

PRIMARY URETHRAL SQUAMOUS CELL CARCINOMA OF THE BULBAR URETHRA IN ELDERLY PATIENT: A CASE REPORT AND REVIEW OF THE LITERATURE

***Dr. Abdelmalik Mouzount, Karam Yatribi, Omar Elallam, Wilfried Mossé, Sanaa El Majjaoui, Hanan ElKacemi, Tayeb Kebdani, Nouredine Benjaafar**

Department of Radiotherapy, National Institute of Oncology Mohamed 5 University in Rabat, Morocco.

***Corresponding Author: Dr. Abdelmalik Mouzount**

Department of Radiotherapy, National Institute of Oncology Mohamed 5 University in Rabat, Morocco.

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ABSTRACT

Primary urethral carcinoma (PUC) is a rare diseases which account for only 1% of all male malignancies. The rarity of the disease has prevented prospective studies and most of the treatment data come from case studies and small case series. Bulbar urethral disease carries a worse prognosis because the diagnosis is often delayed due to the nonspecific symptoms. We report an 82-year-old with urethral squamous cell carcinoma. The man presented with a 5 month history of recurrent urinary tract infection, dysuria and hematuria. The patient refused an aggressive surgery, and was desirous of organ preservation, therefore surgical tumor debulking by transurethral resection was performed, followed by chemoradiation therapy using volumetric modulated arc therapy. The patient showed residual tumor on pelvic MRI performed 2 month after and a salvage surgery was needed. In this paper we discuss the management of PUC with a review of the literature.

KEYWORDS: Urethra, Squamous Cell Carcinoma, Radiotherapy, Chemoradiation, Combined modality therapy.

INTRODUCTION

Primary urethral carcinoma (PUC) is a rare and aggressive cancer, accounting for less than 1% of all urologic malignancies,^[1-4] often underdetected. A recent surveillance epidemiology and end Results (SEER) analysis of 2065 males treated for PUC between 1988 and 2006 showed that the most frequent subtype is transitional cell cancer (77.6%), followed by squamous cell neoplasm (11.9%) and adenocarcinoma (5%).^[2] For male various predisposing factors have been reported including urethral strictures,^[5,6] chronic irritation after intermittent catheterisation/ urethroplasty,^[7-9] and chronic urethral inflammation/ urethritis following sexually transmitted diseases (condylomata associated with human papillomavirus 16).^[10,11] Diagnosis is often delayed because of the nonspecific symptoms,^[12,13] treatment depends on the stage and location of the tumor. Bulbar urethral disease carries a worse prognosis than distal diseases.^[12,14,15] the latter have a greatest opportunity for cure because of their greater accessibility and their earlier presentation. The rarity of the disease has prevented prospective studies, and most of the treatment data come from case studies and small case series.

CASE REPORT

We report an 82-year-old man presented with a 5-month

history of dysuria, recurrent urinary tract infection, associated with hematuria. On physical examination, the prostate and inguinal lymph nodes were not enlarged. Initially he underwent a bladder ultrasound which showed no anomaly. Retrograde urethrogram showed a diffuse stricture of bulbar urethra over 5cm with no evidence of obstruction (fig 1). Urethrocystoscopy revealed a mass in the bulbomembranous urethra. The patient underwent transurethral debulking of the urethral lesion, showing histological evidence of a poorly differentiated squamous cancer of the bulbomembranous urethra, with invasion of the superficial muscle layer. The patient refused aggressive surgery and demand an organ preservation. magnetic resonance imaging (MRI) showed signal abnormalities in the perineum in the posterior wall of the bulbar urethra extended on 8 cm and 2.7 cm height, heterogeneously enhanced after injection of contrast material (fig 2), invading the corpora cavernosa with no lymphnodes detected. Chest and abdominal computed tomography were normal. Considering the patient's age, health status and expectations, the patient was referred to our oncology institute. The case was discussed in multidisciplinary oncological team; adjuvant chemo radiation therapy was planned. The patient subsequently received perineal radiotherapy wich consisted of an Volumetric modulated arc therapy (VMAT). A dose of 66 Gy to the target volume (urethra), with a simultaneous dose of 56 Gy to

the nodal volumes, in 33 fractions was planned, using 2 arcs with 216 control points (fig 4). The patient was treated supine on a customised pelvis board and imaged daily with cone-beam CT for the first three days then weekly thereafter, with concomitant weekly cisplatin chemotherapy at 40 mg/m². Treatment was delivered over 7 weeks with no major incident, except grade 2 diarrhea for a few days. We performed a pelvic MRI 2 month after the chemoradiation that shows a persistence a tumor

residue extended to the penile urethra engulfing the cavernous body measuring 6 centimeters with a maximum thickness of 2 centimeters (fig 3). The patient underwent a penectomy, histopathological examination confirmed the presence of a 6 centimeters squamous carcinoma tumor infiltrating the corpora cavernosa. The patient is disease free on 3 month follow up.

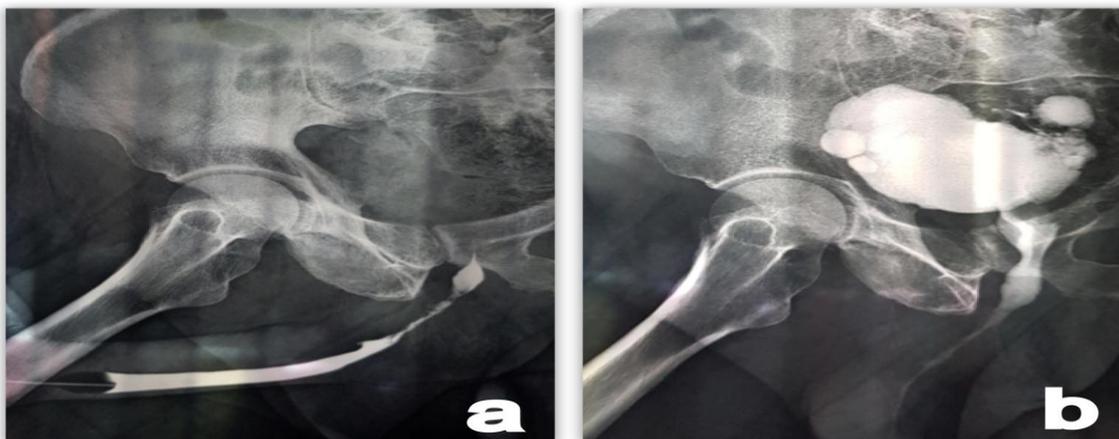


Figure 1: Retrograde urethrogram showing a diffuse stricture of bulbar urethra over 5cm (a); voiding cystourethrogram image reveals a uniformly dilated urethra upstream stricture with multidiverticular bladder (b).

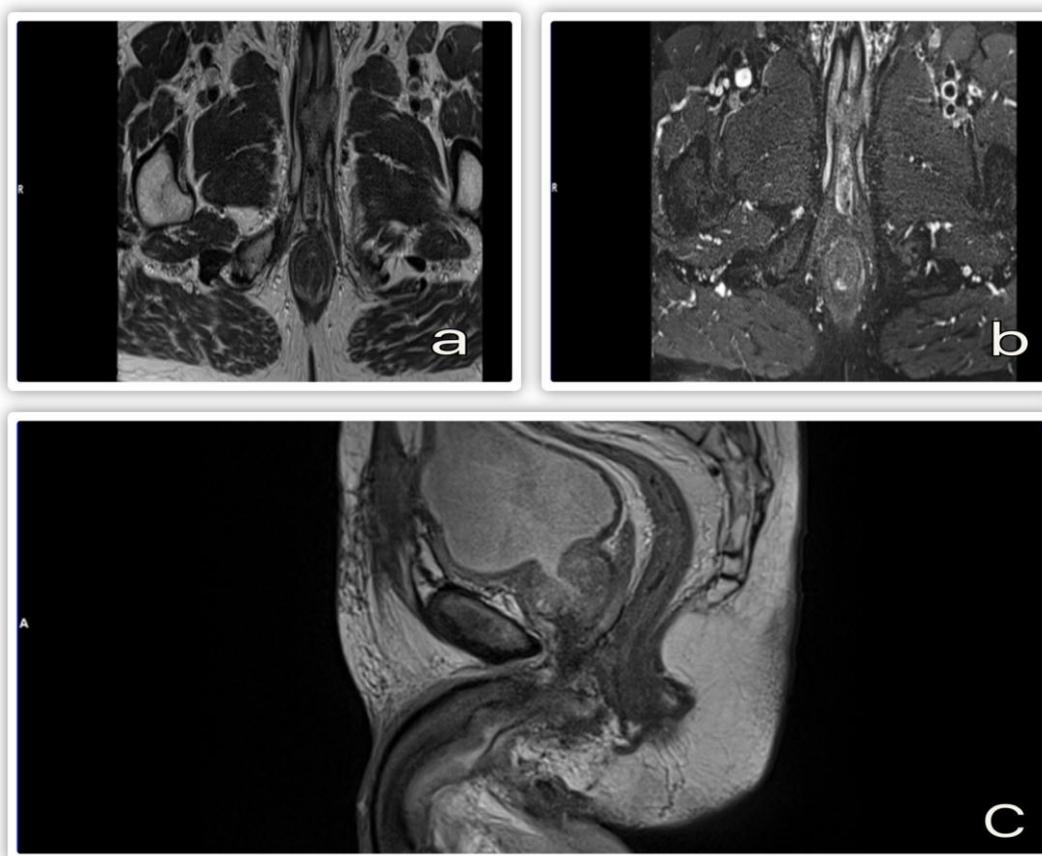


Figure 2: Axial magnetic resonance image T1-weighted (a), T2-weighted (b); and sagittal image (c), showing a residual tumor mass post-chemoradiation.

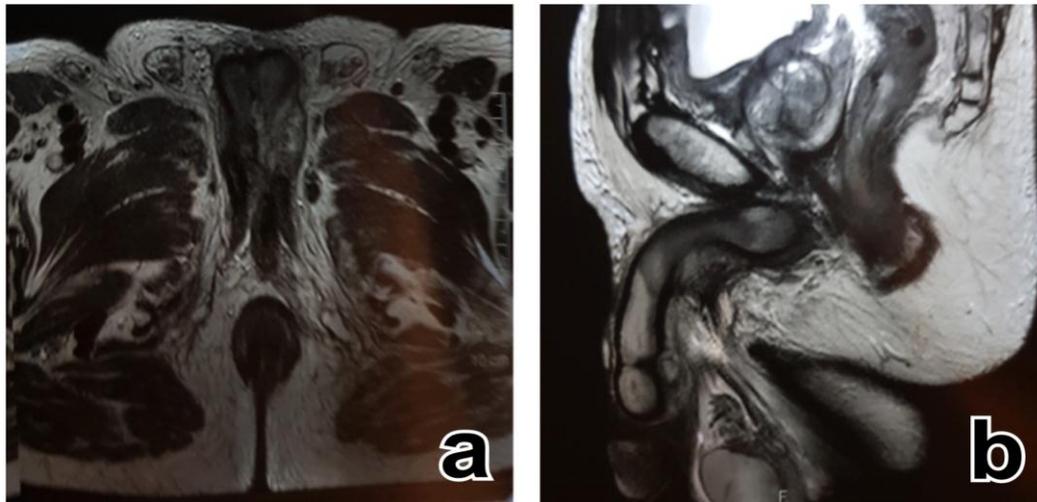


Figure 3: Axial magnetic resonance image (a); and sagittal image (b) T1-weighted, showing a heterogeneously bulbomembranous tumor replacing the urethra.



Figure 4: Representative volumetric modulated arc therapy (VMAT), dose distribution for dual target volumes. with isodose curves overlain planning target volumes (PTVs). 95% isodose shown in orange (62,7 GY), and green (53,2 GY); with representative DVH.

DISCUSSION

Urethral squamous cell cancer (USCC) is a rare cancer, accounting for < 1% of all genito-urinary malignancies,^[1] it generally occurs in the fifth decade of life. In the literature squamous cell carcinoma of the urethra is the predominant histological sub-type for PUC. However this contradicts epidemiological studies as Swartz *et al.* which found that 55% of tumours were transitional cell, 22% were squamous cell and 16% were adenocarcinomas,^[4] and the SEER study, that found that 78% were transitional cell, 12% were squamous cell and 5% were adenocarcinomas.^[2] This variation is due to the fact that in these studies, transitional cell carcinoma (TCC) is reported in patients with pre-existing bladder TCC.

PUC is often diagnosed at an advanced stage 59% of cancers affect the bulbomembranous urethra, while anterior and prostatic urethra account for 33% and 7%, respectively.^[14,15] The most common presenting symptom is urinary obstruction, other symptoms including blood loss (hematuria, contact bleeding), pain (dysuria, dyspareunia or pelvic or perineal pain) may occur.^[16] Chronic inflammation is the main etiopathogenic factor.^[17] The two most important clinical prognostic factors for male PUC are clinical stage and anatomical location of the tumour. In proximal urethral cancers, the signs are not always pathognomonic, they can be confused with stricture or benign prostatic hyperplasia and often retard the diagnosis, while distal lesions are usually easier to detect and have a better prognosis.^[18]

The management of USCC is particularly challenging due to its rarity and the lack of randomized evidence to inform practice. Most information regarding treatment is based on retrospective reviews in which varying treatment modalities are utilized. Radical surgery is usually performed when the tumor is documented in the bulbomembranous urethra, while in cases of distal location of the tumor the approach can be less aggressive, consisting of preserving surgery together with a chemoradiotherapeutic regimen.^[18,19] In our case a surgical approach was advised, but the patient refused and opted for radio-chemotherapy.

The results from treatment with surgery alone for bulbar USCC have been disappointing.^[14] In the series of Dinney *et al.*^[13] 2 of 5 patients with tumors of the anterior urethra and none of the 4 patients with tumors of the bulbomembranous urethra were alive after being treated by surgery alone.

Similarly, radiotherapy alone in cases of bulbomembranous cancer is deleterious, Raghavaiah presented a series of four male patients with primary urethral SCCs: Two patients had bulbar urethral tumor treated by radiotherapy, both patients died from disease progression within 4 and 9 months.^[20]

In 1992, Baskin and Turzan,^[21] described the first report of pathological remission of a male urethral carcinoma treated with penile-preserving surgery followed by combined mitomycin C, 5-FU and radiation therapy. Oberfield *et al.*^[22] Also reported genital preservation in 2 patients with an invasive squamous cell carcinoma of the bulbar urethra with chemotherapy and radiation treatment.

More recently, combined treatment with surgery and chemoradiotherapy was suggested to improve local control, survival and organ preservation. In 2008 Cohen *et al.*^[23] described 18 patients treated on a protocol of definitive external radiotherapy combined with mitomycin and 5-FU. Patients received between 45 and 55 Gy to the pelvis, with gross disease boosted an additional 12 to 15 Gy. Surgery was reserved for salvage. Despite a significant proportion of advanced disease (55% T3-4, 32% N1), almost 83% (15 of 18) of the patients had a complete response to the primary chemoradiation therapy protocol, and the 5-year overall and disease specific survival rates were 60% and 83%, respectively. Of the 15 complete responders, 10 remained disease free and did not require disfiguring surgery. This chemoradiation protocol was based on the treatment of anal canal squamous cell carcinoma reported by Nigro in 1974,^[24] later Sischy *et al.*^[25] reported that anal sphincter preservation was achieved in more than 70-95% cases. Cohen concluded that chemoradiation for invasive urethral squamous cell carcinoma could enable unprecedented potential for organ preservation. In 2015 a retrospective study of 29 patients with invasive PUC, Kent *et al.*^[26] reported similar results.

Recently, intensity-modulated radiation therapy (IMRT) has been used more often in treating prostate cancer, anal cancer and gynecologic malignancies.^[27-29] The use of IMRT allows dose escalation, which has been shown to improve clinical outcomes while simultaneously reducing toxicity by improved organ at risk sparing.^[30,31] Volumetric modulated arc therapy (VMAT) is a novel form of IMRT optimization that allows the radiation dose to be accurately and efficiently delivered in a single 360 gantry rotation. Our patient received a perineal radiotherapy which consisted of an Volumetric modulated arc therapy (VMAT). A dose of 66 Gy to the target volume (urethra), with a simultaneous dose of 56 Gy to the nodal volumes, in 33 fractions was planned, using 2 arcs with 216 control points. No major toxicities were noted.

In locally advanced SCC of proximal urethra, the combination of curative radiotherapy with radiosensitising chemotherapy with curative intent prior to surgery is recommended in the European Association of Urology (EAU) guidelines as an option, however they advocate that patients should be discussed by a multidisciplinary team of urologists, radiation oncologists, and oncologists.^[32] In this case, the patient

did not wish to undergo a radical surgical approach. The medical team had to respect the patient's choice of systemic chemotherapy and radiation therapy. However the patient showed a persistence of a tumor residue on MRI and salvage surgery was needed.

CONCLUSION

Male urethral cancer of the proximal urethra is a rare, aggressive disease. Due to its rarity there is no randomized studies to inform practice. Most information regarding treatment is based on retrospective reviews in which varying treatment modalities are utilized. therefore, few conclusions can be drawn from the published data. Recently combined treatment of chemoradiotherapy with surgery reserved for salvage was suggested to improve local control, survival and organ preservation. However, cases of primary urethral cancer should be discussed by specialists in a multidisciplinary setting. IMRT must be investigated in order to increase treatment efficiency. Meanwhile prospective multi-institutional studies are needed to better define the optimal treatment strategy for this rare disease.

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