Case report

High-dose-rate brachytherapy – a novel treatment approach for primary clear cell adenocarcinoma of male urethra

Shirley Lewis, MD[1], Mahendra Pal, MS[2], Ganesh Bakshi, MS, MCh[2], Yogesh G. Ghadi, MSc[3], Santosh Menon, MD, DNB[4], Vedang Murthy, MD, DNBR[1], Umesh Mahantshetty, DMRT, MD, DNB[1]

[1]Department of Radiation Oncology, [2]Department of Surgical Oncology, [3]Department of Radiation Physics, [4]Department of Pathology, Tata Memorial Centre, Parel, Mumbai, India

Abstract

The incidence of male urethral cancer is rare with age preponderance of 50 to 60 years. The standard management approach is surgery. Here, we present a novel treatment approach for male urethral cancer. Thirty-six year old male, case of primary clear cell adenocarcinoma of urethra who refused surgery, underwent cystoscopic assisted intraluminal HDR brachytherapy. Patient received a dose of 36 Gy in 9 fractions (4 Gy per fraction) followed by a boost of 24 Gy in 6 fractions. At 11 months post treatment, disease is well controlled with no post treatment toxicity so far. Intraluminal brachytherapy seems to be an effective novel treatment for male urethral cancer.

J Contemp Brachytherapy 2015; 7, 3: 248-251
DOI: 10.5114/jcb.2015.52316

Key words: adenocarcinoma, HDR brachytherapy, intraluminal brachytherapy, urethral cancer.

Purpose

Male urethral cancer is extremely rare accounting for < 0.02% of all the cancers. They usually present in 5th-6th decade of life and are often diagnosed in late stages with palpable lymph nodal mass [1]. Most common histology are urothelial carcinomas (75%) and squamous cell carcinoma accounting for 12%. Only 5% are adenocarcinoma or undifferentiated tumors arising from submucosal glandular tissue [2]. Clear cell adenocarcinoma is uncommon. Only seven cases have been reported in literature [3]. The treatment of urethral cancer is challenging given the rarity of the disease and heterogeneity of the treatment strategies used in the reported case series. Surgery is the mainstay of treatment. Alternatively, radiation therapy has also been attempted. Radiation therapy in the form of brachytherapy is usually considered for low volume superficial tumor of the anterior urethra when patients refuse surgery. We report a case of primary clear cell adenocarcinoma of the urethra treated with intraluminal high-dose-rate brachytherapy.

Case summary

Thirty-six year old male presented with complaints of burning micturition and poor urinary flow of 2 months duration. Past history was non-contributory. General and systemic examination did not reveal any abnormal findings. Routine hematological, biochemical – renal and liver function test were within normal limits. Chest X-ray was normal. X-ray urethrogram showed mild to moderate long segment irregular narrowing of the penile with moderate short segment stenosis of the bulbous urethra. Computed tomography (CT) scan of the abdomen showed no abnormal thickening or enhancing focus in the urethra with no evidence of inguinal or intraabdominal lymphadenopathy. Cystoscopy showed multiple papillary lesion involving penile and bulbar urethra 1 cm short of membranous urethra. Membranous and prostatic urethra were free. Urine cytology was suggestive of high grade urothelial carcinoma. However, biopsy revealed clear cell adenocarcinoma (high grade urothelial carcinoma) with no invasion of the lamina propria (Fig. 1). The MIB index was 30-40% and 50% in highest proliferating areas. Magnetic resonance imaging (MRI) showed irregular wall thickening involving penobulbar region of the urethra measuring 5.3 cm in length. The thickening was seen to extend upto the membrano-prostatic junction of the urethra (Fig. 2). Anteriorly, the lesion extended upto fossa navicularis and posteriorly upto prostatic urethra. The bladder was normal. The lesion was confined to the urethra without involvement of the buck's fascia or tunica or corpora. No significant lymphadenopathy seen in the pelvis. The metastatic work-up including screening of the

Address for correspondence: Umesh Mahantshetty, DMRT, MD, DNB, Prof., Tata Memorial Centre, E Borges Road, Mumbai – 400 012, India, phone: +91-22-24177168, ✉ e-mail: drumeshm@gmail.com

Received: 12.05.2015
Accepted: 21.05.2015
Published: 25.06.2015

remaining urinary tract was within normal limits. All the treatment options was discussed with patient in a multidisciplinary tumor board meeting. Since patient refused for radical surgery, radical radiation therapy with high-dose-rate (HDR) brachytherapy alone was offered. The HDR brachytherapy details are as follows.

Radiotherapy technique

Preplanning

Patient was positioned in dorsal position after proper antiseptic dressing and draping. Cystoscopy showed multiple papillary lesion involving the entire penile and bulbar urethra. The growth extended distally about 2 cm from the meatus (at the level of coronal sulcus) involving entire penile, bulbar, and about 1 cm of membranous urethra. Prostatic urethra was free. Bladder neck and bladder mucosa was normal.

Brachytherapy planning

Bladder was catheterized with 3 way foley's catheter no 22. A nylon catheter was introduced through the drain for a length of 34 cm and it was firmly secured to the drain at the distal end. The urine drainage bag was connected to the side tube. Patient underwent MRI based planning. Planning was done using Oncentra brachytherapy planning system (Version 4.3; Nucletron, Elekta, Stockholm, Sweden). The target volumes were contoured on the T2 weighted images. The high risk clinical target volume (HRCTV) was contoured on the MR images, which included the entire membranous urethra in continuity till navicular fossa (around corona glandis) (Fig. 2).

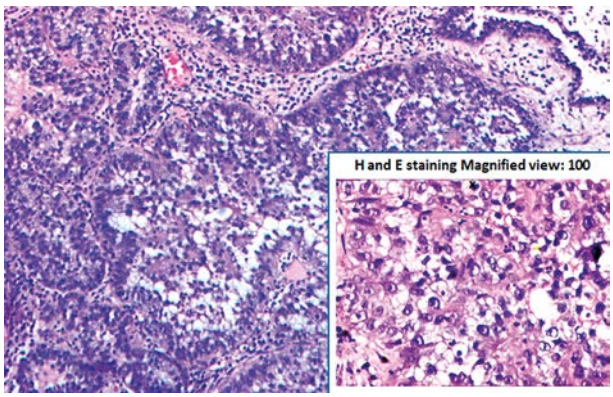

Fig. 1. Clear cell adenocarcinoma of urethra with glandular formations and lining cells showing clear to eosinophilic cytoplasm

Dose prescription

The prescribed dose was 36 Gy in 9 daily fractions of 4 Gy each. The gross disease was covered by 150% of the prescribed dose. The EQD2 ($\alpha/\beta = 10$) was 48 Gy to HRCTV.

The treatment was well tolerated by patient with mild to moderate pain along the urethra, which was relieved with non-steroidal anti-inflammatory drugs.

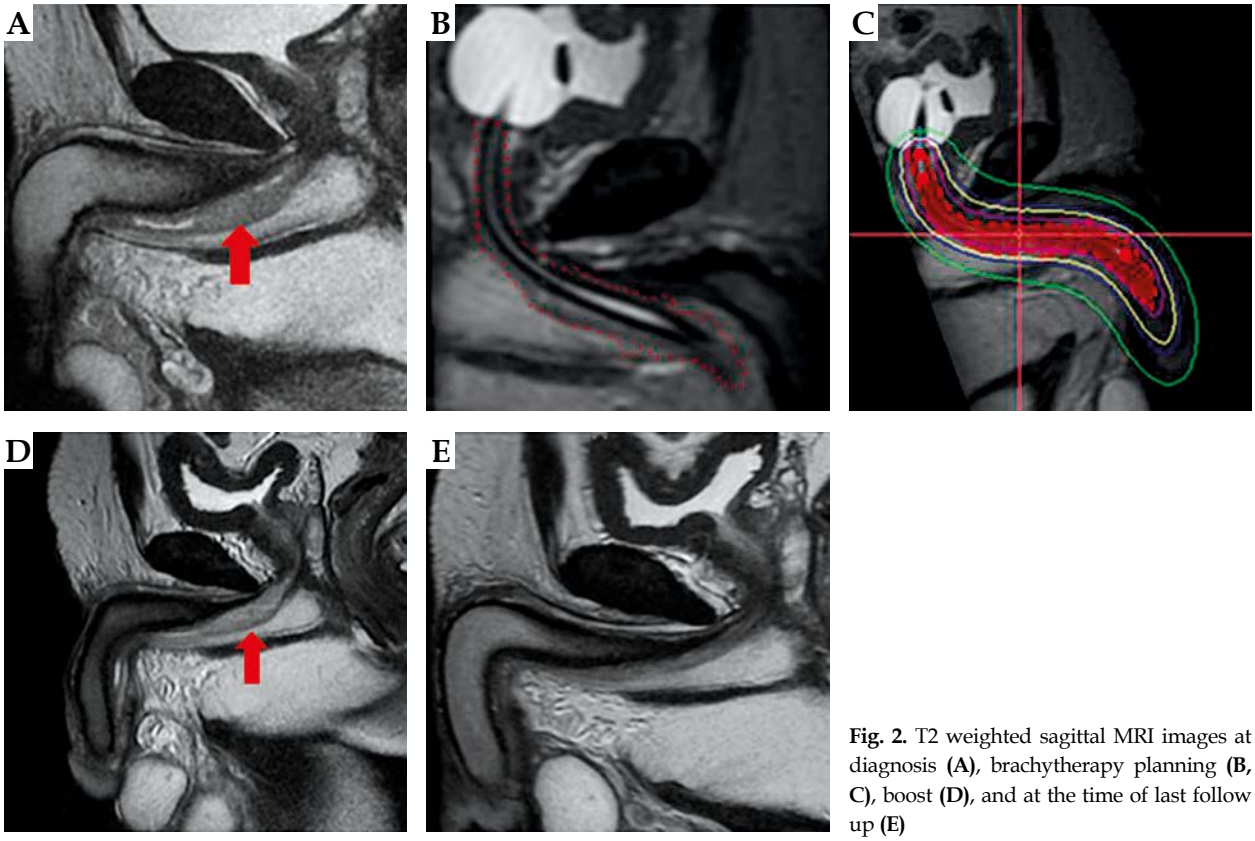

Fig. 2. T2 weighted sagittal MRI images at diagnosis **(A)**, brachytherapy planning **(B, C)**, boost **(D)**, and at the time of last follow up **(E)**

Boost

At 2 months patient was asymptomatic. Cystoscopy showed mild congestion of penile urethra, multiple papillary lesions in penile urethra extending to bulbar urethra. Urethral biopsy showed residual viable clear cell adenocarcinoma of urethra. Magnetic resonance imaging showed irregular wall thickening involving the peno-bulbar region measuring 4.2 cm in length extending to membrano-prostatic junction of urethra. Lesion was confined to urethra without involvement of corpora cavernosa (Fig. 2). He was planned for boost brachytherapy. Patient received a dose of 24 Gy in 6 fractions of 4 Gy each (EQD_2 was 32 Gy).

Patient is clinically well without any symptoms of bleeding, discharge, or pain. On clinical examination, there are no palpable inguinal nodes. A repeat cystoscopy at 11 months of follow up shows mild congestion of penile urethra with complete regression of the growth in the urethra. Magnetic resonance imaging shows residual thickening in peno-bulbar urethra measuring 3.7 cm with regression of lesion in the prostatic urethra. There is significant regression in extent, thickness and signal intensity of the wall thickening in peno-bulbar urethra (Fig. 2). There is no lymphadenopathy in pelvis or inguinal region.

Discussion

Male urethral cancer is very rare. It is very uncommon before the age of 55 years with peak incidence in sixth decade of life and incidence increases with advancing age. There are no specific causative factors identified, however, prior history of sexually transmitted disease, HPV, urethritis, urethral stricture, chronic irritation after urethroplasty, and history of cystectomy for bladder cancer are often implicated [4,5]. Urethral stricture is often coexistent with carcinoma urethra with incidence of 24-76% [6]. The bulbomembranous urethra is the most common site of involvement (60%) followed by penile urethra (30%) and prostatic urethra (10%) [7]. Clear cell adenocarcinomas are very rare. They are thought to be of mullerian origin and more predominantly seen in female urethral cancers. The proposed postulates for its origin are: 1) Mullerian origin, 2) glandular differentiation of urothelium, 3) vesicular adenocarcinoma of non mullerian origin [8]. The most common presenting symptoms are urinary symptoms, hematuria, pain, urethral mass, or an inguinal mass. The main prognostic factors are location and depth of invasion. Anterior lesions tend to be superficial and have a good prognosis. Posterior lesions are deeply invasive and have higher rates of distant metastasis [1].

The literature pertaining to treatment is very sparse, limited only to case reports. Surgery is the curative treatment of urethral carcinoma. It includes transurethral excision, local excision, partial amputation, or radical amputation of the penis. Zeidman *et al*. showed good local control with local excision alone with a disease free survival of 39% [9]. Definitive radiotherapy either or both external beam radiotherapy (EBRT) and brachytherapy have shown good results. The main advantage of radiotherapy is organ preservation. Radiation is usually considered in early lesions of the urethra, or in which patients refuse surgery. For the distal lesions radiotherapy provides good cure rates similar to surgery alone. The dose employed for EBRT ranges from 50 to 75 Gy [10]. Prophylactic nodal irradiation is usually not done. Chemoradiation has been used in locally advanced urethral cancers with a dose of 45-55 Gy. The commonly used chemotherapeutic agents are 5-fluorouracil and mitomycin C. The disease free survival range from 60-100% [11]. Persistent or recurrent disease after radiation is treated with salvage surgery.

For limited disease of the urethra, brachytherapy in combination with conservative surgery or EBRT plays an important role. Lesions of the anterior urethra are accessible for brachytherapy both intraluminal and interstitial. The target volume for brachytherapy includes the intraluminal and the infiltrating portion. Magnetic resonance imaging aids in the accurate delineation of the gross tumour volume (GTV). The clinical target volume includes the GTV, 10 mm margin at each extremity of the lesion and 5 mm margin to the infiltrating portion. Intraluminal brachytherapy is usually limited to superficial lesions that measure no more than 5 mm in depth. Intraluminal brachytherapy is performed with a catheter (closed at one end), or the foley's catheter and afterloaded with radioactive source. There is no guideline on the dose used for brachytherapy. ESTRO recommends a dose of 65 Gy for brachytherapy alone with LDR and 20-25 Gy for boost. The HDR recommended dose is 4-5 sessions of 10 Gy each in 3-4 weeks [12].

Chakrabarti *et al*. reported a case of intraluminal urethral brachytherapy for recurrence of transitional cell carcinoma in the urethral stump. The dose prescribed was 7 Gy in seven weekly fractions at 0.5 cm from the single applicator. Patient had complete regression of the lesion at 1 year post treatment [13]. Dalbagni *et al*. analysed the treatment outcomes of 46 men with primary tumor of the bulbar and anterior urethra and showed an overall survival rate of 42%. There was a difference depending on the location of tumor, with a survival rate of 26% for tumors of the bulbar urethra versus 69% for tumors of the anterior urethra. The overall survival rate was 83% for superficial disease versus 36% for invasive tumors [1]. Brachytherapy is usually well tolerated with minimal side effects. The acute effect of brachytherapy is local inflammation and pain. Sometimes, it may be complicated with local infection. It is self limiting and responds to antibiotics. The late sequelae commonly seen is secondary strictures.

This case report highlights the potential use of radical brachytherapy in early stages of male urethral cancers. The ease of application with good results makes intraluminal brachytherapy an option for organ preservation especially in young males. However, longer follow up is needed.

Conclusions

Radical intraluminal HDR brachytherapy as a treatment option for carcinoma of male urethra is feasible and an attractive option for organ and function preservation.

Disclosure

Authors report no conflict of interest.

References

1. Dalbagni G, Zhang ZF, Lacombe L et al. Male urethral carcinoma: analysis of treatment outcome. *Urology* 1999; 53: 1126-1132.
2. Rabbani F. Prognostic factors in male urethral cancer. *Cancer* 2011; 117: 2426-2434.
3. Gandhi JS, Khurana A, Tewari A et al. Clear cell adenocarcinoma of the male urethral tract. *Indian J Pathol Microbiol* 2012; 55: 245-247.
4. Van de Voorde W, Meertens B, Baert L et al. Urethral squamous cell carcinoma associated with urethral stricture and urethroplasty. *Eur J Surg Oncol* 1994; 20: 478-483.
5. Cupp MR, Malek RS, Goellner JR et al. Detection of human papillomavirus DNA in primary squamous cell carcinoma of the male urethra. *Urology* 1996; 48: 551-555.
6. DeVita Jr VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia 2014.
7. Grabstald H. Proceedings: Tumors of the urethra in men and women. *Cancer* 1973; 32: 1236-1255.
8. Sun K, Huan Y, Unger PD. Clear cell adenocarcinoma of urinary bladder and urethra. another urinary tract lesion immunoreactive for P504S. *Arch Pathol Labor Med* 2008; 132: 1417-1422.
9. Zeidman EJ, Desmond P, Thompson IM. Surgical treatment of carcinoma of the male urethra. *Urol Clin North Am* 1992; 19: 359-372.
10. Heysek RV, Parsons JT, Drylie DM et al. Carcinoma of the male urethra. *J Urol* 1985; 134: 753-755.
11. Licht MR, Klein EA, Bukowski R et al. Combination radiation and chemotherapy for the treatment of squamous cell carcinoma of the male and female urethra. *J Urol* 1995; 153: 1918-1920.
12. Gerbaulet A, Potter R, Mazeron J-J et al. The GEC ESTRO Handbook of Brachytherapy. European Society of Therapeutic Radiology and Oncology, Brussels 2002.
13. Chakrabarti B, Ghorai S, Ray SB et al. Intraluminal urethral brachytherapy for recurrence of transitional cell carcinoma of urinary bladder in urethral stump. *J Contemp Brachytherapy* 2013; 5: 42-44.