Prostate cancer in renal transplant recipients

François Kleinclauss1,2, Marc Gigante1,3, Yann Neuzillet1,4, Marc Mouzin1,5, Nicolas Terrier1,6, Laurent Salomon1,7, François Iborra1,8, Jacques Petit1,9, Luc Cormier1,10 and Eric Lechevallier1,4 for the Renal Transplantation Committee of the French Urological Association (AFU)*

1Renal Transplantation Committee of the French Urological Association, Paris, 2Department of Urology, University Hospital Saint Jacques, INSERM U645, Besançon, 3Department of Urology, University Hospital of Nice, Nice, 4Department of Urology, University Hospital Salvard, Marseille, 5Department of Urology, University Hospital Rangueil, Toulouse, 6Department of Urology, University Hospital, Grenoble, 7Department of Urology, University Hospital Mondor, Creteil, 8Department of Urology, University Hospital Lapeyronie, Montpellier, 9Department of Urology, University Hospital Sud, Amiens and 10Department of Urology, University Hospital Nancy-Brabois, Nancy, France

Abstract

Background. We conducted a retrospective multi-centre study to determine the characteristics of prostate cancer in renal transplant recipients (RTR) and to analyse the relation with immunosuppressive maintenance therapies.

Methods. Patients from 19 French transplant centres diagnosed with prostate cancer at least 1 year after kidney transplantation were included in this study. Data regarding demographics, kidney transplantation, prostate cancer and immunosuppressive treatment were analysed.

Results. Sixty-two patients met the eligibility criteria for this study. Thirty-eight patients (61.3%) received calcineurin inhibitors (CNI) and azathioprine (AZA) with or without steroids, twenty received CNI with or without steroids (32.2%) and four received CNI and mycophenolate mofetil (6.5%). Patients with CNI and AZA immunosuppressive therapy presented more high-stage cancer (T3 and T4) when compared to patients receiving CNI alone (47.5% versus 15%, respectively, \(P = 0.03\)). A non-significant increase in lymph node invasion was found in patients receiving CNI and AZA compared to patients receiving CNI alone (21% versus 5%, \(P = 0.16\)). In the multivariate analysis, the immunosuppressive regimen with CNI and AZA was the only independent risk factor for locally advanced disease (\(P = 0.007\)).

Conclusion. Our results showed that RTR are at risk for early occurrence and for locally advanced prostate cancer, especially when they received a CNI and AZA maintenance immunosuppressive therapy.

Keywords: cancer; immunosuppression; kidney; prostate; transplantation

Introduction

Renal transplant recipients (RTR) are at high risk for de novo cancers, especially skin cancer and post-transplant lymphoproliferative disorder (PTLD) with an incidence 4- to 20-fold higher than that in the general population [1–4]. Genito-urinary (GU) malignancies have been reported to be the second most common malignancies in the RTR population in the United States [5].

The first study of prostate cancer incidence in RTR found it to be similar to the general population [6]. However, with the increased RTR lifespan and recipient age at the time of transplantation and better screening practices, prostate cancer has become frequent in this population. This first evaluation of prostate cancer incidence by Penn [6] was discussed by authors finding an increased incidence of this cancer in RTR with a risk 2- to 5-fold higher than that in the general population [4,7–9].

The role of immunosuppressive therapy in the carcinogenesis among RTR was the subject of many works [6,10], but their role in prostate cancer occurrence is unclear. However, many arguments obtained in vitro or in experimental animal models are in favour of a key role of immunosuppression on prostate adenocarcinoma occurrence. In a previous work, we have demonstrated that the
anti-lymphocytes globulins, involved in the occurrence of skin cancers through an induced severe lymphopenia [11], were not involved in prostate adenocarcinoma occurrence [12]. Calcineurine inhibitors (CNI) were involved in the occurrence of post-transplant malignancies [10]. Several works showed that CNI increase in vitro and in vivo aggressiveness and progression of prostate adenocarcinoma tumour cells [13,14]. Moreover, it was demonstrated in an experimental model of prostate adenocarcinoma in rats that cyclosporine increased the incidence of metastatic forms [14] through an increased secretion of transforming growth factor-β that supports aggressiveness and mobility of tumour cells [15]. Azathioprine (AZA) was involved in skin cancer occurrence because of the direct carcinogenic effect of the molecule [16]. Nevertheless, no links with prostate adenocarcinoma occurrence was found. Conversely to AZA, mycophenolate mofetil (MMF) does not seem to be associated with an increased risk of post-transplant malignancies in registry or multi-centre studies [17–19]. Prostate cancer incidence in RTR under MMF is still unknown. The mTOR inhibitors do not seem to be involved in the occurrence of prostate cancer in RTR. Rapamycin was shown to reduce the incidence of post-transplantation cancers including prostate cancer [20–22], and some molecules derived from the rapamycin were tested on the prostate adenocarcinoma cell lines resulting in an inhibition of the growth of tumoural cells [23,24].

All these data demonstrated a complex relationship between immunosuppressive drugs and prostate tumour cells and suggested that immunosuppressive therapies could interfere with the natural evolution of prostate cancer in RTR.

The objectives of our study were to analyse prostate cancer characteristics according to the immunosuppressive maintenance regimen used and to evaluate the potential relation between the immunosuppressive maintenance regimen and the prostate cancer evolution in RTR.

Patients and method

We conducted a multi-centre retrospective study regarding the immunosuppressive treatment in patients who developed prostate cancer after kidney transplantation. Twenty-two French renal-transplant centres belonging to the Renal Transplantation Committee of the French Urological Association (AFU) were asked to participate in this study. The survey concerned the sociodemographic characteristics of RTR, the diagnosis, staging, treatment modalities and evolution of prostate disease, as well as the type and duration of immunosuppression. Nineteen (86%) of the twenty-two centres contacted, responded to the initial enquiry and all included patients in the study. The inclusion criteria were as follows: kidney transplantation at least 1 year before prostate cancer diagnosis and a functioning kidney graft at the time of prostate cancer diagnosis. Patients with more than one renal transplant and the same immunosuppressive treatment for all grafts were included in the study. The global immunosuppression duration was calculated by adding the treatment time of each transplant period. Patients with multiple changes in immunosuppressive drug’s family before prostate cancer occurrence were excluded.

Data from 66 patients, transplanted between June 1983 and May 2005, presenting prostate carcinoma after renal transplantation were collected. Among these 66 patients, 3 were excluded from the study because the transplant-cancer interval was <1 year and another patient was excluded because of a non-functioning graft at the time of cancer occurrence. No patient was excluded because of multiple changes in immunosuppression during the transplantation period. Therefore, data regarding 62 patients (60 patients with a first transplant and 2 patients with a second transplant) with prostate cancer at least 1 year after kidney transplantation were analysed.

Prostate cancer (PCA) detection was performed with prostate-specific antigen (PSA) level and digital rectal examination (DRE). Nevertheless, the use of a systematic screening of PCA depended on team customs and may vary over time. All PCA were biopsy proven.

Categorical variables were analysed using the chi-square test and Fisher’s exact test when applicable. Continuous variables were analysed parametrically using Student’s t-test and non-parametrically using the Kruskal–Wallis test or the Mann and Whitney test. For univariate analysis, $P<0.05$ defined a statistical significance.

Regarding the findings of the univariate analysis, we performed a multivariate analysis (logistic regression) adopting locally advanced prostate cancer (extraprostatic disease, T3, T4, N+, M+; TNM Classification 2002) occurrence as endpoint. Different variables, such as age at diagnosis, age at transplantation, history of immunosuppression-induced cancer, immunosuppressive maintenance therapy as well as immunosuppression duration, were included in the logistic regression model to evaluate the risk factor of locally advanced prostate cancer in RTR.

Results

During the study period (September 2004–December 2006), ~8500 RTR were annually followed by the different centres participating in the study. Sixty-two RTR were definitively included in this study (prevalence: 0.72%). Mean patient age was 69.2 ± 6.8 years (range 50.8–75.1). The mean age at the time of kidney transplantation was 58 ± 7 years. Causes of end-stage renal disease were glomerulonephritis (41%), polycystic liver and kidney disease (15.4%), nephroangiosclerosis (12.8%), chronic interstitial nephritis (7.6%), focal and segmentary hyalinosis (5.1%), diabetes (2.5%) and undetermined cause (12.8%). Only two patients underwent retransplantation (3.1%). All patients were under CNI with or without AZA and/or steroids according to usual protocols in each centre. Maintenance immunosuppressive treatment consisted of CNI associated with AZA with or without steroids in 38 patients (61.2%), CNI with or without steroids in 20 patients (32.2%) and CNI and MMF in 4 patients (6.4%). All grafts were functioning at the time of cancer occurrence and the serum creatinine level was $154 ± 51 \mu\text{mol/l}$.

The mean age at prostate cancer diagnosis was 63.4 ± 5.8 years. Prostate cancer was suspected because of serum PSA elevation in 36 patients (59.0%), DRE in 7 patients (11.3%) and symptoms in 7 patients (11.3%). In all cases,
prostate carcinoma was confirmed by echo-guided prostate biopsies. The remaining 12 patients (19.3%) were diagnosed by the histopathology analysis after transurethral resection of the prostate for lower urinary tract symptoms. All prostate cancers were adenocarcinoma. No patient had a family history of prostate cancer but seven patients had a previous history of immunosuppression-induced neoplasia (five skin cancers, one post-transplantation lymphoma and one native kidney cancer). The mean time between transplantation and prostate cancer occurrence was 67 ± 42 months. The median PSA level was 7.6 ng/ml (range 1.6–597). According to the TNM 2002 classification from UICC, 19 patients (30.6%) of 62 had clinical stage T1, 21 (33.9%) stage T2, 12 (19.3%) stage T3, 1 (1.6%) stage T4, N+ (8.1%) and M+ (1.6%) patients. Twelve patients (19.3%) had extraprostatic invasion (T3, T4, N+, M+ TNM classification 2002). Twelve patients (19.3%) presented with a metastatic disease at the time of diagnosis. Metastasis was localized in lymph nodes in only six cases and the remaining six patients presented with lymph-node invasion with associated bone (5/6) or lung (1/6) metastasis. Gleason score showed 42 (67.7%) well or moderately differentiated tumours (Gleason score < 7) and 20 (32.3%) poorly differentiated tumours (Gleason score ≥ 7).

Thirty patients (48.4%) underwent radical prostatectomy through a suprapubic (23/30) or perineal (7/30) approach. Unilateral (8/19) or bilateral (11/19) lymphadenectomy was performed in 19 patients. Most of the patients with a PSA level <10 ng/ml and a Gleason score <7 did not undergo lymphadenectomy. Histopathology analysis found 9 (30%) pathological stage T1 (pT1), 14 (46.7%) pT2 and 7 (23.3%) pT3. Only two patients with pT3 stage disease presented with positive margins after radical prostatectomy. Four patients underwent additional external radiotherapy after radical prostatectomy. External radiotherapy was used in nine patients (14.5%) and brachytherapy in one case. Seventeen patients (27.4%) received chemical hormone therapy while four patients (6.4%) underwent bilateral orchietomy.

CNI were stopped after cancer diagnosis and switched to rapamycin in three patients. CNI doses were decreased in four other patients. AZA was stopped in nine and decreased in six patients especially in patients presenting with extraprostatic disease. To summarize, immunosuppression was changed in 22 patients (18 patients with extraprostatic cancer invasion).

At the mean follow-up of 24.7 ± 24 months, 48 patients (80.0%) were alive and 2 patients were lost to follow-up. Among the living patients, 35 (72.9%) were disease free and 13 (27.1%) a recurrence of the prostate disease. Seven of the twelve deaths were due to prostate cancer. Five renal transplant (8.1%) were lost during the prostate cancer treatment. Serum creatinine of the functioning graft after treatment was 189 ± 135 µmol/l and no significant difference was found between the creatinine level before and after treatment (P = 0.21).

We performed a statistical analysis to evaluate the effect of the different immunosuppressive protocols on prostate cancer. We compared patients receiving CNI associated with AZA with or without steroids (Group 1) and patients receiving CNI with or without steroids but without AZA (Group 2). Due to the small number of patients receiving CNI with MMF (n = 4), this group (Group 3) was not included in the statistical analysis. Nevertheless, these data are shown in Tables 1 and 2. Groups 1 and 2 were not different regarding the mean age at the time of transplantation and cancer occurrence, the time between transplantation and cancer diagnosis and the cause of end-stage renal disease (Table 1). All grafts were functioning at the time of cancer diagnosis in both groups, but a slightly lower serum creatinine level was observed in Group 1 patients compared to Group 2 patients (147 ± 86 versus 188 ± 83 µmol/l, respectively, P = 0.05). We observed a non-significant increase in the serum creatinine level after the treatment of prostate cancer in each group but no significant difference was shown between the two groups. The CNI treatment duration was similar in both groups (68.9 ± 39 months in Group 1 versus 65.8 ± 45 months in Group 2, P = 0.6).

### Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 20)</th>
<th>Group 3 (n = 4)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cancer occurrence (years)</td>
<td>63.1 ± 5.6</td>
<td>62.8 ± 6.2</td>
<td>68.5 ± 4.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Age at transplantation (years)</td>
<td>57.6 ± 6.3</td>
<td>57.3 ± 7.2</td>
<td>66.7 ± 4.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Time transplant—cancer (months)</td>
<td>71 ± 40.6</td>
<td>67 ± 45.9</td>
<td>20 ± 8.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Time dialysis—cancer (months)</td>
<td>66 ± 69.2</td>
<td>63 ± 80.3</td>
<td>55 ± 19.7</td>
<td>0.70</td>
</tr>
<tr>
<td>Duration CNI (months)</td>
<td>68.9 ± 39</td>
<td>65.8 ± 45</td>
<td>20.3 ± 8.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration AZA (months)</td>
<td>68.9 ± 39</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Associated cancer</td>
<td>4 (10.5%)</td>
<td>4 (20%)</td>
<td>0</td>
<td>0.42</td>
</tr>
<tr>
<td>Nadir of creatinine (µmol/l)</td>
<td>118 ± 44</td>
<td>131 ± 52</td>
<td>122 ± 34</td>
<td>0.48</td>
</tr>
<tr>
<td>Creatinine at diagnosis (µmol/l)</td>
<td>147 ± 86</td>
<td>188 ± 83</td>
<td>164 ± 48</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine after treatment (µmol/l)</td>
<td>151 ± 47</td>
<td>250 ± 200</td>
<td>155 ± 48</td>
<td>0.14</td>
</tr>
<tr>
<td>Functioning graft after treatment</td>
<td>32 (84%)</td>
<td>17 (85%)</td>
<td>4 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>34.7 ± 32</td>
<td>35.3 ± 40</td>
<td>24.3 ± 24</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Group 1: calcineurin inhibitors and azathioprine with or without steroids.
Group 2: calcineurin inhibitors with or without steroids.
Group 3: calcineurin inhibitors and mycophenolate mofetil with or without steroids.
CNI: calcineurin inhibitors; AZA: azathioprine.
*Group 1 versus Group 2.
The AZA treatment duration was 68.9 ± 39 months in Group 1 (Table 1).

The diagnostic modalities were similar in both groups with most of the cancers diagnosed with an increased PSA level (Table 2). The rate of poorly differentiated tumours was not different in either group (28.2% in Group 1 versus 40% in Group 2, \(P = 0.86\)). There was a statistically significant difference regarding the clinical stage of prostate cancer. The immunosuppression protocol incorporating CNI and AZA was found to be related to locally advanced and aggressive cancer. The rate of TNM stage T3 was higher in Group 1 (44.7% versus 15%, respectively, \(P = 0.04\)) and the only stage T4 was observed in a patient receiving CNI and AZA. Moreover, the lymph node invasion rate was slightly but not significantly higher in patients under CNI and AZA than in patients receiving CNI only (21% versus 5%, respectively, \(P = 0.1\)). Metastasis rate was 10.5% in Group 1 versus 5% in Group 2 (\(P = 0.6\)). Thus, localized cancer (T1 and T2) and locally advanced cancer (T3, T4, lymph nodes invasion and metastasis) were 52.6% and 47.3% in Group 1 and 85% and 15% in Group 2, respectively (\(P = 0.03\)). The follow-up and treatment modalities were not different in either group. At a mean follow-up of 36 months, 48.6% of Group 1 and 68.4% of Group 2 patients were alive with no recurrence (\(P = 0.26\)). The recurrence rate seemed to be slightly higher in Group 1 than in Group 2 (29.7% versus 10.5%, respectively) but this difference was not significant (\(P = 0.2\)) and probably due to the higher rate of advanced disease in Group 1. Death rate by prostate cancer was similar in both groups (13.5% in Group 1 versus 10.5 in Group 2, \(P = 0.9\)).

Only four patients received CNI and MMF as immunosuppressive treatment. The mean age at cancer diagnosis and transplantation was 68.5 ± 4.8 and 66.7 ± 4.8, respectively. Three patients had a localized cancer (T1 25% and T2 50%) and one patient had a locally advanced disease (T3 stage). None of them showed lymph node invasion or metastasis. Three patients underwent a radical prostatectomy and one patient a watchful waiting. At the mean follow-up of 24.3 ± 24 months, all patients were alive without the recurrence and no grafts were lost. Mean serum creatinine at the end of treatment was 155 ± 48 μmol/l.

In the multivariate analysis, the only significant independent risk factor for a locally advanced cancer disease was CNI- and AZA-based immunosuppressive maintenance regimen (Table 3). RTR receiving CNI and AZA had a 9.5-fold higher risk to develop an extraprostatic disease when compared to patients receiving CNI alone (OR: 8.7; CI 95% 1.8–42.1; \(P = 0.007\)). The age at transplantation (≥60 years versus <60 years) and cancer occurrence (≤65 years versus >65 years), the presence of associated cancer and the immunosuppression duration (≤24 months and >60 months versus 24–60 months) were not independent risk factors (Table 3).

**Discussion**

Increased risk of cancer in allograft recipients is now well described and has been attributed to the activation of oncogetic viruses, chronic inflammation and non-specific immunosuppression.

If prostate cancer incidence was first underestimated [6,25], recent studies reported an increased incidence of prostate cancer in RTR compared to general population [3,8]. Kasiske et al. reported a 3-year post-transplant prostate cancer incidence of 1.74% in the United States [3] and Cormier et al. reported a prevalence of 1% for the
French Renal Transplantation Committee [8]. Our results were similar to a calculated prevalence of 0.72%. Several hypotheses could explain this increased incidence. First and foremost, RTR became at risk for neoplasia associated with increased age as their survival has increased. Second, the follow-up of serum PSA levels and the use of a systematic screening may increase the rate of cancer detection. Third, long-term immunosuppression is known to favour neoplasia occurrence [26], although its impact on prostate adenocarcinoma is still unclear.

Few reports of prostate cancer after transplantation have been published: three series with 21, 18 and 8 patients developing prostate cancer after kidney transplantation [8,27,28]. To our knowledge, our series is the largest series of prostate cancer in RTR. Prostate cancer in transplanted patients seems to occur earlier in RTR than in the general population [8,27,28]. Our results confirmed this early occurrence, with a mean age of 63 years at the time of diagnosis while the mean age of occurrence in the French general population is around 70 years [29]. One should hypothesize that this is due to an earlier diagnosis rate rather than an earlier occurrence phenomenon because this particular population receives frequent medical examinations. Nevertheless, in these studies as in our study, a systematic screening was not performed in all centres [8]. Moreover, studies about prostate cancer screening never demonstrated a decrease in the age of diagnosis in patients who underwent systematic screening [30,31]. Another argument in favour of an earlier occurrence of prostate cancer in RTR is furnished by studies about prostate cancer in HIV-infected patients. Prostate cancer occurred earlier in HIV-infected patients than in control populations [32,33] and the HIV infection duration (corresponding to an immunodepressed state) was correlated with cancer occurrence [32].

Contrary to the previous studies that found a greater number of patients with localized cancers in the transplant population compared to the general population [8,27], we showed a high rate of locally advanced disease (TNM T3/T4 36%) and metastatic disease (19.3%). Because of the potential difference in screening protocol, any comparison between RTR and the general population is difficult. Nevertheless, data from the European Randomized Study of Screening for Prostate Cancer showed a rate of locally advanced and metastatic disease of 15.5% and 1.3%, respectively in the screened group (n = 17635) versus 23% and 11.6% in the non-screened population (n = 17513) [34]. Our results showed a higher rate of locally advanced cancer in RTR compared to published rates in the general population whether screening was performed or not. One argument explaining this high rate of the locally advanced form of cancer could be the low level of testosterone. Patients with end-stage renal disease, as well as some RTR, are known to present with low testosterone level [35,36] which has been demonstrated to be associated with advanced pathological stage [37]. Another argument is the impact of an immunodepression state on prostate cancer progression.

Cormier et al. previously hypothesized a relation between immunosuppression and disease stage based on the fact that in their study, four out of six patients with advanced cancer (TNM 2002, T3 and T4) received a maintenance therapy associating CNI, AZA and steroids [8]. In our study, we demonstrated that a maintenance immunosuppressive therapy including CNI and AZA with or without steroids was associated with a significant higher rate of locally advanced (TNM 2002, T3 and T4) or metastatic (TNM N+ and M+) disease compared with protocols including CNI with or without steroids (47.3% and 21% versus 15% and 5%, respectively, P = 0.03). The multivariate analysis showed CNI and AZA maintenance therapy as the only independent significant risk factor for locally advanced prostate cancer. No correlation was found between immunosuppression duration and prostate cancer grade. The rate of poorly differentiated tumours was not dependent on the immunosuppression protocol used and no relation between cancer stage or differentiation and immunosuppression duration was shown.

The impact of the immunosuppressive regimen on the PCA evolution in RTR could hypothesize a viral origin for PCA. Several studies have recently shown that human papillomavirus (HPV) as well as human herpes virus 8 infection was not associated with PCA occurrence [38,39]. Nevertheless a recent case report described an association of polyoma virus BK (BKV) infection with p53 gene mutations in a patient with PCA [40]. Further studies are needed to confirm the relation between BK virus infection and PCA occurrence.

It is the first time, to our knowledge, that a relation between immunosuppression and prostate cancer progression in RTR is formally demonstrated. The mechanisms of these interactions between prostatic tumour cells and the association of CNI and AZA remain unclear and further studies are needed to elucidate it. Although it has been suggested that rapamycin was associated with the low incidence of post-transplant malignancies [20–22,41], further clinical studies evaluating specifically the incidence of prostate cancer in RTR under rapamycin are needed to confirm the low

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Table 3. Multivariate analysis of risk factors studied for locally advanced prostate cancer occurrence, following kidney transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis ≤ 65 years (versus &gt; 65 years)</td>
<td>0.39 (0.06–2.50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age at transplantation ≥ 60 years (versus &lt; 60 years)</td>
<td>1.35 (0.19–9.58)</td>
<td>0.76</td>
</tr>
<tr>
<td>Associated cancer</td>
<td>1.63 (0.22–11.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>CNI and AZA therapy (versus CNI alone)</td>
<td>8.7 (1.8–42.12)</td>
<td>0.007</td>
</tr>
<tr>
<td>Immunosuppression duration ≤ 24 months (versus 24–60 months)</td>
<td>0.22 (0.02–2.03)</td>
<td>0.18</td>
</tr>
<tr>
<td>Immunosuppression duration ≥ 60 months (versus 24–60 months)</td>
<td>0.47 (0.09–2.39)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

CNI: calcineurin inhibitors; AZA: azathioprine.
incidence of PCA and to recommend immunosuppression changes. Prostate cancer screening still remains controversial in the general population. Our study highlights particular characteristics of prostate cancer in the RTR population. First, prostate cancer appears sooner in RTR than in the general population. Second, we observed a high rate of advanced or metastatic disease and third, the stage of the disease seems to be related with the immunosuppressive therapy used. Based on these findings, RTR should be considered at risk for locally advanced prostate cancer and we strongly recommend, like others authors, a systematic screening of prostate cancer in RTR by an annual serum PSA level and DRE [8,27].

Conclusion

We reported here, to our knowledge, the largest series of prostate cancer in RTR. Our results showed that prostate cancer natural history in this particular subgroup is different than in the general population. It occurs earlier and seems to be more aggressive with a high rate of locally advanced disease and lymph node invasion. Moreover, it is the first time that a relation between prostate cancer stage and immunosuppression therapy was demonstrated. Based on these results, the Renal Transplantation Committee of the French Urological Association strongly recommends an annual screening of prostate cancer in RTR and to discuss, when possible in aged recipients, alternative options to the association between CNI and AZA.

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Conflict of interest statement. None declared.

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