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Radiotherapy in prostate cancer after kidney transplant: review of the literature and report of 6 cases

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Abstract

Background: Patients who received a kidney transplant (KT) are described in literature as a group with a higher incidence of malignant neoplasms compared to the general population. Cancer development after KT has become a major issue, as a remarkable percentage of patients are diagnosed with cancer. Treatment of prostate cancer (PCa) in renal transplant recipients (RTRs) is a challenging issue that has been discussed by many authors over the years, but evidence is sparse and often includes conflicting reports. Among the therapeutic options for PCa in these patients, prostate irradiation represents a valuable alternative to surgery or other systemic therapies, as RTRs are often ineligible for these treatments.

Objective: To report six cases treated at our institution between 1998 and 2017 and discuss the available literature.

Methods: Patients' characteristics were reported along with biochemical status at diagnosis, type of immunosuppressive treatment, radiation therapy technique, and dose to transplanted kidney.

Results: Overall, prostate irradiation was delivered respecting the dose constraints and patients showed good tolerance with no reports of acute or late transplanted kidney injury.

Conclusions: Our experience confirms that prostate radiotherapy for RTRs is feasible and effective and represents a valid option that should be considered by the multidisciplinary team.

Keywords

prostate cancer, kidney transplant, radiotherapy

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Introduction

Patients who received a kidney transplant (KT) are described in the literature as a group with a higher incidence of malignant neoplasms compared to the general population. Cancer development after KT is an important issue, as a large percentage of these patients are diagnosed with cancer.[1] The immunosuppressive agents employed in renal transplant recipients (RTRs) are held accountable for the rising number of malignancies, which are mainly represented by nonsolid neoplasms such as lymphomas. According to some authors, the number of urologic cancers such as prostate cancer (PCa) after KT has increased[2]; that could be partly explained by prolonged survival after transplant and the rising age of RTRs.[3] Evidence on this topic is sparse and often includes conflicting reports. Some articles report a low incidence rate of PCa, so that an active surveillance program in this

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Table 1. Patient characteristics.

Characteristics	Values
Number of patients	6
Age at RT, y, median (range)	60.8 (50–67)
Time from KT to PCa diagnosis, y	7.66 (4–12)
PSA at PCa diagnosis, ng/dL, mean (range)	7.36 (4.7–16)
Prostatectomy, n	1
Dose to transplanted kidney, Gy, mean (range)	0.73 (0.40–1.21)
Acute GU toxicities	4 G1
Acute GI toxicities	0
Late GU toxicities	0
Late GI toxicities	1 G3
Follow-up, y, median	5.25

GI: gastrointestinal; GU: genitourinary; KT: kidney transplant; PCa: prostate cancer; PSA: prostate-specific antigen; RT: radiotherapy.

population is not recommended.[1] Nevertheless, treatment of PCa in RTRs is a challenging issue that has been discussed by many authors over the years.[4]

Prostate irradiation is a therapeutic option that needs to be explored as this subset of patients is often excluded from surgical or medical interventions due to possible toxicities. A previous case report and literature review from our institution was published in 2011.[5] Since then, a growing number of studies has enriched our knowledge about this particular issue, and the evolution of radiotherapy (RT) delivery assets has led to an improvement in the treatment of PCa in these patients.[6]

We report six cases treated at our institution between 1998 and 2017 and explore the available literature about the use of RT for this specific subset of patients.

Methods

We report a case series of PCa in six patients who received renal transplant. Data between 1998 and 2017 were collected. Patients' characteristics were reported along with biochemical status at diagnosis, type of immunosuppressive treatment, radiation therapy technique, and dose to transplanted kidney. Acute and late toxicities, such as urologic complications, were recorded using Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03).[7] All patients underwent periodic checks with the nephrologist of the transplant center. Graft function was monitored by creatinine clearance, serum creatinine, and glomerular filtration rate. Biochemical or radiologic relapses were listed. Details are provided in Table 1.

Results

In the prespecified period, radiation therapy was used to treat six different patients who received renal transplant. The mean follow-up was 59.2 months.

At the time of treatment in 1998, patient 1 was a 63-year-old man who was diagnosed with PCa 12 years after transplant. He underwent definitive treatment with radiation therapy (total dose 72 Gy) while he was on corticosteroids and other immunosuppressive agents. Details about dose to renal transplant were not available. He had a biochemical relapse 6 years after RT and was then prescribed hormone therapy. The patient experienced acute G1 cystitis and G1 proctitis but had no long-term complications. At the time of last follow-up, after 5 years of hormones, the patient had good Performance Status, functioning graft, and no evidence of relapse.

Patient 2 was a 50-year-old man who had received 2 renal transplants (the first in 1984) and was later diagnosed with a poorly differentiated adenocarcinoma (Gleason Score 4+5) in 2010. His immunosuppressive therapy consisted of sirolimus, mycophenolate, and prednisone. He underwent radical prostatectomy but prostate-specific antigen (PSA) levels had not fallen to zero after surgery, so he was offered adjuvant RT. He was treated with a total dose of 70 Gy on the prostatic bed. The treatment plan did not yield a remarkable dose on the transplanted kidney but could not spare the final tract of urethra from a significant amount of dose. Mean dose to transplanted kidney was 0.8 Gy. Nevertheless, the patient did not experience urologic acute or late toxicities but reported a G1 proctitis during treatment. At the time of last follow-up, the patient was alive and well with good renal function and no evidence of relapse.

Patient 3 was a 63-year-old patient who received a renal transplant in 2007 and underwent prostate biopsy resulting in adenocarcinoma (Gleason Score 3+3) in 2014. He was offered a curative radiotherapeutic treatment with a hypofractionated regimen (70.2 Gy in 26 fractions). Mean dose to transplanted kidney was 1.21 Gy. The patient did not report urologic complications but experienced severe proctitis (G3 CTCAE) that led to hospitalization and creation of a colostomy. After the treatment, no rise in PSA levels was recorded; the renal graft was monitored by nephrologists with no sign of dysfunction.

Patient 4 was 58 years of age at the time of diagnosis in 2015. He received a KT in 2007 and was on immunosuppressive therapy based on corticosteroids, tacrolimus, and everolimus. A biopsy revealed a prostatic adenocarcinoma (Gleason Score 3+4) and curative RT was offered. The treatment was administered using a volumetric modulated arc therapy (VMAT) technique in 38 fractions for a total dose of 76 Gy. Mean dose to transplanted kidney was 0.54 Gy. There were no acute toxicities, but the patient has experienced G2 late proctitis with recurrent occurrence of hematochezia. After RT, PSA levels have been constantly decreasing and were at their lowest at the time of last follow-up. Renal function was preserved. Dose–volume histogram and other treatment planning images are shown in Figures 1 and 2.

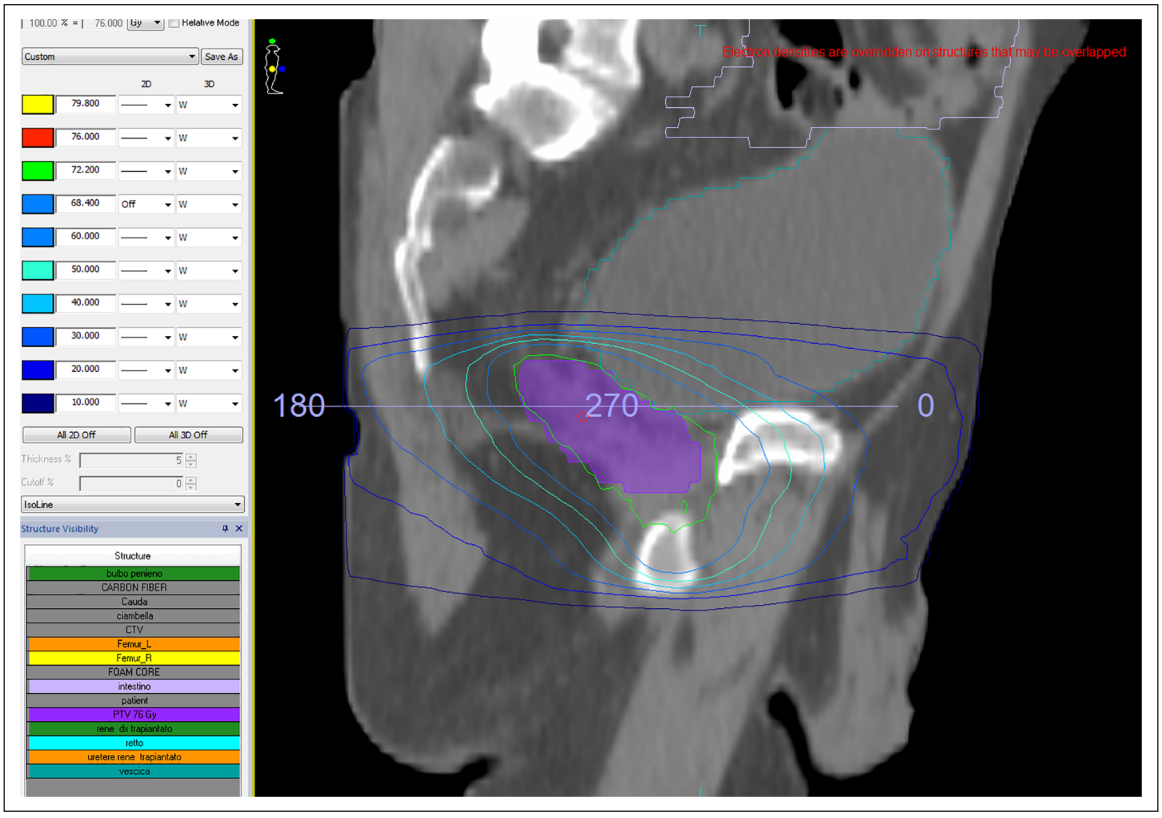

Figure 1. Isodoses with target and organs at risk.

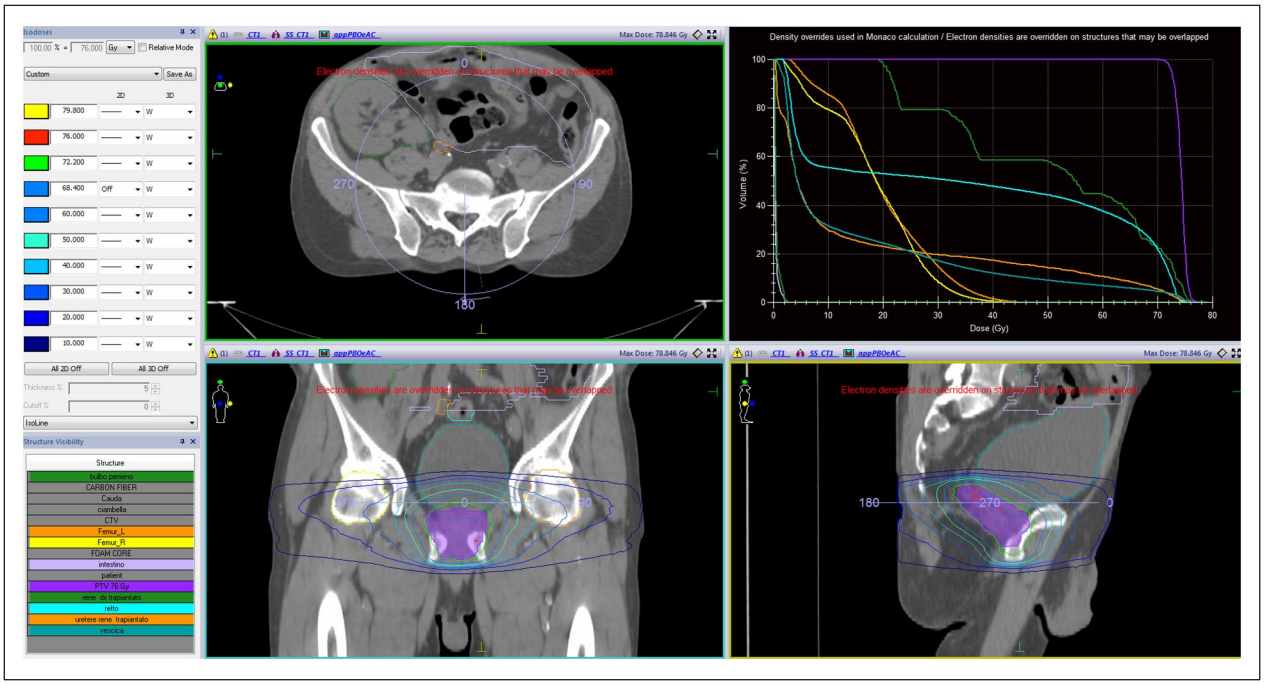

Figure 2. Isodoses with target and organs at risk and dose–volume histogram (DVH).

Patient 5 was treated at our institution in 2016, almost 5 years after transplant, at age 67. After the insertion of four cylindrical gold fiducial markers, he underwent stereotactic body RT (SBRT) on the prostate for a total dose of 36.25 Gy in five fractions. Mean dose to transplanted kidney was 0.40 Gy. No acute or late toxicities were reported.

Patient 6 underwent KT in 2007. In 2012, when he was 64, the patient was diagnosed with prostatic adenocarcinoma (Gleason Score 3+3). The malignant tissue involved the basal and postero-superior portion of the left prostatic lobe, in close contiguity with the left seminal vesicle. The treatment consisted of curative RT administered in 38 fractions for a total dose of 76 Gy. Details about dose to renal transplant were not available. The patient experienced acute G1 cystitis and G2 proctitis but had no long-term complications. In December 2013, the patient experienced severe chronic kidney disease, possibly due to chronic rejection. For this reason, he had to undergo dialysis treatment. In 2017, he was diagnosed with squamous lung cancer and treated with chemotherapy and RT, but ultimately died in 2018 of metastatic lung cancer. During this period, no sign of relapse of prostatic disease was recorded.

For patients 1, 3, and 6, the irradiation technique consisted of a nine-field arrangement, with 18-MV photon beams.

For patient 2, the irradiation technique consisted of a four-field arrangement, with 18-MV photon beams.

For patient 4, treatment was administered using a VMAT technique in 38 fractions for a total dose of 76 Gy.

For patient 5, treatment was delivered through SBRT on the prostate for a total dose of 36.25 Gy in five fractions.

In the context of toxicities, ureteral stenosis is an aspect to consider. The doses delivered to the uretero-neocystostomy were calculated to range from less than 20 Gy to more than 45 Gy, depending on bladder repletion. Except for patient 6 (who died of lung cancer), the duration of follow-up was not reported.

Discussion

RT for PCa in RTRs is relatively unexamined. Lately, a growing number of studies investigating this challenging field have been published, primarily consisting of case reports and series.

Patients who receive KT are vulnerable. Increased risk of cancer in allograft recipients is well known and has been attributed to the activation of oncogenic viruses, chronic inflammation, and nonspecific immunosuppression. The role of immunosuppressive therapy in carcinogenesis among renal transplant patients has been outlined in many works, but its role in PCa incidence is unclear. A nationwide register study that was recently carried out in Sweden[7] sought to demonstrate a possible correlation between post-transplantation immunosuppression and PCa outcomes in male RTRs. Data from 133 Swedish men who had been diagnosed with PCa after KT between 1996 and 2016 were analyzed and compared to a control group of men who had not received KT. The results showed that recipients were not more likely than age-matched controls to be diagnosed with any or high-risk or metastatic PCa. The authors also posit that patients with low-risk PCa on androgen-suppression therapy can be eligible for transplant. Other articles support an expansion in organ transplantation eligibility criteria and explored options such as active surveillance instead of treatment in RTRs with low and very low PCa.[8]

Published studies have not found an association between renal transplant and increased incidence of PCa, although a rise in the number of cases may have been reported by some authors as a result of the increasing age of RTRs. An association between risk and aggressiveness has not yet been established.[9] A recent review reported that outcomes of PCa treatment seemed promising and did not appear to be inferior to PCa treatment in the general population; the article investigated all kinds of treatments for PCa, including surgical patients.[4] The use of RT is a valuable option in transplanted patients with PCa or other pelvic malignancies, as surgery or chemotherapy may not be feasible in this population. The location of a renal allograft, usually in the right iliac fossa near blood vessels included in target volume, places the kidney at risk for irreversible damage if high-dose radiation is delivered to the iliac and obturator lymph nodes or to other pelvic organs.[10]

A mean dose <4 Gy for the transplanted kidney is recommended by several publications. Many authors report preserved renal function after RT, especially when using intensity-modulated RT.[5] The dose received to transplanted kidney is crucial to assess possible renal toxicity after RT. Only two of our patients (3 and 4) had these data available.

Although brachytherapy is widely used in PCa, as recently pointed out by Tang et al.,[11] the 6 patients in our series underwent external beam RT in relation to the clinical and literature data available at the time of treatment.

Ureteral stenosis was considered as a dose-related effect. Mouzin et al.[12] described ureteral stenosis in a case series in two out of eight treated patients.

The patients included in our case series did not experience severe acute or late effects affecting graft functionality; the mean doses to transplanted kidney respected the recommendations on constraints and only one patient experienced biochemical recurrence several years after the treatment.

Our experience confirms that prostate RT for RTRs is feasible, is effective, and represents a valid option that should be taken into account by the multidisciplinary team.

Declaration of conflicting interests

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