Original paper

Iodine-125 prostate seed brachytherapy in renal transplant recipients: an analysis of oncological outcomes and toxicity profile

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Abstract

Purpose: Prostate cancer is among the most common non-cutaneous neoplasms affecting renal transplant recipients (RTRs). Available treatments including radical prostatectomy and external beam radiotherapy carry a risk of damage to the transplanted kidney, ureters, or bladder. We assessed the safety and efficacy of Iodine-125 (^{125}I) prostate seed brachytherapy as an alternative to surgery and radiotherapy in these individuals.

Material and methods: We retrospectively reviewed our brachytherapy database to identify patients with a prior history of renal transplantation, who had undergone seed implantation for localized prostate cancer. Long term PSA control and treatment related toxicity, including graft dysfunction, urinary, rectal, and sexual complications, were assessed and compared with published outcomes for surgery and external beam radiotherapy.

Results: Of 1054 patients treated with permanent seed implantation from 2002-2012, we identified four who had a prior history of renal transplantation. Mean time from renal transplantation to prostate cancer diagnosis was 13 years. Mean follow-up after seed implantation was 44 months (range 12-60 months). All four patients remain free of PSA progression. No peri-operative complications were experienced following seed implantation, and all four patients continued to have normal graft function. Long term urinary and rectal function scores were comparable to reported outcomes for seed brachytherapy in the non-transplant population.

Conclusions: ^{125}I prostate seed brachytherapy is associated with high rates of biochemical control and minimal toxicity to the renal graft in RTRs. This treatment should be considered as an alternative to surgery in managing RTRs with localized prostate cancer.

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Key words: brachytherapy, ^{125}I, prostate cancer, renal transplant, seeds.

Purpose

Prostate cancer is the commonest malignancy, and second biggest contributor to cancer mortality among men. Interstitial prostate brachytherapy, surgery, and external beam radiotherapy are widely accepted curative treatment options for organ confined prostate cancer [1]. Renal transplant recipients (RTRs) are known to have a much higher risk of developing malignancies, due to chronic immunosuppression and antigenic stimulation [2]. Whilst skin cancers and lymphoproliferative disorders constitute the majority of these, genitourinary (GU) malignancies are the next most common neoplasms affecting RTRs [2,3]. Some studies have reported a 2 to 5 fold higher incidence of prostate cancer in RTRs than the general population [3-6]. Also, an increasing number of transplant recipients are being diagnosed with prostate cancer, attributable in part to the growing acceptance of PSA screening, but also due to longer survival of transplant recipients, and an increase in the number of older male transplant patients [7]. Prostate cancer also tends to occur at a younger age in transplanted patients than the general population [2].

These trends suggest that prostate cancer may become an important contributor to morbidity and mortality in this group, who are now better managed and less likely to die of post-transplant infections or cardiovascular complications. The available evidence describing prostate cancer treatment outcomes in renal transplant recipients however, remains very limited. Published work has mainly consisted of case reports and small surgical series, with heterogeneity in the outcomes reported and in general, less focus on long term cancer control as much as the immediate peri-operative course.

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Radical prostatectomy has been supported as a treatment for localized prostate cancer in renal transplant patients, but still carries a risk of injury to the transplanted kidney, ureters or bladder. Damage to the graft can result from blood loss during the operative procedure or direct trauma due to the position of the transplanted kidney in the iliac fossa. Being immunosuppressed, these patients are also at a higher risk of infection and problems with wound healing [7]. Various approaches to prostatectomy have been described in RTRs, including radical retropubic prostatectomy (RRP), laparoscopic, and transperineal techniques, but limited follow-up and highly selected patient cohorts (mostly Gleason 6, clinical T1c, and mean PSA levels less than 5 ng/mL) in these series raise uncertainty as to long term biochemical outcomes and toxicity with a surgical strategy [8].

Wagener *et al.* described a six-port transperitoneal approach to robot-assisted laparoscopic radical prostatectomy (RALP) in a 71 year old renal transplant patient with Gleason 7 localized prostate cancer [9]. In this patient, pelvic lymph node dissection was only undertaken on the contralateral side to the transplanted kidney. The procedure took greater than 3.5 hours to perform with a blood loss of 300 mL. Though the post-operative course was uncomplicated, no data on long term PSA control or toxicity was provided. Smith *et al.* also retrospectively identified all patients who had undergone robot-assisted radical prostatectomy (RARP) for localized prostate cancer (n = 228), who were transplant recipients (n = 3). Two patients required modification of their port placement in order to avoid damaging the renal allograft. All three patients were reported to have undetectable PSAs and be continent at twelve months follow-up [10].

External beam radiotherapy to the prostate has also been used in RTRs with disappointing results, including biochemical relapse free survival rates of only 50%, and graft failure or distal ureteric obstruction in 38% [2,11]. The renal allograft location in the pelvis makes it technically challenging to deliver high doses of radiotherapy whilst avoiding damage to the graft. Contemporary definitive external beam radiotherapy regimens generally aim to deliver doses exceeding 70 Gy. The kidney is a highly radiosensitive organ, with increasing risk of clinically significant renal dysfunction being induced beyond mean doses of 15 Gy [12]. Dose to the femoral heads is also of particular importance in RTRs, as the use of corticosteroids and other immunosuppressive drugs in this group places them at a higher risk of avascular necrosis than the general population [2]. Attempts to minimize dose to organs at risk have included dose reduction or compromising the planning target volume (PTV), both of which could diminish the efficacy of treatment [2]. While surgery is often favored for these reasons, the risks of surgery mentioned earlier, together with the possibility that adjuvant radiotherapy may not be altogether avoided in those with adverse pathological features following prostatectomy, are factors which warrant serious consideration [2]. Moreover, the potential for future transplants in the event of graft failure is something that must be considered in managing RTRs with prostate cancer either with a surgical or radiotherapeutic approach.

A third option in RTRs, which has been used to treat localized prostate cancer for decades, and has the appeal of minimal invasiveness and a favorable toxicity profile, is transperineal interstitial permanent prostate brachytherapy [1,13,14]. A key advantage of prostate brachytherapy is that it enables a highly conformal dose distribution, with rapid dose fall off with increasing distance from the radiation sources, thereby allowing preservation of both oncological efficacy and functioning of the renal graft. Published results on the utility of seed brachytherapy in RTRs are lacking. We report on our experience and long term outcomes in RTRs treated with Iodine-125 (^{125}I) prostate seed brachytherapy at an established institution.

Material and methods

Patient characteristics

Four renal transplant recipients were identified as having undergone seed implantation at the St George Hospital Cancer Care Centre between 2002-2012. Reasons for kidney transplantation included chronic glomerulonephritis (n = 2), hypertensive nephropathy (n = 1), and polycystic kidney disease (n = 1). All patients were receiving maintenance immunotherapy. Two patients had a previous diagnosis of immunosuppression-related non-melanomatous skin cancer, including one with metastatic cutaneous squamous cell carcinoma to the parotid and upper cervical lymph nodes treated with surgery and radiotherapy. All patients had functioning grafts at the time of prostate cancer diagnosis, with a mean serum creatinine clearance level of 113 µmol/L (range 80-145). One patient had been experiencing chronic graft rejection since undergoing kidney transplantation two years prior to seed brachytherapy, but his creatinine level had stabilized at 145 µmol/L before undergoing seed implantation. None of the patients received neo-adjuvant or adjuvant hormonal therapy. Table 1 illustrates demographic and tumor characteristics of the treated cohort.

Database

The department's prospective brachytherapy database BrachyNet was reviewed to identify all renal transplant recipients who were treated with ^{125}I prostate seed brachytherapy from the commencement of our program in October 2002, until June 2012. Implantation technique is described. Data on PSA control and treatment toxicity was obtained from BrachyNet. The main endpoints of interest were PSA progression free survival and long term treatment related toxicity, including urinary and rectal function, potency, and graft function. The results of validated questionnaires designed to capture information on patients sexual, urinary, and rectal function at baseline and last available follow-up for each patient were compared. Questionnaires comprised the International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), and Expanded Prostate Cancer Index Composite (EPIC) Bowel Assessment [15-17]. Information on graft function, including creatinine clearance (µmol/L) before and after seed implantation was obtain-

ed from patients clinical records and correspondence from their renal physician. PSA progression free survival was calculated from the date of seed implantation to the date of PSA progression, or last available follow-up. The Phoenix definition (nadir PSA + 2.0) was used to define PSA progression [18]. Descriptive statistics (mean, median, range, standard deviation [SD]) were used to summarize patient, tumor, and treatment details.

Seed implantation technique

All implants were undertaken according to a pre-planned, modified peripherally loaded seed pattern, as described previously by the Seattle group [19]. Under general anesthesia, patients were placed in the dorsal lithotomy position, and the bladder filled with 250 mL of dilute contrast via an indwelling catheter. Transperineal needle placement and deployment of pre-loaded ^{125}I seeds was undertaken using transrectal ultrasound and fluoroscopic guidance. Median operative time for the cohort was 70 minutes (range 55-90 minutes). The indwelling catheter was removed during recovery and all patients were discharged on the day of implantation. All four patients experienced an unremarkable post-operative course. Figure 1 is a post-operative computed tomography scan which illustrates the distribution of radioactive ^{125}I seeds in relation to the allograft in one study patient.

Minimum follow-up for the cohort was 12 months (range 12-60 months).

Results

Toxicity

Mean International Prostate Symptom Score (IPSS) at last follow-up was 5 ± 4.1, compared with 3 ± 3.6 at baseline. Mean International Index of Erectile Function (IIEF) score was 8 ± 11.7, compared with 5 ± 4.6 at baseline, and mean Expanded Prostate Cancer Index Composite (EPIC) bowel assessment score was 22 ± 4.7 compared with 23 ± 3.8 at baseline [15-17]. No patient experienced graft dysfunction following seed implantation. Mean creatinine clearance level post-operatively was 98 µmol/L (range 76-120). Figure 2 illustrates the difference in IPSS, IIEF, and EPIC scores from baseline to last available follow-up for each of the four patients. There was no significant deviation in bowel function from baseline to post-treatment. All four patients had erectile dysfunction predating their brachytherapy. Three patients experienced a return of urinary function to near baseline levels. The fourth patient was continuing to experience clinically significant voiding symptoms compared to baseline, but was only 12 months out from seed implantation. His symptoms were managed successfully with alpha blockers. No patient required urinary catheterization at any point following seed implantation.

PSA control

After a mean follow-up of 44 months (range 12-60 months), all patients were alive with no evidence of PSA relapse or distant failure. One patient was being treated with surgery and radiotherapy for metastatic cutaneous squamous cell carcinoma to the axilla more than three years after undergoing prostate brachytherapy and his PSA has remained undetectable. Of patients who had sufficient post-treatment follow-up to achieve a PSA nadir (n = 3), median nadir PSA was 0 (range 0-0.14 ng/mL).

Table 1. Patient and tumor characteristics

Factor	*N* (%)
Age	
Median (range)	64 (61-66)
Smoking status	
Current	0 (0)
Never	3 (75)
Ex-smoker	1 (25)
Comorbidities	
Hypertension	3 (75)
Ischemic heart disease	2 (50)
Diabetes mellitus	1 (25)
Other cancer	2 (50)
Years from transplant	
Median (range)	13 (6-17)
Immunosuppressant therapy	
Cyclosporine	2
Tacrolimus	1
Sirolimus	1
Mycophenolate mofetil	1
Prednisone	3
Clinical Stage	
T1c	3 (75)
T2a	1 (25)
iPSA	
Mean ± SD	8.9 ± 3.8
Gleason score	
7	3
8	1
Hormonal therapy	
Yes	0 (0)
No	4 (100)
Baseline IPSS (0-35)	
Mean ± SD	3 ± 3.6
Baseline IIEF Score (0-25)	
Mean ± SD	5 ± 4.6
Baseline EPIC Bowel Score (8-62)	
Mean ± SD	23 ± 3.8

N – number of patients, iPSA – initial prostate specific antigen level, SD – standard deviation, IPSS – International Prostate Symptoms Score, IIEF – International Index of Erectile Function, EPIC – Expanded Prostate Cancer Index

Discussion

Genitourinary (GU) malignancies are becoming an increasingly important source of morbidity and mortality

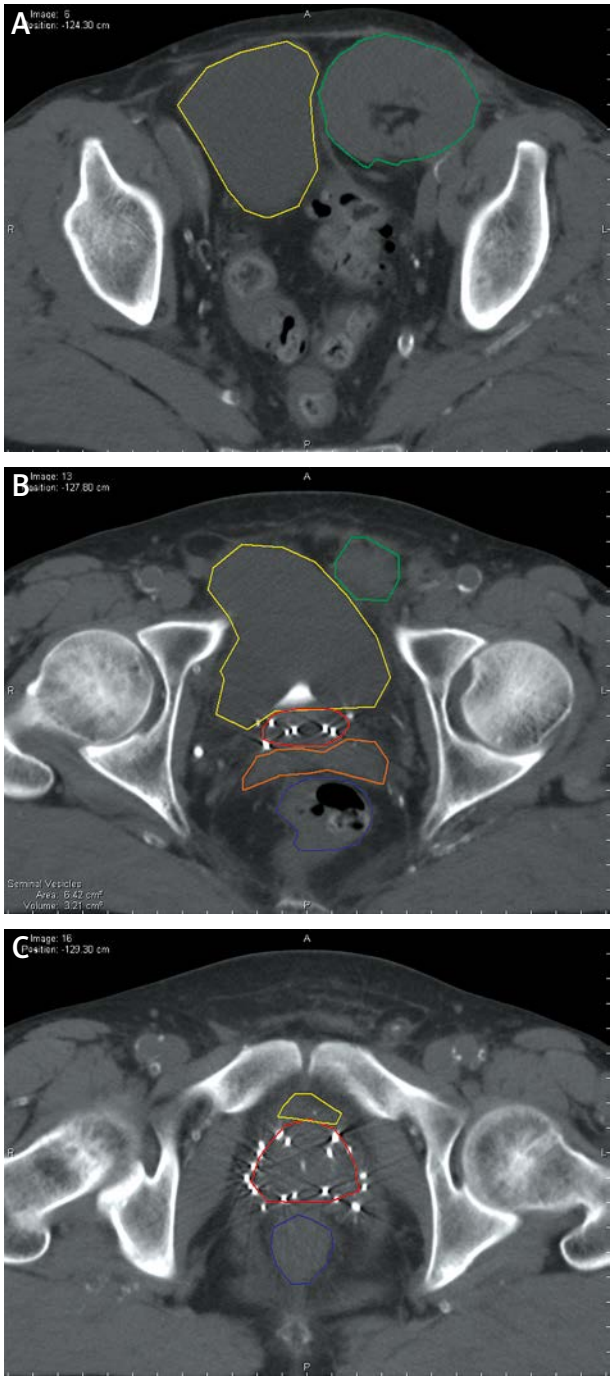

Fig. 1. Distribution of radioactive Iodine-125 seeds on computed tomography scan in relation to the allograft in one study patient. (A) Mid-portion of renal graft, (B) inferior portion of graft and superior-most intraprostatic seeds, (C) mid-portion of prostate.
Green – renal allograft; red – prostate; yellow – bladder; orange – seminal vesicles; blue – rectum

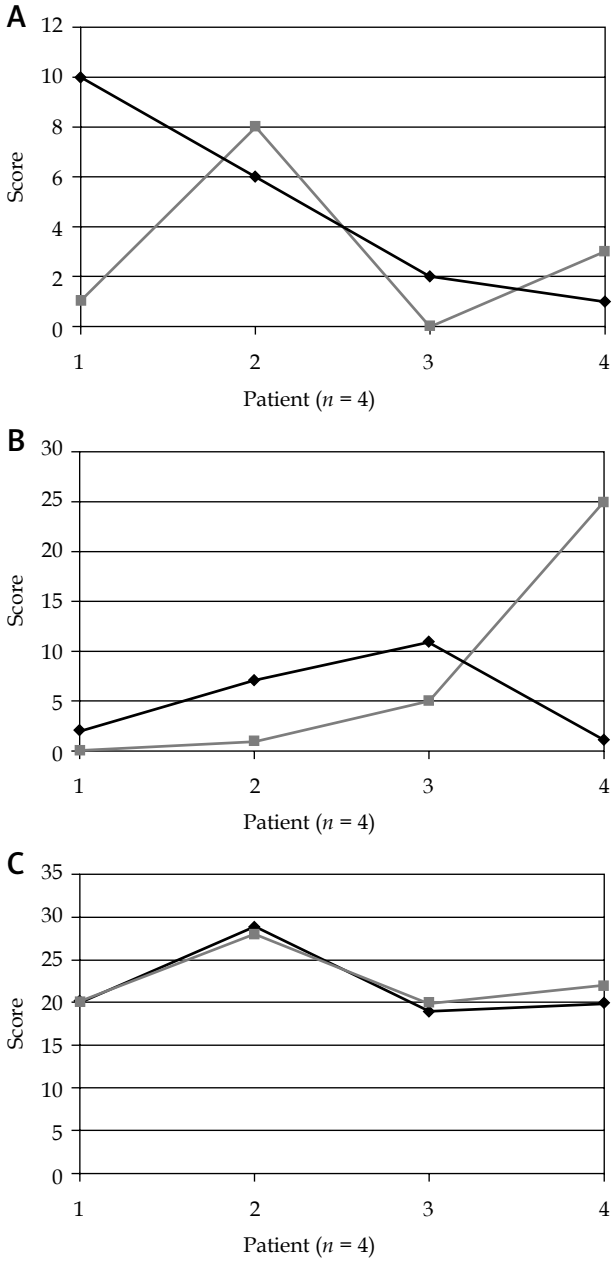

Fig. 2. (A) Difference in International Prostate Symptom Score (top), (B) International Index of Erectile Function (middle), and (C) Expanded Prostate Cancer Index Composite bowel assessment scores (bottom) from baseline to last available follow-up for each of the four patients.
Grey line – baseline score; black line – follow-up score

in RTRs [7]. Because of advances in immunosuppressive therapy for RTR, half-lives for both living and cadaveric grafts have almost doubled, to 21.6 years, and 13.8 years, respectively. Management of GU tumors can be a challenge in these patients, as available definitive therapies can significantly impact on graft survival and function. The likelihood of death with a functioning graft is three times greater in RTRs with a GU malignancy than in those without [20].

Problems can be encountered when attempting to treat RTRs with external beam radiotherapy, due to proximity of the graft to the treatment region, and the inherent radiosensitivity of this organ to even modest doses of radiation [12]. Whilst successful treatment of the prostate alone with definitive radiotherapy to 70 Gy has been reported in RTRs, this was associated with biochemical recurrence in 25%, as well as graft failure in one patient

and ureteric obstruction in a further two, which could precipitate future graft dysfunction [11].

Though surgery has traditionally been considered the preferred treatment approach, graft function can also be threatened through prolonged operative times and blood loss, intra-operative trauma to the pelvic renal graft, or post-operative bladder dysfunction [7]. Moreover, while pelvic lymph node dissection may not be routinely performed during RRP, there is some evidence to suggest that patients on more heavy maintenance immunosuppressive therapy are more likely to present with locally advanced tumors and lymph node invasion [6]. This has two important implications. Firstly, oncological outcomes could be compromised with surgery in those with nodal involvement as comprehensive pelvic nodal dissection may be limited by the location of the graft. Secondly, those with unfavorable histopathology such as margin involvement or seminal vesicle invasion may not be able to avoid post-operative radiotherapy, which would compound the toxicity of therapy, including risk of damage to the renal graft. Both these modalities also require consideration of the possibility of future graft failure and the potential for new graft placement. Approximately one third of RTRs will require a new transplant due to graft failure, and this can be complicated by previous radiation or surgery [21,22].

Prostate brachytherapy can potentially overcome the complications experienced with external beam radiotherapy by enabling 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. Although seed brachytherapy is considered a standard treatment option for localized prostate cancer, outcomes have not been specified for RTRs. A recent review by Coombs *et al.* described prostate cancer outcomes in seven of their brachytherapy patients who were also organ transplant recipients [23]. Three of these were renal transplant patients, with the remainder being heart transplants. While the difficulties mentioned above in treating renal transplant recipients with respect to the graft being in close proximity to the radiation field are less of an issue with heart transplant patients, of relevance is that after a minimum follow-up of three years, the transplanted patient subset had comparable rates of biochemical control 85%) to non-transplant patients (n = 307) treated at the same center [23]. Biochemical control rates were equally high in our series, with all four patients being free of prostate cancer relapse at a mean follow-up of 44 months. Moreover, RTRs who underwent seed implantation at our institution continued to have normal graft function following treatment according to pre and post-implant serum creatinine clearance levels.

Temporary urinary sequel in the form of an increased IPSS have been reported to occur in approximately 20% of patients beyond 12 months after permanent seed brachytherapy [24]. These have generally comprised of flares, and the majority of these patients will respond to alpha blockers or anticholinergics. Chronic IPSS increases are seen in less than 5% of brachytherapy patients [24]. Of the patients beyond 12 months of implantation in our study, all reported a follow-up IPSS that was within two points of their baseline score. All four patients had no significant deviation in their EPIC scores from baseline. The impact of treatment on sexual function was difficult to assess in this cohort, due to significant erectile dysfunction existing prior to seed implantation. As such, it is likely that long term erectile function after seed implantation would be confounded by other medical conditions in this population.

Our mean operative time of 75 minutes in the seed cohort also compares favorably to surgical series, where operative times more than twice this duration have been reported [3,9]. Due to its minimal invasiveness compared to prostatectomy, all patients were able to be discharged on the same day as their seed implant and experienced no complications during their post-operative course.

Finally, though immunosuppression has been implicated in malignant cell growth, it remains uncertain as to whether prostate cancer runs a more aggressive course in RTRs [25]. Our patients all presented with localized tumors and were free of disease relapse at last available follow-up. Nevertheless, a larger patient cohort and longer follow-up would be required to ascertain the natural history of this disease in RTRs.

Conclusions

^{125}I prostate seed brachytherapy was associated with favourable biochemical outcomes and minimal toxicity, and should be considered as an alternative to surgery in renal transplant patients.

Disclosure

Authors report no conflict of interest.

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