26–28]. Furthermore, in clinical studies, sirolimus has also been associated with a decreased incidence of *de novo* post-transplant malignancies (including prostate cancer) in RTR [29]. In non-transplant patients, sirolimus is currently tested in preclinical and clinical studies for treatment of solid organ tumours, including prostate cancer [30,31].

Conclusion

In conclusion, RRP is safe and feasible for management of localized prostate cancer in patients with kidney allograft being under immunosuppressant therapy. However, concern about impairment of graft function, infection and wound healing remains important.

Conflict of interest statement. None declared.

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