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

M. Raschid Hoda, Amir Hamza, Francesco Greco, Sigrid Wagner, Olaf Reichelt, Hans Heynemann, Kersten Fischer and Paolo Fornara

Clinic for Urology and Kidney Transplantation Centre, Martin Luther University Halle/Wittenberg, Ernst-Grube-Strasse 40, 06120, Halle, Germany

Correspondence and offprint requests to: Raschid M. Hoda; E-mail: rhoda@ucsd.edu

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 antigen 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 hematuria 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 (R1+: 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 antigen; 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-
Gleason sum biopsy

<table>
<thead>
<tr>
<th>Variable</th>
<th>KTx + RRP</th>
<th>RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>16</td>
<td>294</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>61.8 ± 8</td>
</tr>
<tr>
<td>Range</td>
<td>51–66</td>
<td>49–77</td>
</tr>
<tr>
<td>Time since KTx (months)</td>
<td>Mean ± SD</td>
<td>81.2 ± 19.1</td>
</tr>
<tr>
<td>Mean PSA ± SD (ng/mL)</td>
<td>4.7 ± 1.4</td>
<td>6.32 ± 1.7</td>
</tr>
<tr>
<td>Gleason sum biopsy</td>
<td>5–6</td>
<td>11/16 162/294</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>5/16 86/294</td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>0 46/294</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>2.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

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

The approach 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 pelvic 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 antigen (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 mycophenolate 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 (R1: 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 pT3a/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 1. Characteristics of the patient's population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>KTx + RRP</th>
<th>RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>16</td>
<td>294</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>61.8 ± 8</td>
</tr>
<tr>
<td>Range</td>
<td>51–66</td>
<td>49–77</td>
</tr>
<tr>
<td>Time since KTx (months)</td>
<td>Mean ± SD</td>
<td>81.2 ± 19.1</td>
</tr>
<tr>
<td>Mean PSA ± SD (ng/mL)</td>
<td>4.7 ± 1.4</td>
<td>6.32 ± 1.7</td>
</tr>
<tr>
<td>Gleason sum biopsy</td>
<td>5–6</td>
<td>11/16 162/294</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>5/16 86/294</td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>0 46/294</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>2.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

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

**Table 2. Operative outcomes and complications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>KTx + RRP</th>
<th>RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery time (mean ± SD; min)</td>
<td>108 ± 3.988–188</td>
<td>89.1 ± 4.1 *(65–182)</td>
</tr>
<tr>
<td>Estimated blood loss (mean ± SD; mL)</td>
<td>211.1 ± 87.128–498</td>
<td>349 ± 102*(200–980)</td>
</tr>
<tr>
<td>Intra-operative transfusion (mean ± SD; mL)</td>
<td>1/16 (6.2%)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Hospital stay (mean ± SD; d)</td>
<td>10.1 ± 3.4</td>
<td>9.4 ± 1.8</td>
</tr>
<tr>
<td>Complications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged haematuria</td>
<td>6.2% (1/16)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Rectal lesion</td>
<td>0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Revision</td>
<td>0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Urinary leakage</td>
<td>6.2%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Duration of catheterization (days)</td>
<td>12.4</td>
<td>10.3</td>
</tr>
</tbody>
</table>

SD, standard deviation; KTx, kidney transplantation; RRP, retropubic radical prostatectomy. *P < 0.05.
Pathological state, %  
Gleason sum after RRP  
3418 M. R. Hoda  
paring perineal and RRP have reported no significant differ-
ations and only two minor complications, which resolved
quired a blood transfusion. There were no major complica-
period at our institution. All the present patients returned to
no significant increased blood loss, transfusion requirement
KTx, kidney transplantation; RRP, retropubic radical prostatectomy.
\*P < 0.05.

Discussion

Malignancy is a well-recognized complication of trans-
plantation. The increased incidence has been attributed to
the decreased immuno-surveillance, activation of oncogenic
viruses, chronic stimulation of the immune system and immuno-
suppression [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 in 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 pre-
ferred method of treatment of organ-confined prostate can-
cer in kidney transplant recipients, specifically using the
retropubich approach. Data from this study reveal that the
RRP is clinically and oncologically safe in patients after re-
nal 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 re-
quired a blood transfusion. There were no major complica-
tions 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 com-
paring perineal and RRP have reported no significant differ-
ences 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 pa-
ents [16].

Surgical therapeutic options for localized prostate cancer in renal transplant patients being under immuno-
suppression include retropubic, perineal or laparoscopic radical prostatectomy (LRP) [5,18]. However, which one
of the procedures constitutes the optimal clinical and on-
cological therapeutic strategy is still a matter of debate. Nevertheless, pitfalls in management of PCs in renal trans-
plant 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 out-
come 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 ret-
ropubic 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 pos-
itive 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 mean-
time, there are some few reports on LRP in RTR. Thomas
et al. reported on transperitoneal LRP in three kidney trans-
plant 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 in-
jury 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
the transplant graft. External beam therapy, as a non-surgical op-
tion for management of localized PCs 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%). Fur-
thermore, a significant obstruction of the terminal ureter
occurred in two patients [21]. However, given these re-
results, the safety of this method is somewhat question-
able, 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 immunosuppressant. 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 Pt-en-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.

References


Received for publication: 26.12.09; Accepted in revised form: 15.3.10