Advances in Radiation Oncology (2019) **4**, 487-491

advances
in radiation oncology

www.advancesradonc.org

Teaching Case

Pathologic Complete Response After Chemoradiation of a Massive Primary Urethral Carcinoma

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Received 24 January 2019; revised 26 February 2019; accepted 27 February 2019

Introduction

Primary carcinoma of the urethra is rare. Analysis of Medicare Surveillance, Epidemiology, and End Results data from 1973 to 2002 indicated an incidence of 4.3 per million in men and 1.5 per million in women.[1] The most common histologic subtype of urethral carcinoma is squamous cell.[2] Patients usually present with advanced-stage disease and often have a poor outcome with a 5-year overall survival of approximately 40%.[1,3] We describe the successful use of chemoradiation therapy (CRT) in a patient with massive, locally advanced, urethral squamous cell carcinoma (SCC).

Case History

A 60-year-old male patient presented with urinary obstruction and worsening pelvic pain. His medical history was significant for a diagnosis of urethral stricture 7 years prior, treated with direct vision internal urethrotomy. He remained asymptomatic until 5 months before presentation, when he began experiencing urinary obstruction. The patient was diagnosed with chronic prostatitis and treated with antibiotics at another medical facility.

His symptoms worsened, and a computed tomography (CT) scan revealed a 6.8 × 5.4 × 6.2 cm mass at the base of the penis involving the corpora spongiosum with no lymphadenopathy. Cystoscopy showed inflammation in the bulbar urethra, and the patient was diagnosed with urethral stricture.

On presentation to us, he was unable to sit in a chair because of pain in his perineum. Physical examination revealed a tender palpable mass in the perineum, with induration extending to the anal canal and no palpable lymphadenopathy. Core biopsy from the mass revealed invasive keratinizing SCC with tumor necrosis (Fig 1A). Immunostaining for p16 protein and human papillomavirus (HPV) RNA were negative (Figs 1C and D). A magnetic resonance imaging (MRI) scan of the abdomen and pelvis demonstrated a 6.3 × 9.9 × 7.4 cm mass expanding the bilateral corpora cavernosa and spongiosum, encasing the regional urethra, and abutting the pubic symphysis with no nodal involvement. A CT scan of the chest was negative for distant disease. He received a diagnosis of clinical stage T3N0M0 in accordance with the guidelines of the American Joint Committee on Cancer, 7th edition.

In view of the extensive disease, neoadjuvant CRT with consideration for subsequent surgery or brachytherapy was recommended, and pain management also consulted.

The patient underwent CT simulation in the supine position with the legs opened in a frog-leg arrangement to minimize skin reactions. Dental wax was used for bolus

Sources of support: This work was funded by The John and Pembroke France Noble Oncology Research Fund.

Disclosures: The authors have no conflicts of interest to disclose.

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https://doi.org/10.1016/j.adro.2019.02.005

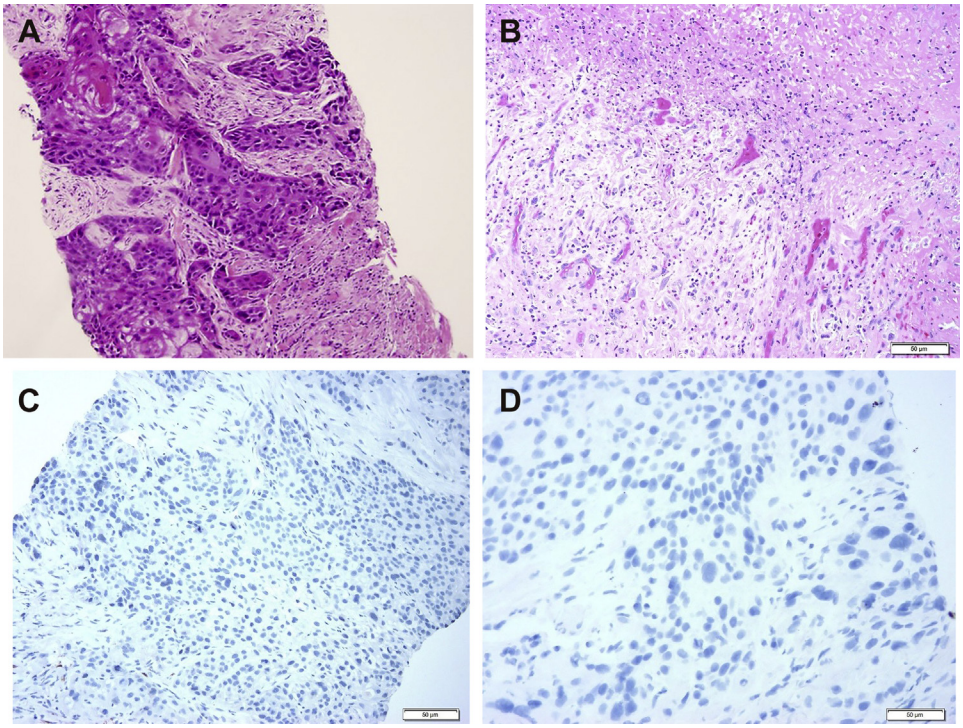

Figure 1 (A) Pretreatment biopsy reveals moderately to poorly differentiated infiltrating squamous cell carcinoma. Tumor cells are arranged in cords and nests, with large hyperchromatic nuclei, cytoplasmic keratin formation, necrosis, and increased mitotic activity (hematoxylin and eosin stain, 20×). (B) Posttreatment specimen reveals marked reactive change, focal fibrosis, and inflammatory infiltrates, with no residual tumor (hematoxylin and eosin stain, 20×). (C) Immunostain and (D) RNA stain for human papillomavirus p16 on the untreated tumor were negative.

on the base of the penis and to keep the tip of the penis out of field, and wet gauze was used on the involved portions of the scrotum. Custom Styrofoam molds supported the scrotum and maximized reproducibility of scrotal positioning. Gross tumor volume was delineated on the basis of the CT and MRI findings with 5 to 10 mm clinical target and 8 to 10 mm planning target volume expansions.

Treatment consisted of intensity modulated radiation therapy using 6 and 15 MV photons, with a planned cumulative dose to the involved scrotal region of 50.4 Gy in 1.8 Gy daily fractions and a total dose to the primary of 73.8 Gy. Daily cone beam CT was used for positioning and setup verification. The initial treatment volume encompassed the entire pelvis to include gross disease, scrotum, base of the penis, elective pelvic lymph nodes in the lower pelvic region, and the inguinal and femoral regions to a dose of 50.4 Gy. Subsequently, the plan was coned down to boost the gross disease to 73.8 Gy.

Concurrent chemotherapy consisted of 4 cycles of cisplatin 70 mg/m^2 every 21 days plus 5-fluorouracil 1000 mg/m^2 on days 1 to 5 with growth factor support. During the initial 2 weeks of radiation, clinical examination and daily cone beam CT scans suggested an interval tumor enlargement, including increasing edema of the scrotum and development of a draining fistula from the posterior scrotum. Repeat CT showed right posterior lateral bladder diverticulum and an enlarged enhanced fungating mass measuring 15.3 × 11 × 8.2 cm with solid and cystic components, centered in the posterior urethra with involvement of the base of the penis and prostate gland and loss of fat planes with the anus (Figs 2A, B, and C). In view of seeming progression of disease, the treatment plan was expanded to include increased disease extent at the base of the penis and inferiorly to the perineal skin with addition to bolus to that area.

Over the following weeks, the patient reported a marked reduction in pain and a gradual reduction in drainage from the fistula, as well as improvement in dietary intake and weight. Per the National Cancer Institute toxicity criteria, the treatment toxicities included grade 3 pain in the perineal area, grade 1 anorexia, and grade 2 dermatitis, which did not require treatment breaks or dose reduction.

Four weeks after treatment, CT showed residual mass-like soft-tissue abnormality measuring 1.5 × 2.5 cm, along with a 2 × 4.9 cm fluid-filled abscess at the base of the penis. Urology service believed that CRT would be unlikely to achieve a complete response given the large volume and location of the disease at presentation and counseled the patient for surgical removal of

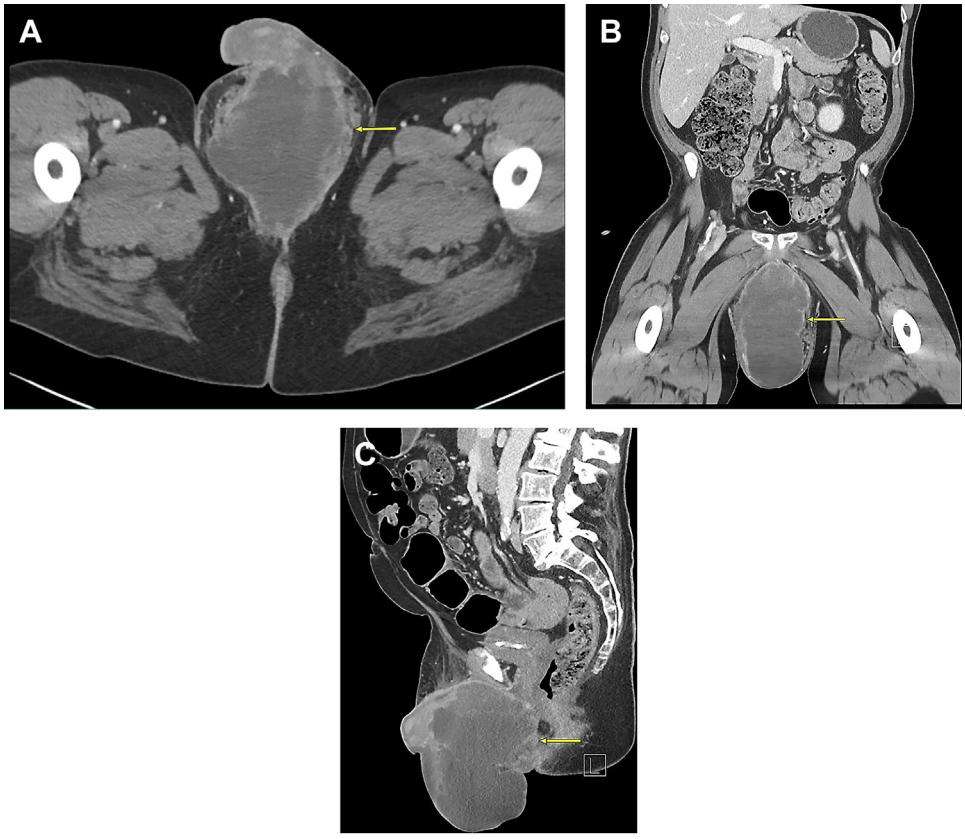

Figure 2 Computed tomography scans with (A) axial, (B) coronal, and (C) sagittal views. Yellow arrow identifies lesion. Tumor has solid and cystic components with loss of fat plane between the mass and anus.

residual disease, with secondary palliative intent of eliminating the leaking urinary fistula. Confirmatory diagnostic needle biopsy was discussed as an alternative option. The patient was counseled on the extent and side effects of undergoing such a surgery, but he opted to proceed with radical surgery. Eight weeks after completion of CRT, he underwent a proximal partial penectomy with rectus flap, total urethrectomy, cystoprostatectomy with the creation of ileal conduit with bilateral ureteral stents placed, and bilateral pelvic lymphadenectomy.

Operative histopathology testing found no tumor in the urethra, prostate, or lymph nodes; negative margins; and no lymphovascular invasion, consistent with stage ypT0N0 (Fig 1B). The patient developed a surgical wound infection with methicillin-resistant *Staphylococcus aureus* with a rim-enhancing fluid collection in the pelvis, for which a drain was placed. He was admitted multiple times for acute osteomyelitis of pubic symphysis, muscle flap necrosis, and sepsis from perineal wound dehiscence. The patient underwent a psychiatric evaluation for anxiety and crying spells associated with his complicated recovery.

After 3 months of intravenous antibiotics, a gradual decrease in pain and drainage from the perineal wound was observed, with radiologic evidence of a decrease in pelvic fluid collection. Tumor surveillance to date has included pelvic CT and MRI scans every 3 to 6 months. After 28 months of close follow-up, the patient remains disease-free with healed perineal fistula and normal bowel function and without pain, but he continues under psychiatric management for depression.

Discussion

Urethral SCC is a rare and challenging condition. Historically, urethral carcinoma was treated primarily with surgery, involving combinations of urethterectomy, partial penectomy, cystoprostatectomy with urinary diversion, and lymph node dissection, which are often associated with long-term morbidity, body image issues, and a decline in quality of life. Kieffer et al analyzed quality of life in patients undergoing partial penectomy and lymph node dissection and reported significant issues with orgasm, appearance concerns, life interference, and urinary function.[4] In addition, treating patients with surgery alone has yielded suboptimal results, with a treatment failure rate up to 75%, as demonstrated in a number of case reports.[5,6]

The impact of HPV status on treatment outcome is not well documented for urethral carcinoma. Weiner et al

Table 1 Published reports on multimodality treatment of squamous cell carcinoma

Reference	Year	Stage	No. of patients	Chemotherapy	Radiation dose	Adjuvant	Outcome
Cohen et al[11]	2008	T2N0 (11%) T3N0 (44%) T4N0 (11%) TxN1 (6%) TxN2 (28%)	18	5-fluorouracil and mitomycin C	45-55 Gy/25 fractions	Salvage surgery in selected cases	54% 5-y DFS with CRT 72% 5-y DFS with CRT and salvage surgery
Gheiler et al[14]	1998	Locally advanced SCC	3	5-fluorouracil and cisplatin	45 Gy	Distal urethrectomy	50% DFS
Oberfield et al[15]	1996	Locally advanced SCC	2	5-fluorouracil and mitomycin C	45 Gy		100% DFS at 4 y
Tran et al[16]	1995	Stage IV B SCC	1	5-fluorouracil and mitomycin C	55.80 Gy in 31 fractions		100% DFS at 5.5 y
Shah et al[17]	1985	Locally advanced SCC	1	5-fluorouracil and mitomycin C	30 Gy		100% DFS at 2.8 y
Licht et al[18]	1995	Locally advanced SCC	4	5-fluorouracil and mitomycin C	30-50 Gy		Median survival 43-98 mo
Lutz et al[19]	1995	Locally advanced SCC	1	5-fluorouracil and mitomycin C	51.2 Gy		Disease-free at 16 mo
Baskin et al[20]	1992	Locally advanced SCC	1	5-fluorouracil and mitomycin C	40 Gy in 20 fractions	Distal urethrectomy with en bloc resection of adjacent corpora cavernosa	100% DFS reported
Hussein et al[12]	1990	Locally advanced SCC	6	5-fluorouracil and cisplatin	45-54 Gy	Salvage surgery in 2 patients	DFS 26-32 mo
Johnson et al[21]	1989	Locally advanced SCC	1	5-fluorouracil and mitomycin C	40 Gy in 20 fractions		DFS 28 mo
Memon et al[22]	2011	Locally advanced SCC	1	5-fluorouracil and cisplatin	60 Gy in 30 fractions	Salvage surgery	Symptom control for 5 mo
Hara et al[23]	2004	Locally advanced SCC	2	5- Fluorouracil and Cisplatin	60 Gy in 30 fractions		One LR at 42 mo. The other is disease free at 27 mo

Abbreviations: CRT = chemoradiation therapy; DFS = disease-free survival, LR = local recurrence; SCC = squamous cell carcinoma.

reported an HPV-positive incidence of 29% and association with longer overall survival in men with urethral cancer.[7] Our patient demonstrated a complete response to treatment despite being HPV negative.

Given the effectiveness of CRT in other cancers, several case reports have documented outcomes of patients with urethral SCC who were treated in a similar fashion.[8-12] Kent et al reported on 29 men (88% with ≥T3 or node-positive disease) who were treated with CRT of 45 to 55 Gy plus 5-fluorouracil and mitomycin-C, which resulted in complete clinical response in 79% of patients.[13] Cohen et al analyzed 18 men who were treated with CRT, with 5-year overall and disease-free survival rates of 60% and 80%, respectively.[11] Gheiler et al treated 21 patients, of whom 62% were disease free at a median follow up of 42 months. Ta to T2 tumors had higher rates of freedom from recurrence (89%) compared with T3 to T4 tumors (42%).[14] Table 1 summarizes the published clinical experience.[15-23] Serrano et al emphasized that, if patients are given an option of organ preservation with CRT, they are extremely likely to opt for this over surgery because of the reduced morbidity.[5] Current National Comprehensive Cancer Network guidelines recommend CRT for cT3/T4 and cN0-2 disease, with or without consolidative surgery.[24]

To our knowledge, this is the first report in which CRT with curative intent was attempted for a tumor of this size (>10 cm) and pathologic complete response documented. Given the volume of disease, we elected to deliver a higher dose compared with other reports previously discussed (73.8 Gy vs 30-60 Gy, respectively). We hypothesize that the higher dose in combination with the node-negative disease status may be behind the dramatic response in our patient. Although surgical consolidation was performed and allowed confirmation of complete response, the associated morbidity of surgery and the questionable added benefit suggests this may be unwarranted. This paradigm is also supported by the experiences of Cohen et al[11] and Kent et al,[13] who noted that patients who did not respond to primary CRT ultimately

died of disease, regardless of salvage treatment. Our experience suggests that CRT is highly effective in the treatment of locally advanced urethral carcinoma and that surgical consolidation may add little to no benefit at a cost of high morbidity.

Conclusions

Our experience suggests that even very large urothelial cancers can be effectively treated with CRT alone.

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