Renal transplant recipients are a population usually considered at a higher risk of malignancies, mostly skin cancer and lymphoproliferative disorder. In recent years, prostate cancer in renal transplant recipients has become more frequent. This is probably due to the growing age and the longer survival of the transplanted patients. We report the case of a 50-year-old man with prostate cancer and renal allograft, who received radiotherapy after prostatectomy at the Institute of Radiotherapy of the University of Florence. Radiotherapy is part of the standard treatment for many cases of prostate cancer. According to the few series reported in the literature and also to our experience, radiation therapy is feasible also in renal transplant recipients with accurate treatment planning.

Key words: renal transplantation – prostate cancer – radiotherapy

INTRODUCTION

Renal transplant recipients (RTR) are a population usually considered at a higher risk of malignancies, mostly skin cancer and lymphoproliferative disorder, with an estimated incidence 4- to 20-fold higher than that in the general population (1-4). In the US Renal Data System, urologic malignancies are reported as the second most common neoplasm in the renal transplanted population (5).

In recent years, prostate cancer in RTR has been becoming more frequent. This is probably due to the growing age and the longer survival of the transplanted patients, as it is known that prostate cancer incidence increases with increasing age. Despite this growing interest, there are still a few series reported in the literature about this issue and there is a lack of data regarding the best treatment available to these patients.

Radiotherapy is one important option for prostate cancer treatment, in the adjuvant and also in the radical setting, but the anatomical position of a renal allograft in the pelvis can creates serious difficulties for the radiation oncologist from a technical point of view. For this reason, the surgical approach is the gold standard, but in intermediate- and high-risk patients, adjuvant treatment is still required. Only a few cases of prostate cancer in RTR treated with adjuvant radiotherapy are reported in the literature.

We report the case of a 50-year-old man with prostate cancer and renal allograft, who received radiotherapy after prostatectomy, at the Institute of Radiotherapy of the University of Florence. Radiotherapy is part of the standard treatment for many cases of prostate cancer. According to the few series reported in the literature and also to our experience, radiation therapy is feasible also in renal transplant recipients with accurate treatment planning.

The patient’s medical history is significant: when he was 13, he underwent surgery for a congenital vesico-urethral malformation; for 10 years, his renal function was stable with a creatinine of 0.8–1.2 mg/dl, but at the age of 23 years, he presented with renal failure and he was put on dialysis. One year later, the patient underwent the first renal transplantation, but he suffered a rejection after just 11 months. Consequently, he was started again on dialysis until a second renal transplantation, performed when he was
40 years old. Currently, his renal function is still pretty well compensated with a creatinine value between 1.8 and 2 mg/dl. His maintenance immunosuppressive therapy consists of sirolimus and mycophenolate mofetil. As relevant co-morbidities, the patient is moreover affected by post-transfusional chronic C hepatitis and hypothyroidism, after radioiodine therapy for a papillary carcinoma.

In April 2010, at the routine prostate-specific antigen (PSA) evaluation, it was found to be at an increased value of 6. He underwent biopsy that showed prostate adenocarcinoma, and so he underwent retropubic prostatectomy and bilateral lymphadenectomy; the histology revealed prostatic adenocarcinoma, with a Gleason score of 5 + 4, with extension to the right seminal vesicle and to the apex and posterior margins. The final stage was pT3b, pN0. The staging was negative for metastases. Post-operative PSA was 0.09.

Owing to the prognostic factors of the patient, antiandrogen treatment was started and radiotherapy was recommended, and so he was sent to our evaluation for adjuvant treatment.

For treatment planning, computed tomographic (CT) images were obtained in the supine position; his bladder was full and the rectum was empty. Five millimeter slices were obtained and a three-dimensional (3D) radiotherapy planning Pinnacle system (Philips Medical System, Bothell, WA, USA) was used for contouring and for dose computation. The clinical target volume (CTV) and organs at risk (OAR; bladder, rectum, renal graft, and femoral heads) were outlined in each slice. The CTV was defined as follows: the superior margin involved the bladder neck and included the original site of the base of the seminal vesicles; the inferior margin was located 15 mm cranially from the penile bulb, or at the apex, the anterior margin included the anastomosis and the urethral axis and the posterior margin was the outer rectal wall. The planning target volume (PTV) was obtained expanding the CTV with an 8 mm wide margin in all directions and 6 mm posteriorly to reduce the dose to the rectal wall.

In our Institution, the post-operative treatment is usually performed with a 3D conformal radiotherapy technique and four coplanar beams at 0°, 90°, 180° and 270° are used (‘Box technique’). The dose usually prescribed is between 66 and 70 Gy with a dose of 2 Gy each day, for 5 days every week. Under normal conditions, with this technique, it is possible to reach a good coverage of the target with a safe dose to the OAR.

In the current case, it was important to obtain an optimal coverage of the PTV and at the same time reduce the dose to the OAR, in particular to the bladder, terminal ureter and especially to the graft. Some options could be the reduction in the dose or the exclusion of the graft from the field of radiation; all these possibilities could result in a high risk of compromising the efficacy of the treatment.

Our decision was to employ the intensity-modulated radiotherapy (IMRT) technique. The sharp dose gradients created with IMRT can make the high-dose region conform to the PTV and limit the doses to the OAR.

Five coplanar beams were used at 45°, 105°, 180°, 255° and 315°. The energy was 10 MV for all the beams. The mean number of monitor units was 124 for each beam.

The dose prescribed to the PTV was 70 Gy, 2 Gy daily for 5 days a week. Details of the treatment planning with the doses delivered to the critical organs are reported in Table 1; Fig. 1 illustrates an axial CT image, with treatment beams and isodose lines; the 95% isodose line (the green line) provides adequate coverage of the PTV (orange contour).

We kept particular attention on the dose delivered to the femoral heads, since we know that in RTR, considering the large use of corticosteroids and other immunosuppressive drugs, there is a higher risk of hip avascular necrosis than in the general population (6). Our plan showed that both the femoral heads received a maximum dose of <40 Gy.

The treatment was delivered with an Elekta Synergy linear accelerator that is equipped with imaging tools include 3D cone-beam imaging. The image control mechanism during the treatment consisted of a cone beam for the first 5 days of treatment and then weekly, after correction of the position based on the mean error.

During radiotherapy, the patient was evaluated each week with a clinical visit, and side effects were registered and graded according to the Common Toxicity Criteria Adverse Events v.4 (CTCAEv4). During the treatment, the patient did not complain of urinary and gastrointestinal toxicity, except for mild cystitis (G1). Moreover, he performed regular

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**Table 1. Treatment planning details**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume (cc)</th>
<th>Minimum dose (D_{\text{min, Gy}})</th>
<th>Maximum dose (D_{\text{max, Gy}})</th>
<th>Mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV</td>
<td>292.56</td>
<td>53.73</td>
<td>76.70</td>
<td>70.22</td>
</tr>
<tr>
<td>Rectum</td>
<td>69.59</td>
<td>2.30</td>
<td>75.03</td>
<td>44.66</td>
</tr>
<tr>
<td>Bladder</td>
<td>221.05</td>
<td>2.68</td>
<td>73.97</td>
<td>49.30</td>
</tr>
<tr>
<td>Graft</td>
<td>247.99</td>
<td>0.01</td>
<td>1.88</td>
<td>0.36</td>
</tr>
<tr>
<td>Right femoral head</td>
<td>125.92</td>
<td>2.08</td>
<td>41.66</td>
<td>23.67</td>
</tr>
<tr>
<td>Left femoral head</td>
<td>129.74</td>
<td>1.93</td>
<td>47.00</td>
<td>21.43</td>
</tr>
</tbody>
</table>
evaluations of the renal function with monitoring of creatinine clearance.

After adjuvant radiotherapy, the patient was enrolled in our institutional protocol of follow-up, consisting of a clinical evaluation, PSA dosage and renal function evaluation 1 month after the end of the treatment and every 4 months thereafter. At the last follow-up, the patient was well without signs of recurrence.

DISCUSSION

Only a few reports exist about prostate cancer in patients after kidney transplantation, mainly representing case studies and including a short follow-up.

The RTR population is at higher risk of ex novo cancer, especially skin and lymphoproliferative diseases. Also genitourinary malignancies are more frequent in this group of patients, with a 100-fold increase in perineal, vulvar, scrotal and penile tumors (5). A study by Penn (7) did not show any significant difference in the incidence of prostate cancer between RTR and the general population. Also Sheil (8) did not find differences in the incidence of prostate cancer in the two populations. More recent studies have changed the general point of view, showing an increased risk of developing prostate tumor after renal transplantation. In his series of patients, Cormier et al. (9) reported 28 cases of prostate cancer, out of 2338 RTR followed up, with a prevalence of 1%. Kasiske et al. (3) reported a 3-year post-transplant prostate cancer incidence of 1.74% in the USA. Also Birkeland et al. (10) reported an increased incidence, with a standardized incidence ratio of 2.1. One of the largest series in the literature is reported by Kleinclauss et al. (11) who collected 62 prostate cancers out of 8500 RTR, with a prevalence of 0.72%.

Prostate cancer in transplanted patients seems to occur earlier in the renal transplanted population than in the general one. The patient we reported received a diagnosis of prostate cancer when he was 50 years, earlier than the mean age of occurrence in the general population, that is, around 70 years and similar to what has been reported by other authors.

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

A definitive reason for this higher incidence is still unknown. Because there is no systematic screening, any comparison between the general population and RTR is more difficult than for other forms of cancer in RTR. It is probable that an important role is played by the longer survival of transplanted patients. Although it is not systematic, screening may be more frequent than that in the general population of the same age because physicians follow transplant patients at least once a year, and the opportunity to have clinical examination or PSA testing done is more important.

Lastly, the role of immunosuppressive therapy in the carcinogenesis among renal transplant patients was outlined in many works, but its role in prostate cancer occurrence is unclear. The impact of immunosuppression on virus-induced cancers in RTR is well known and immunosuppressive agents such as azathioprine and cyclosporine have been previously identified as being carcinogenic; calcineurin inhibitors were found to be able to increase with in vivo and in vitro aggressiveness and progression of prostate cancer cells (12,13). Conversely to azathioprine, mycophenolate mofetil and mammalian target of rapamycin inhibitors, the immunosuppressive drugs used in the current patient were never found linked to a higher risk of post-transplantation de novo cancer (14–16). Furthermore, rapamycin has also showed a protective effect from cancer in RTR and some molecules derived from the rapamycin were tested on the

Figure 1. Dose distributions with planning target volume, organs at risk and isodoses.
prostate adenocarcinoma cell lines resulting in an inhibition of the growth of tumoral cells (17–19).

External beam radiotherapy is commonly used for the treatment of perineal or pelvic malignancies with excellent results. If a kidney transplant patient develops a pelvic malignancy, the real and potential risks to the graft are relevant and impact on the decision to treat. Options include avoidance of radiotherapy, reducing the dose or limiting the field of irradiation or moving the graft out of the field of radiation. The location of a renal allograft places the kidney at risk for irreversible damage if high-dose radiation is delivered to the iliac and obturator lymph nodes. RTR patients, because of the anatomical location of the graft, can be difficult to treat with radiation therapy in a conventional way. To avoid renal complications, ranging from proteinuria to acute or chronic renal failure, a transplanted kidney has to receive a dose below defined thresholds.

In the literature, few cases of RTR treated with radiotherapy for prostate cancer are reported. Konety et al. used conventional adjuvant radiotherapy, with a mean dose of 65 Gy, in three patients with intracapsular prostate cancer with shielding of the graft. Two patients were still alive after a follow-up of 46 months, while one patient was died of an unrelated cause. The authors did not report about acute or chronic side effects of the treatment, especially of what concerns the allograft (21). Mouzin et al. in 2004 was the first to report among eight renal transplanted patients, treated with modern conformal radiotherapy for prostate cancer. After a median follow-up of 28 months, two patients experienced a biochemical relapse, two patients died of other causes than prostate cancer, while the other four patients remained free of recurrence. Acute side effects were not different from those in the general population treated with the same treatment. One patient experienced renal failure, 3 months after the end of the radiotherapy, while the other seven patients conserved a normal functional allograft. With furosemide-stimulated diethylenetriaminepentaacetic acid renograms, obstruction of the terminal ureter was found in two out of these seven patients (22).

In the current series, the doses delivered to critical organs such as the bladder (mean dose 49 Gy) and the rectum (mean dose 44 Gy) were similar to those observed in other reports, in line with the absence of anatomic alterations of the pelvis after renal transplantation.

The thresholds reported to induce complications in 5% (TD5/5) or 50% (TD 50/5) of irradiated kidneys within 5 years were 23 and 28 Gy, respectively, as reported by Emami et al. (20).

In our case, the dose delivered to the graft (1.88 Gy) remained well below the former threshold.

Another concern in RTR is the irradiation of the femoral heads because of the risk of hip avascular necrosis due to chronic steroids and immunosuppressive drugs and further increased by hip irradiation. Compared with the standard four-field radiotherapy technique, five coplanar beams with IMRT, used in the current report, allowed to spare the femoral heads from irradiation, with a mean dose lower than 24 Gy, similar to what was reported by Mouzin.

The last known concern is the dose delivered to the terminal part of the donor ureter, which is a critical structure because of its proximity to the target volume and its fragile blood supply that originates from the transplanted renal artery. The dose to the terminal ureter cannot be definitely measured because its position varies from one radiotherapy session to the other, depending on bladder repletion. Therefore, we performed each daily radiation treatment with a full bladder, since this may provide a simple but effective means of reducing the risk of late side effects to the donor ureter.

**CONCLUSIONS**

Radiotherapy is part of the standard treatment for many cases of prostate cancer. According to the few series reported in the literature and also to our experience, radiation therapy is feasible also in RTR with accurate treatment planning. With the increasing incidence of prostate cancer in the RTR population, some clinical trials exploring acute and chronic side effects should be recommended.

**Conflict of interest statement**

None declared.

**References**


