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Low-dose-rate brachytherapy for prostate cancer in renal transplant recipients

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ABSTRACT

PURPOSE: Prostate cancer (PCa) is the most common malignancy among men and one of the most common neoplasms affecting renal transplant recipients (RTRs). The available treatments for localized PCa among the general population (GP), surgery and external beam radiotherapy, carry a risk of damage to the transplanted kidney, the ureters, and the bladder and therefore tend to be avoided by most groups. The objective of this study was to assess the efficacy and feasibility of low-dose-rate brachytherapy (LDR-BT) for PCa in RTRs.

METHODS AND MATERIALS: We carried out a retrospective review on all RTRs diagnosed of PCa who had undergone LDR-BT at our institution between 2000 and 2015. Nine patients met these criteria, but 1 did not fulfill the followup. Hence, we analyzed 8 patients. We reviewed all clinical data for PCa and graft function in these patients and compared the results with the GP.

RESULTS: Mean baseline prostate-specific antigen was 6.8 ± 1.9 ng/mL. All PCa had a Gleason score of 6 and were classified as low risk according the Europe Association of Urology guidelines. Mean followup after seed implantation was 48 ± 12.8 months. All 8 patients remain free of prostate-specific antigen failure. Five-year progression-free survival, cancer-specific survival, and overall survival rates were 100%, 100%, and 62.5%. There was no specific toxicity associated with LDR-BT, and there were no acute adverse events affecting the graft.

CONCLUSIONS: LDR-BT is a feasible and acceptable treatment for localized PCa in RTRs. Oncological outcomes are similar to the GP, and there is minimal toxicity to the renal graft.

Keywords: Brachytherapy; Prostate cancer; Renal transplant

Introduction

The number of renal transplant recipients (RTRs) has gradually increased in recent years. In 2016, Spain reached a historical record of 2994 renal transplants (RTs) [1]. The profile of RTRs has also changed: patients are older, graft survival has improved, and cardiovascular and infection-related morbidity and mortality rates have decreased. On the other hand, RTRs show a higher risk of developing malignancies as a result of chronic immunosuppression, oncogenic viruses, antigenic stimulation, and complex donor-recipient interactions [2, 3]. As a consequence, malignancies have become an increasingly important factor in RTRs morbidity and mortality.

The incidence of prostate cancer (PCa) in RTRs has not been well established: according to some reports, it is similar to that of the general population (GP) [4−10], although recent studies mention an incidence of four- to five-fold higher [11−16] and an upward trend [17].

Despite this, there are no randomized studies or guidelines establishing the best therapeutic option for localized

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PCa in RTRs. Only a systematic review of the different therapeutic options has been published recently [18], concluding that oncologic outcomes do not appear to be worse or complications are more frequent in RTRs than in the GP. Radical prostatectomy is the treatment of choice in most studies, with oncologic outcomes similar to those in the GP [3,16,19−30]. However, the complexity of this technique increases in RTRs because of the distorted anatomy and the limited exposure of the pelvis. Moreover, the location of the graft compromises the ipsilateral lymph node dissection. As for external radiotherapy (RT), it is usually avoided to prevent potential risks of iatrogenic complications involving the transplanted ureter, the bladder, and the graft itself [31]. A key advantage of prostate brachytherapy (BT) is that it enables a highly conformal dose distribution with rapid dose fall-off and increasing distance from the radiation sources, thereby allowing the preservation of both oncological efficacy and functioning of the renal graft. Prostate BT can potentially overcome the complications caused by external beam radiotherapy because it allows for a highly conformal radiation treatment to be delivered to the target volume with a steep dose gradient surrounding this region, thereby limiting toxicity to neighboring organs at risk. [32−34]. Furthermore, the oncologic outcomes of this technique in RTRs seem equivalent to those of the GP [35−37].

In this article, we review the literature on this subject and present our experience with low-dose BT for the treatment of PCa in the largest cohort of RTRs published so far.

Material and method

Study methodology

We carried out a retrospective review on all male RTRs with a functioning graft at the time of PCa diagnosis. The review included patients treated at the University Hospital Virgen del Rocío between 2000 and 2015. A total of 16 patients of 869 RTRs were identified—6 had received radiotherapy, 1 had undergone radical prostatectomy, and 9 had received BT. These 9 patients qualified to participate in the present study, but only 8 were finally evaluated because 1 was lost in the followup.

We collected all the clinical data available on the PCa (prostate-specific antigen [PSA] levels at diagnosis, digital rectal examinations, prostate volumes, Gleason scores, the number of cylinders involved, risk groups), graft function at diagnosis, oncologic outcomes (nadir PSA, time to nadir, biochemical recurrence-free survival, cancer-specific survival, overall survival), and graft function immediately after BT.

At the same time, we compared the clinical characteristics and oncologic outcomes of RTRs to those of the GP with PCa who had received BT between 2007 (onset of BT in our institution) and January 1st, 2015, a total of 258 patients.

PCa screening, low-dose BT, and followup at the University Hospital Virgen del Rocío

At the University Hospital Virgen del Rocío, we carry out a systematic PCa screening by measuring PSA levels and performing annual digital rectal examinations in all patients eligible for renal transplantation and RTRs over 50 years of age [38].

The baseline tests of the two groups (GP and RTRs) with suspected PCa included PSA measurement, digital rectal examination, and ultrasound-guided transrectal biopsy. No bone scan was required when the Gleason score was $\leq$7, PSA $<$20 or PSA $<$10, and in the cT2 stage. No CT scans or additional MRI scans were carried out in cT1−cT2 stages with a Gleason score $\leq$7 and PSA $<$20 following the guidelines established by the Health authorities of our autonomous community (Consejería de Salud de la Junta de Andalucía) in 2005 and 2011. [39,40].

According to these guidelines, low-dose BT is indicated for patients who meet the following criteria: T1a−T2b; PSA levels $\leq$10; and a Gleason score $<$7, IPSS $<$20, Qmax $>$10 mL/min, and prostate volume $<$50 cc. Since 2015, the University Hospital Virgen del Rocío's protocols have been adjusted to the recommendations of the Europe Association of Urology for PCa regarding indication of BT [41].

Iodine-125 seeds were implanted into the prostate transperineally using ultrasound guidance with the VariSeed (Varian Medical Systems, Palo Alto, CA) planning system.

All patients underwent clinical control measures and PSA level measurements every 3 months for the first year, every 6 months for the next 4 years, and once a year for the following 5 years.

Biochemical recurrence was defined following the Phoenix criteria (Nadir + 2) [42]. However, since 2014, we have added two more consecutive peaks in PSA levels over the Phoenix definition to prevent mistaking biochemical failure for PSA bounce and avoid the need for additional biopsies and other unnecessary tests [43].

Statistical analysis

Qualitative variables were expressed as absolute frequencies and percentages, whereas quantitative variables were expressed as mean values and standard deviations. Data were represented in contingency tables and analyzed using Fisher's exact test or χ^2 test for qualitative variables and variance analysis or Student's *t*-test for quantitative variables. Survival analysis was conducted using Kaplan-Meier curves and log-rank tests. All statistical analyses were performed using the software package IBM SPSS 19.0 (SPSS. Inc., Chicago, IL).

Literature review

We additionally reviewed all articles on RTRs with PCa that were treated with BT published between 1990 and July 2017 in PubMed/Medline. Predetermined search words