

Case Report

Palladium interstitial implant in combination with external beam radiotherapy and chemotherapy for the definitive treatment of a female urethral carcinoma



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ABSTRACT

Primary urethral cancer is a rare diagnosis, especially in females. This report presents the utilization of a palladium interstitial implant and a review of the retrospective data published on the management of female urethral cancer. Excellent local control and survival has been obtained with the use of a palladium interstitial implant in combination with external beam radiotherapy and concurrent chemotherapy. This modality represents a novel and effective way to treat primary urethral cancer in females.

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A 57 year-old female with a 40 pack-year smoking history presented with a three to four week history of dribbling urine and pain. Despite multiple evaluations and placement of a Foley catheter, her pain was unrelieved. A computed tomography (CT) scan of the abdomen and pelvis was obtained revealing a large mass at the base of the bladder with bladder distention and bilateral hydronephrosis. After successful placement of a Foley catheter her symptoms improved. An exam under anesthesia with cystoscopy was performed, confirming the suburethral mass approximately 4 centimeters in size. Biopsies of the suburethral mass revealed a mucin producing, poorly differentiated carcinoma and some features of adenocarcinoma with lymphovascular space invasion. The tissue showed strong cytokeratin 7 (CK7) positivity and rarely positive p63 cells. There was some controversy as to the origin of the disease and therefore prostate-specific antigen (PSA) testing was recommended. PSA positivity can confirm the origin as Skene's paraurethral glands, the homolog of the prostate gland (Wang et al., 2012). In this case, a PSA stain was negative, which is more common with mucinous adenocarcinomas and does not rule out urethral origin (Chan et al., 2000). A pelvic magnetic resonance imaging study (MRI) revealed a circumferential mass involving the entire urethra from the bladder to the introitus, measuring 40 × 37 × 40 mm, which was homogeneously enhancing and displaced the anterior vaginal wall posteriorly

(Fig. 1). Notably, there were no morphologically abnormal lymph nodes, giving the final diagnosis of stage II disease; T2N0M0.

The following treatment options were presented: 1) anterior pelvic extenteration with resection of the anterior vagina, uterus, fallopian tubes, ovaries and bladder with formation of a conduit; 2) concurrent chemoradiotherapy; and 3) continued observation. The patient opted for concurrent chemoradiation with external beam radiotherapy to the pelvis, followed by an interstitial implant to the periurethral tumor. External beam radiation therapy was delivered to the pelvis using a 7 field intensity modulated radiation therapy (IMRT) plan with 6 megavoltage (MV) photons. Radiation was delivered once daily, five days per week, at 1.8 Gray (Gy) per day, for a total of 28 treatment days. The target volume, including the primary tumor and at-risk lymph nodes, was contoured to ensure adequate coverage. Concurrent cisplatin was administered weekly throughout radiotherapy. Halfway through treatment, the Foley catheter that had remained in place since diagnosis was removed without difficulty and the patient continued to void normally without complications.

At the completion of the external beam radiotherapy, both an interstitial high dose rate (HDR) treatment with a Syed template and utilization of a low dose rate (LDR) treatment with palladium-103 seeds were considered. To inform this decision, a transrectal ultrasound volume study was performed. The imaging appearance and location of the tumor bore a remarkable resemblance to a typical prostate gland, with an eccentric urethra (Fig. 2). The tumor was suitable for a palladium implant when using criteria frequently used to assess the utility of a seed implant in prostate cancer patients, namely size and lack of interference of the pubic arch. Both an LDR implant as well as an HDR

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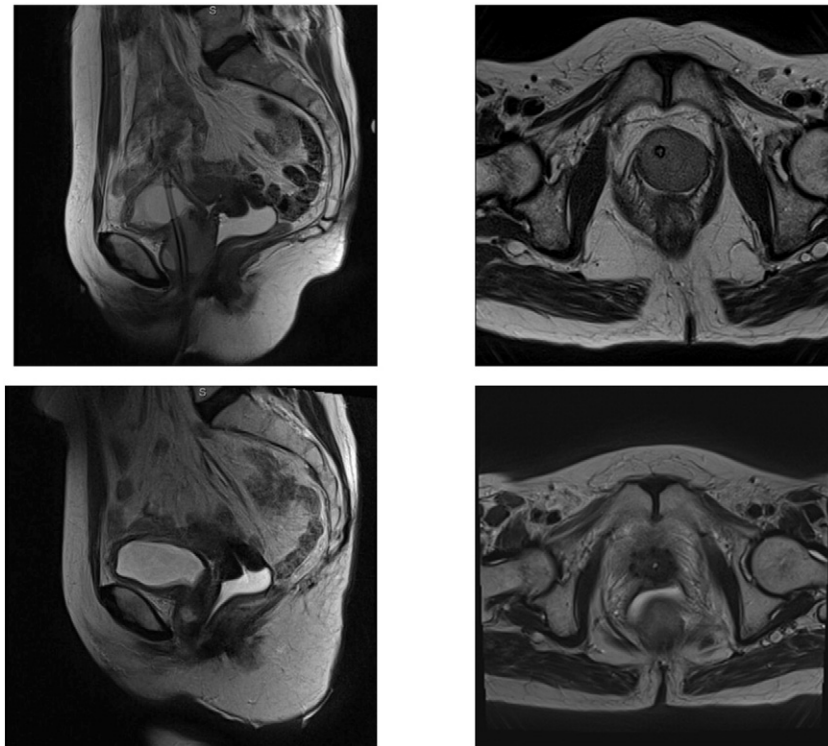


Fig. 1. Upper row: T2-weighted sagittal and axial MRI at initial diagnosis revealing a 4 cm periurethral mass with a Foley catheter traversing the lesion. The lesion is diffusely enhancing with some areas of hyperintensity. Lower row: T2-weighted sagittal and axial MRI at 5 months post-treatment, revealing no discrete or identifiable periurethral mass, and no regional lymphadenopathy to suggest recurrence.

implant were considered good treatment options, but we had no data or experience to support the idea that either an LDR or HDR technique had superiority for control or toxicity. Given our large institutional experience treating men with LDR implants with pelvic external beam radiotherapy for prostate cancer, we felt confident that we could predict the probability of toxicities to the rectum, bladder and urethra using an LDR implant in this case. Although we were concerned about the possibility of seed aggregation in a rapidly responding tumor, which would favor an HDR technique, we felt this was unlikely to be the case in this patient. Even so, we used palladium-103, which has a shorter half-life than iodine-125, to reduce the risk of overdose to the urethra if the tumor responded rapidly. HDR would have been the preferred treatment in cases where rapid regression of tumor was anticipated, or in cases where the disease was more irregularly shaped, or in a distribution that less resembled the anatomy of a prostate gland.

Seventeen days after completion of the external beam portion of the radiotherapy treatment, the patient was implanted with fifty palladium-103 interstitial seeds to a total dose of 100 Gy. Intra-operative fluoroscopy is displayed in Fig. 3. The total activity was 105.955 millicurie (mCi). The gross tumor volume (GTV) was 18.11 cc, the volume receiving 100% of the dose (V100%) was 17.48 cc (96.49%) and 90% of the volume (D90%) received at least 117.63 Gy (117.63%). Thirty percent of the urethra (D30%) received 150.7% of the dose, and 5% of the urethra (D5%) received 163.3% of the dose. The bladder V100% was 4.05 cc, the dose to 3 cubic centimeters (cc) (D3cc) was 118.33 Gy, and the dose to 1 cc (D1cc) was 179.75 Gy. The rectum V100% was 0.09 cc, the D3cc was 27.69 Gy, and the D1cc was 45.48 Gy. Fig. 4 shows a representative cross section of the post-implant dosimetry.

Five months later, as part of routine follow-up, a pelvic MRI revealed a significant response to therapy with no discrete residual

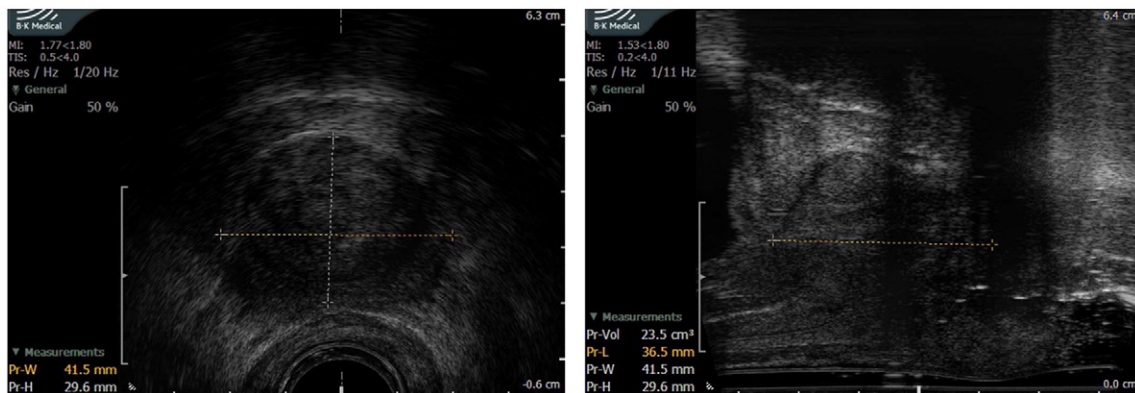


Fig. 2. Transrectal ultrasound volume study pre-implantation axial and coronal images. The urethral tumor displays a remarkable resemblance to a typical prostate gland. The dimensions of the tumor are displayed in the lower left of the images.

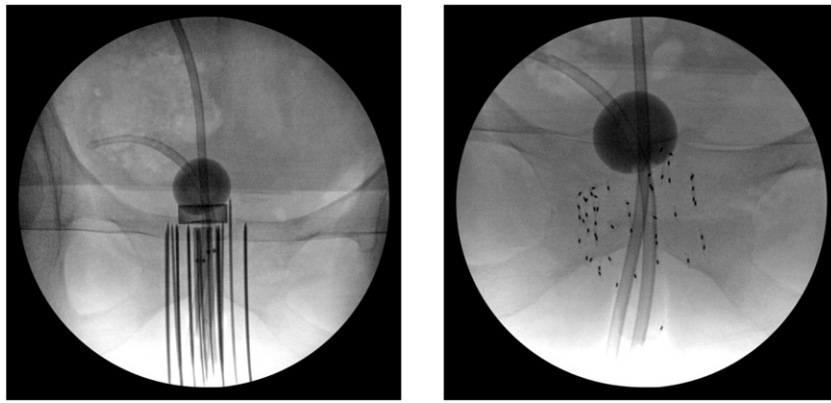


Fig. 3. Intra-operative fluoroscopy images taken at the time of implantation. The left-hand image displays the needle guides with a Foley catheter in place, and the right-hand image displays the palladium seeds in place at the end of the procedure.

mass identified (Fig. 1). Grade 1 dysuria was the only residual side effect from treatment. Otherwise, the patient was voiding normally without any complaints or complications. One and a half years after completion of treatment, the patient returned for routine follow up without clinical or radiographic evidence of disease and near complete resolution of dysuria. An American Urological Association (AUA) symptom score was completed and she scored a 3/35 (1 for frequency, 2 for nocturia). A CT scan of the abdomen and pelvis revealed the interstitial seeds in place, with no evidence of recurrent tumor or suspicious lymphadenopathy. Unfortunately, the patient had resumed smoking, although she was trying to cut back; she will return to our clinic on a yearly basis for routine follow up.

Primary urethral cancer in females is a rare disease, with an annual incidence of approximately 4.3 per million population in men and 1.5 per million population in women (Swartz et al., 2006). The most common histologies are urothelial cell carcinoma and squamous cell carcinoma, with urothelial more commonly arising in the proximal one third of the urethra, and squamous arising in the distal two-thirds, followed by adenocarcinoma (Swartz et al., 2006; Derksen et al., 2013). A high percentage of patients present with locally advanced disease at diagnosis, which portends a poor prognosis and survival (Derksen et al., 2013; Dayyani et al., 2013). Tumor histology and size have also been shown to be independent predictors of outcomes, with adenocarcinoma and tumors greater than 4 cm portending a worse prognosis with 5-year cause specific survivals of 0% and 19% respectively (Grigsby, 1998).

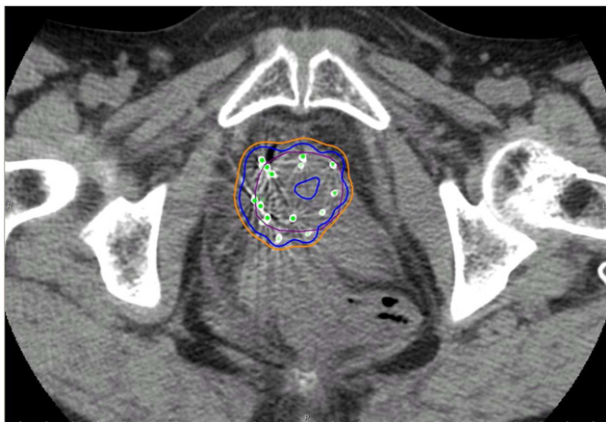


Fig. 4. Post-implant dosimetry. The purple contour represents the GTV, the green dots represent the palladium seeds, the dark blue line represents the 150 Gy isodose line (150% of the dose), and the orange line represents the 100 Gy isodose line (100% of prescription dose).

Treatment options include surgery, radiotherapy, or the combination. Given the rarity of the disease, there is a paucity of literature on outcomes and a lack of consensus on recommendations. The utilization of radiotherapy alone (external beam, interstitial implants, or the combination) for definitive management has been reviewed, albeit with small numbers of patients (Micaily et al., 1997). A sizeable retrospective review evaluating forty four women treated for urethral cancer with surgery, radiotherapy, or the combination reported a local control rate of 32% when patients received radiotherapy alone (Grigsby, 1998). Of the forty four women included in this study, only 24 were treated with radiotherapy alone, and the authors could not prove a benefit to dose-escalation (Grigsby, 1998). A second, larger, retrospective study from the 1990s evaluating ninety-seven women reported 5-year local control of 64% for all patients, although worse outcomes were reported when the entire length of the urethra was involved, and survival at 5 and 15 years was 41% and 22% respectively (Garden et al., 1993). In this study, patients who received interstitial therapy had better survival compared to those treated with external beam alone, with the use of radium-226 needles and after loading iridium-192 wires for interstitial implants (Garden et al., 1993). The authors recommended external beam radiation in combination with an interstitial implant for patients who could not receive surgery (Garden et al., 1993). Similar to the case reported here, two patients treated with concurrent cisplatin and capecitabine along with external beam radiation to the pelvis and an interstitial implant with Iridium had local control at 14 months and three years after treatment (Libby et al., 2010).

The use of chemotherapy has been evaluated as well, although with a small number of studies published on the utilization of this modality. Several small series have shown good response rates and outcomes with neoadjuvant and/or concurrent chemotherapy with the combination of surgery and/or radiotherapy (Dayyani et al., 2013; Cohen et al., 2008). Neoadjuvant platinum-based regimens have been shown to elicit a response rate of up to 72%, and combined with surgery patients had an overall survival of 31.7 months (Dayyani et al., 2013). A review of the use of chemoradiation for men with primary urethral cancer reported a complete response rate of 83%, with a 5 year overall survival of 60% and disease specific survival of 83% (Cohen et al., 2008). The authors suggest that perhaps data from concurrent chemoradiation for other cancers of the genitourinary tract like anus, bladder, vagina, vulva and cervix can be extrapolated to urethral cancer to improve outcomes (Dayyani et al., 2014). For patients that choose to forego surgical treatment, or for whom surgical resection is not an option, chemoradiation is an excellent alternative and allows for organ preservation, as well.

While the use of brachytherapy has been reported for treatment of urethral cancer, this is the first report, to our knowledge, of a female patient treated with a palladium-103 interstitial implant in combination with external beam radiotherapy to the pelvis for urethral carcinoma. The use of a palladium-103 implant is not

only more convenient for the patient, but also less morbid than surgery or high dose rate brachytherapy procedures and avoids the need for hospitalization. This combination of treatment modalities might be considered for patients with discrete urethral tumors accessible by transperineal implant approaches who choose to forgo surgery, or for whom surgery is not an option. Our experience shows that this treatment option can be safe and effective in appropriately selected patients.

Conflicts of interest

None.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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