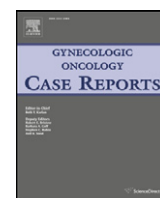


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Case Report

Successful management of female urethral carcinoma with radiation therapy and concurrent chemotherapy

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Introduction

Carcinoma of the female urethra is a rare neoplasm that accounts for less than 0.1% of all cancer types in women (Johnson and O'Connell, 1983). A standard treatment regimen has yet to be established due to the relative scarcity and variability of this neoplasm. The location and clinical stage of the disease dictate the method(s) of treatment used. In the past, distally located and early stage tumors had been managed with surgery or single modality radiotherapy alone. However, when single modality approaches have been used for female urethral carcinoma, local recurrences ranged from 36 to 60% and three year survival 0–29% (Foens et al., 1991). Therefore, distal lesions not amenable to surgical resection with negative margins are now managed with external beam radiation therapy followed by brachytherapy. Likewise, proximally located and more advanced tumors often are treated in a similar manner in an effort to preserve anatomy and maintain urinary function.

The concurrent use of radiation therapy and chemotherapy for female urethral carcinoma has led to improvements in local control, systemic control and overall survival (Libby et al., 2010; Nicholson et al., 2008). We describe the successful treatment of two patients with squamous cell carcinoma of the female urethra, both treated with external beam radiation therapy and concurrent chemotherapy followed by low dose rate interstitial brachytherapy.

Case 1

A 55 year-old female presented with a two month history of obstructive urinary symptoms. Physical examination revealed a mass involving the anterior vagina and urethra without clinically evident inguinal adenopathy. A pelvic MRI demonstrated a 3.5 cm enhancing proximal urethral mass with suspected invasion of the bladder neck and anterior vagina. Initial staging CT scans did not show any evidence of adenopathy or distant metastasis. Cystoscopic biopsy yielded squamous cell carcinoma. Anterior pelvic exenteration was planned but subsequently aborted intraoperatively because of bilaterally enlarged pelvic lymph nodes. An ileal conduit urinary diversion and bilateral pelvic lymph node sampling was performed. Bilateral lymph node involvement was found on final pathology, yielding stage IV (cT3c or pN2M0) disease.

Postoperatively, the patient received radiation therapy with concurrent chemotherapy. The patient was treated with 4500 cGy of external beam radiation therapy delivered to the pelvis with 18-MV photons through a four-field box arrangement. The inguinal lymph nodes were supplemented to a total dose of 4500 cGy through electron fields because of clinical enlargement. Following this, a low dose rate iridium-192 interstitial implant delivered an additional 1500 cGy to the urethral tumor. CT was used to develop the plan, but the patient was treated prior to the advent of 3D planning, so makeshift planning was constructed. The volume covered included the original tumor, urethra and margin.

Cisplatin and 5-fluorouracil (5-FU) were initiated on day 1 of radiation therapy. Continuous intravenous infusion of 5-FU was administered at 750 mg/m² for 6 days (days 1–3 and 29–31, total 4500 mg/m²) and 60 mg/m² of cisplatin on days 1 and 29.

Side effects included acute grade 3 dermatitis, grade 2 mucositis and grade 1 hematologic toxicity (nadirs: WBC-3.0, Hgb-10.6, Plt-145). The patient did not experience any GI toxicity and urinary toxicity was minimal as the ileal conduit was placed prior to RT. The patient actually increased urethral voiding during RT, likely from decreased tumor size. Recurrent episodes of distal vaginal mucositis were observed for the first 5 years following treatment, though each episode resolved with medication. The patient was free of recurrence at last follow up evaluation, 90 months after completing all treatment.

Case 2

A 41-year old female presented with a one month history of vaginal bleeding and pelvic pain. Pelvic examination revealed bleeding

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from the urethral meatus and a tender, friable urethral mass extending 4 cm proximally from the meatus. Cystourethroscopy demonstrated obliteration of the urethral lumen by the mass and a percutaneous supra-pubic catheter was placed. Biopsy of the mass revealed invasive squamous cell carcinoma. Pelvic MRI revealed a 3.5 cm long urethral mass with invasion of the anterior vaginal wall without mucosal involvement (stage T3N0M0). Staging CT scans and a bone scan did not demonstrate regional nodal or distant metastatic disease.

The patient received 4500 cGy to the pelvis, including the inguinal lymph nodes, with 18-MV photons through anterior and posterior opposing fields. Two weeks after completing external beam radiation, a low dose rate iridium-192 interstitial implant delivered an additional 2500 cGy to the urethral tumor over 46 h. The same protocol of concurrent chemotherapy that was used in *Case 1* was applied to this patient.

The patient tolerated radiation therapy well and experienced only grade 3 desquamation in the three weeks following treatment, without any GI or urinary toxicities. The patient's post-treatment course was complicated by persistent dysuria and distal vaginal pain. Pelvic examination 7 months after treatment revealed a 2 cm firm area at the distal urethral region. PET imaging showed intense activity in the region of the posterior urethra and biopsy revealed benign fibromuscular tissue with reactive fibrosis. The patient developed soft tissue necrosis of the distal anterior vagina 14 months after treatment and was successfully treated with hyperbaric oxygen therapy. At 23 months, she developed a urethral stricture requiring dilation, though urinary symptoms are now well controlled with an alpha-blocking agent. The patient was free of recurrence and asymptomatic at last follow up, 47 months after treatment.

Discussion

The rarity of female urethral carcinoma has resulted in a lack of consensus on the optimal management. Likewise, the limited number of cases has made it difficult to prospectively evaluate the various treatment approaches. The most common current management of distally located lesions that are not amenable to complete surgical resection with negative margins is external beam radiotherapy followed by brachytherapy (Grigsby and Herr, 1996). Patients with proximally located lesions and more advanced disease require a multidisciplinary approach that includes radiation therapy, chemotherapy and possibly surgery.

The clinical stage of the tumor has been shown to be the strongest predictor of disease free survival rates (Gheiler et al., 1998). A study by Gheiler et al. showed that in women with distal urethral cancer, the 5-year disease free survival rate approached 90% whereas for proximal urethral carcinoma the disease-free survival rate was 40% (Gheiler et al., 1998). A similar study by Weghaupt et al. demonstrated an overall 5-year survival rate of 71% for women with distal urethral tumors and 50% for those with proximal urethral tumors (Weghaupt et al., 1984). The greater likelihood of nodal involvement seen in proximal lesions is the reason for the significant disparity in disease free survival rates in patients with proximal versus distal tumors.

Many women with proximal urethral carcinoma remain asymptomatic until their disease is relatively advanced, thereby increasing the probability of nodal involvement. A study by Foens demonstrated the importance of treating the inguinal nodes when they found that only 1 in 10 (10%) patients who received inguinal irradiation developed groin failures whereas 13 of 25 (52%) patients who did not receive inguinal irradiation developed groin failures (Foens et al., 1991).

When conventional, single-modality management is used for urethral carcinoma, local recurrences range from 23 to 60% (Dalbagni et al., 2001; Foens et al., 1991; Garden et al., 1993). Foens et al. demonstrated that the local failure rate for the group treated with surgery alone was greater (60%) than the local failure rate for the groups

treated with radiation therapy alone (36%) or combined surgery with radiation (25%). A study by Dalbagni et al. found that 15 of 20 (75%) patients who underwent surgery alone had local failure while no local recurrence was seen in ten patients who received neoadjuvant radiation therapy before surgery (Dalbagni et al., 2001). These retrospective studies provide support that combined modality therapy offers the highest likelihood of eradicating disease.

Multiple series have demonstrated that superior local and inguinal control rates have been achieved with combined external beam and interstitial irradiation (Johnson and O'Connell, 1983; Weghaupt et al., 1984; Licht et al., 1995). Milosevic et al. was among the first to establish a significant improvement in local control with the addition of interstitial irradiation. This study demonstrated that patients treated with external beam radiation followed by brachytherapy had a 77% local control rate at 7 years compared to a 32% local control rate for patients treated with external radiation alone (Milosevic et al., 2000). Furthermore, a series by Foens found that 8 of 14 (57%) patients treated with combined radiation therapy were alive without disease at three years compared with 2 of 7 (29%) patients treated with external beam therapy alone and 0 of 7 (0%) patients treated with brachytherapy alone (Foens et al., 1991).

Overall, external beam therapy followed by interstitial brachytherapy in female urethral carcinoma has yielded 5-year disease-free survival rates of 70–90% for early stage tumors and rates of 20–30% for more advanced tumors (Forman and Litcher, 1992). The disparity in survival rates has led to the addition of concurrent chemotherapy for proximal, higher stage lesions. A combination of radiation therapy and chemotherapy using 5-fluorouracil and cisplatin has been shown to provide effective treatment for locally advanced urethral carcinoma in females (Hussein et al., 1990). A single institution study by Gheiler demonstrated the benefits of combination therapy, as 88% of patients treated with RT and concurrent 5-FU/cisplatin were alive NED at five years (Gheiler et al., 1998). This combination approach of radiation therapy and multi-agent radiosensitizing chemotherapy improves local and distant disease control.

While the patients in the report by Gheiler et al. and in our series were treated with cisplatin and 5-FU, other chemotherapy regimens also have been shown to be efficacious in treating female urethral carcinoma, including TIP (paclitaxel, ifosfamide and cisplatin) and capecitabine and cisplatin (Libby et al., 2010; Nicholson et al., 2008). In a case study by Nicholson et al., a patient with squamous cell carcinoma of the female urethra was treated with the addition of paclitaxel and ifosfamide to cisplatin, in a neoadjuvant fashion, prior to cisplatin concurrently with radiation therapy. This regimen was chosen based upon previous studies demonstrating response rates of greater than 80% when taxanes and platinum (+/– ifosfamide) were used to treat squamous cell cancers of the cervix (Buda et al., 2005). In a case series by Libby et al., two patients with adenocarcinoma of the female urethra were treated with cisplatin and capecitabine concurrently with radiation therapy (Libby et al., 2010).

Tumor down-staging with neoadjuvant chemotherapy prior to surgical resection may be considered an alternative to definitive chemoradiation therapy. In a study by Milowsky et al., sequential chemotherapy with doxorubicin and gemcitabine (AG) followed by paclitaxel, ifosfamide and cisplatin (TIP) resulted in a major response in 73% of patients with metastatic or advanced transitional cell carcinoma of the urothelium (Milowsky et al., 2009). The choice of surgery or concurrent chemoradiation for locoregional control should be based upon which modality offers the highest likelihood of disease control and maintenance of continence and sexual function.

Conclusion

Owing to its relative rarity, there are no standard treatment guidelines for female urethral carcinoma, and many different approaches have been used. In tumors not amenable to complete

surgical resection, we recommend the combination of external beam radiation, concurrent chemotherapy and consolidative interstitial brachytherapy. This approach is well-tolerated and review of the limited available literature demonstrates improved outcomes compared to single modality therapy.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of interest statement

No competing interests were present in the composition of this manuscript.

Author contributions

WM composed the entire manuscript in its original form and researched all of the literature pertinent to the topic. KB revised the manuscript critically and made changes to the portion of the paper pertaining to the treatment regimen. MS was the radiation oncologist who treated the patients. All authors have read and approved the final manuscript.

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Appendix A. Staging classification

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Non-invasive papillary, polypoid or verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades periurethral muscle
T3	Tumor invades anterior vaginal or bladder neck
T4	Tumor invades other adjacent organs

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node 2 cm. or less in greatest dimension

N2	Metastasis in a single lymph node more than 2 cm. but not more than 5 cm. in greatest dimension, or multiple lymph nodes, none more than 5 cm. in greatest dimension
N3	Metastasis in a lymph node more than 5 cm. in greatest dimension

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
N1	Distant metastasis

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