External Urethral Orifice Metastasis of Cervical Cancer Treated With Intraluminal Urethral Brachytherapy Using a Lumencath Applicator: the First Case Report

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Case report

Keywords: cervical cancer, metastasis, urethral orifice, radiation therapy, brachytherapy

Posted Date: June 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-600228/v1

Version of Record: A version of this preprint was published at Advances in Radiation Oncology on October 1st, 2021. See the published version at https://doi.org/10.1016/j.adro.2021.100828.

Abstract

Background: This is the first case report of external urethral orifice metastasis in primary cervical cancer.

Case presentation: The patient was histologically diagnosed with cervical squamous cell carcinoma, which involved not only the lower third of the vagina but also isolated metastasis of the external urethral orifice. We performed definitive chemoradiotherapy with weekly cisplatin and external beam radiation therapy followed by brachytherapy (BT). Considering tumor involvement, we used the Tandem, Cylinder, and Lumencath applicators to treat not only the cervix and vagina but also the entire urethra in BT sessions. The prescribed BT dose was 24 Gy in four fractions. The average clinical target volume (CTV) D90 of the cervix, vagina, and urethra in BT sessions were 7.3, 6.0, and 5.6 Gy, respectively. The average CTVs of the urethra in D0.1 cc and D1 cc were 18.1 Gy and 9.0 Gy, respectively. No grade ≥3 acute and late toxicities were observed during the 9-month follow-up. We achieved excellent local control for both primary tumor and external urethral orifice metastasis of cervical cancer.

Conclusion: This rare case report suggested that gynecologists and radiation oncologists should keep in mind to examine not only the cervix and vagina but also the external urethral orifice for patients with primary cervical cancer. Intraluminal urethral BT using the Lumencath applicator is a good treatment option for cervical cancer with urethral involvement.

Background

Cervical cancer is the fourth most common malignancy in women worldwide, with more than 300,000 deaths reported in 2018.[1] The staging of cervical cancer is obtained by combining the findings of physical examination, endoscopic procedures (hysteroscopy, cystoscopy, and proctoscopy), and imaging modalities according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines.[2] These guidelines also indicate that suspicious lesions should be confirmed by biopsy. Recently, definitive chemoradiotherapy has played a more important role in the treatment of patients with locally advanced cervical cancer. Physical examination is the most important part of cervical cancer staging for both gynecologists and radiation oncologists. We reported an extremely rare case of isolated external urethral orifice metastasis of primary cervical cancer. Moreover, we achieved excellent local control for both primary tumor and external urethral orifice metastasis when performing brachytherapy (BT) using a Lumencath applicator. Therefore, we report herein the first case of external urethral orifice metastasis of primary cervical cancer with a literature review.

Case Presentation

A 78-year-old woman presented with a small amount of genital bleeding, and she was diagnosed with cervical squamous cell carcinoma (SCC). The primary tumor was observed in the cervix, which also involved the lower third of the vagina (Fig. 1A). Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT were performed. Pre-treatment MRI images are

shown in Fig. 2. The patient was diagnosed with cervical SCC stage IIIA based on the FIGO guidelines, and definitive chemoradiotherapy was planned. At the time of consultation with the Radiation Oncology Department, we noticed swelling of the external urethral orifice, which showed gross findings similar to those of the cervix and vagina (Fig. 1B). No abnormal findings were observed in the vulva or clitoris. In addition, no urological symptoms (urination pain, hematuria, dysuria) were observed. We performed a biopsy of the external urethral orifice, which was histologically diagnosed as having metastatic SCC (Fig. 3). P40 immunostaining of the specimen of the primary tumor and external urethral orifice was performed. Both specimens were positive for p40 immunostaining and the same staining pattern (Fig. 3). As a result, the patient was diagnosed with external urethral orifice metastasis of the cervical cancer. The patient's clinical stage was T3aN0M1, IVB (TNM classification, 8th edition). Unfortunately, we did not perform cystoscopy or urinary cytology. The pre-treatment SCC antigen level was 6.5 ng/mL. We planned definitive chemoradiotherapy with weekly cisplatin (40 mg/m^2) and external beam radiation therapy (EBRT) followed by BT. The EBRT dose was 50.4 Gy delivered in 28 fractions for the whole pelvis and vulva. A midline block (3 cm width at the isocenter) was inserted into the treatment field after delivering 30.6 Gy/17 fractions to the whole pelvis and vulva. After 30.6-Gy irradiation, we added weekly definitive BT. Considering tumor involvement, we used the Tandem and Cylinder (Elekta, Sweden) and Lumencath applicators (Nucletron Operations BV, Veenendaal, the Netherlands) to treat not only the cervix and vagina but also the entire urethra in BT sessions. The diameter of the Lumencath applicator was 6 French with a length of 150 cm (Fig. 4A). For remote after-loading, we used microselectron HDR-V3 with Oncentra Brachy (Elekta, Sweden) with Ir-192. We performed CT-based image-guided brachytherapy in every BT session. The procedure for intraluminal urethral BT is shown in Fig. 4. First, we inserted a dummy source into the Lumencath applicator. Second, a Lumencath applicator with a dummy source was inserted into a 16-French, two-way Foley catheter. We created a hollow cap of the Foley catheter using a putty-type dental vinyl silicone impression material (GC, Japan) to prevent urinary backflow. We inserted a 16-French Foley catheter with a Lumencath applicator inserted into the urethra and fixed it. Finally, we inserted the Tandem and Cylinder applicators into the cervix and vagina. We delineated the clinical target volume (CTV) for the cervix, vagina, and urethra. The prescribed BT dose was 24 Gy in four fractions at the CTV_{cervix}; CTV_{vagina}, 5 mm from the Cylinder applicator; and $CTV_{urethra}$, 2 mm from 16-French Foley catheter. The average CTV D90 of the cervix, vagina, and urethra in BT sessions were 7.3, 6.0, and 5.6 Gy, respectively. The average CTVs of the urethra in D0.1 cc and D1 cc were 18.1 Gy and 9.0 Gy, respectively. The total biologically equivalent doses in 2 Gy fractions (Gy_{EQD2}) of EBRT (30.6 Gy/17 fractions) plus BT (24 Gy/4 fractions) based on the linear-quadratic model for CTV D90 of the cervix, vagina, and urethra were 72.5 Gy_{EQD2}, 62.5 Gy_{EQD2}, and 59.8 Gy_{EQD2}, respectively, assuming an α/β ratio of 10. Weekly cisplatin was administered for five courses. As a result, we achieved excellent local control for both primary tumor and external urethral orifice metastasis of cervical cancer (Fig. 6). Post-treatment SCC antigen level decreased to within the normal range. Acute toxicities included grade 1 cystitis, urethritis, and grade 2 dermatitis of the vulva and diarrhea. Late toxicity was only grade 1 frequent urination (which existed before therapy and did not worsen after treatment). No grade ≥ 3 acute and late toxicities were observed during the 9-month follow-up.

Discussion

Primary urethral tumors are rare. The Surveillance, Epidemiology, and End Results study has reported that the annual age-adjusted incidence rates of primary urethral tumors are 4.3/million in men and 1.5/million in women in the United States.[3] Histologically, transitional cell carcinoma is the most common type (55%), followed by SCC (21.5%) and adenocarcinoma (16.4%). In addition, urethral metastatic tumors are rare.[4] There are only few reports of urethral metastatic tumors of urological and colorectal carcinomas.

In contrary, locally advanced cervical cancer often involves the vagina. However, cutaneous metastasis, including the vulva arising from cervical cancer, is also rare.[5, 6] Only a few cases of vulvar skin metastasis of cervical cancer have been reported in the Korean literature.[7–10] In these cases, vulvar skin metastasis is observed as a recurrence after the initial treatment. The interval between the diagnosis of cervical cancer and that of cutaneous metastasis was 8–131 months. The main clinical manifestations were erythematous papules, nodules, and vesicles in the vulva.

In addition, we found only six case reports of clitoral metastasis of cervical cancer.[11–16] The main manifestations of clitoral metastasis are clitoral pain and enlargement. However, in our case, no metastatic lesions were observed in the vulva or clitoris. To the best of our knowledge, the present case is the first report of external urethral orifice metastasis in primary cervical cancer. The external urethral orifice can easily be overlooked on physical examination of patients with cervical cancer not only by gynecologists but also by radiation oncologists. Moreover, in the present case, there were no urological symptoms (urination pain, hematuria, dysuria). Therefore, this rare case report suggested that gynecologists and radiation oncologists should keep in mind to examine not only the cervix and vagina but also the external urethral orifice for patients with primary cervical cancer.

Considering tumor involvement, we performed EBRT followed by intraluminal urethral BT using the Lumencath applicator to treat the entire urethra. Recently, guidelines on primary urethral carcinoma published by the European Association of Urology have described the role of radiotherapy.[17] Milosevic et al. have reported 34 women with primary urethral carcinoma treated with radiotherapy.[18] Twenty patients (59%) received BT with or without EBRT. The 7-year actuarial overall and cause-specific survival rates were 41% and 45%, respectively. Large primary tumor bulk and treatment with EBRT alone (no BT) were independent poor prognostic factors for local tumor recurrence. In their study, BT reduced the risk of local recurrence by a factor of 4.2.

The largest retrospective study of treating primary carcinoma of the female urethra with radiotherapy was published by the University of Texas M.D. Anderson Cancer Center.[19] Eighty-six patients received radiotherapy alone: 35 were treated with a combination of EBRT and interstitial BT, 21 received EBRT only, and 30 received interstitial BT only. The cumulative doses ranged from 40 to 106 Gy (median, 65 Gy). The 1-, 2-, and 5-year local control rates in 84 evaluable patients were 72%, 65%, and 64%, respectively. Of note, pelvic toxicity in patients achieving local control was considerable (49%), including urethral stenosis (n = 11), fistula or necrosis (n = 10), and cystitis and/or hemorrhage (n = 6), with 30% of the reported

complications graded as severe. Higher doses correlated with a greater incidence of complications but not with improved local control.

Dose constraints for the female urethra in high-dose-rate BT (HDR-BT) are unknown. Therefore, we used urethra dose constraints in the HDR-BT of prostate cancer as a reference. The American Brachytherapy Society HDR prostate BT guidelines provide guidance on organs-at-risk dose constraints.[20] The Radiation Therapy Oncology Group 0321 study (EBRT 45 Gy followed by HDR-BT 19 Gy/2 fractions for prostate cancer) has demonstrated a higher urethral dose associated with greater acute/late genitourinary toxicities.[21] Based on these available data, we aimed to prescribe a 100% dose (6 Gy per fraction) in the BT session at the $CTV_{urethra}$, 2 mm from a 16-French Foley catheter, which is nearly equal to the urethral mucosa. As a result, the averages of $CTV_{urethra}$ D90, urethra D0.1 cc, and D1 cc were 5.6 Gy, 18.1 Gy, and 9.0 Gy, respectively. However, in only short-term follow-up, there were no grade ≥ 3 acute and late toxicities, and we achieved excellent local control for both primary tumor and external urethral orifice metastasis of cervical cancer. Intraluminal urethral BT using the Lumencath applicator is a good treatment option for cervical cancer with urethral involvement. Further follow-up is needed to determine the late toxicities of this treatment.

Conclusion

This is the first case report of external urethral orifice metastasis of primary cervical cancer treated with intraluminal urethral BT using the Lumencath applicator. Although in only short-term follow-up, intraluminal urethral BT using the Lumencath applicator is a good treatment option for cervical cancer with urethral involvement.

Abbreviations

BT : brachytherapy; CTV : clinical target volume; FIGO : the International Federation of Gynecology and Obstetrics; SCC : squamous cell carcinoma; CT : Computed tomography; MRI : magnetic resonance imaging; PET : positron emission tomography; EBRT : external beam radiation therapy; Gy_{EQD2} : biologically equivalent doses in 2 Gy fractions; HDR: high-dose-rate.

Declarations

Ethics approval and consent to participate / Consent for publication

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

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding.

Authors' contributions

YT conceptualized the project and obtained the data used for the study. All authors contributed to data analysis and editing of the article.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

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Figures

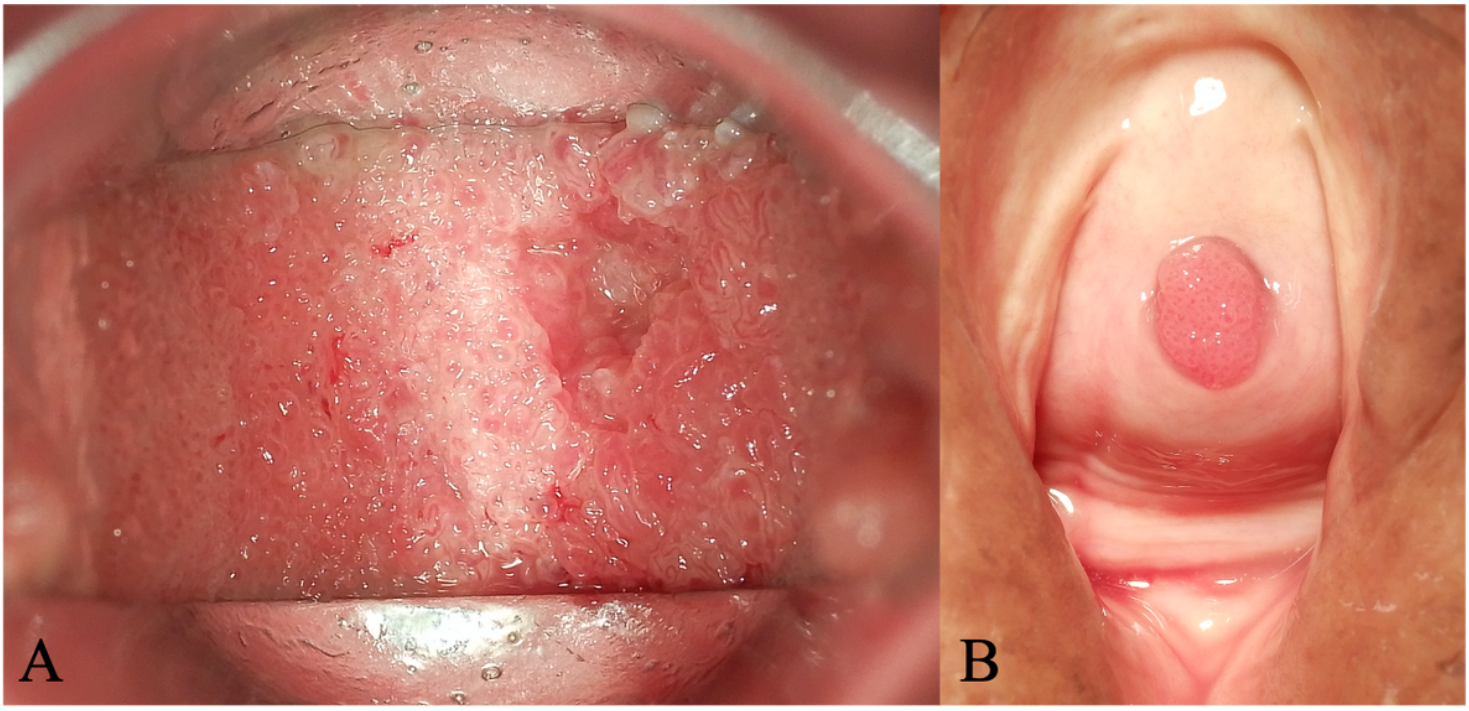

Figure 1

Pre-treatment gross findings of the cervix (A) and the external urethral orifice (B). There were similar gross tumors in the cervix and the external urethral orifice.

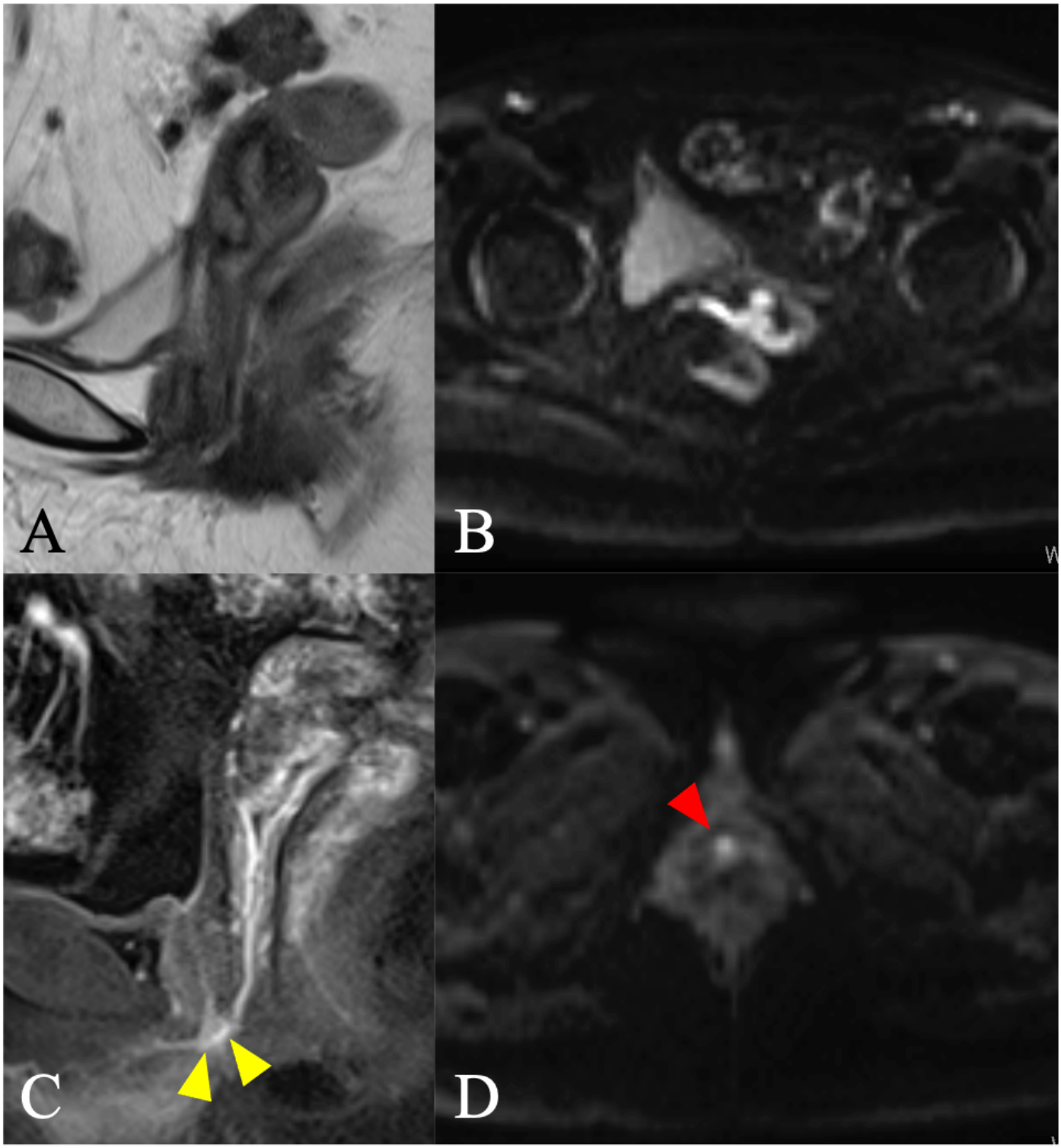

Figure 2

Pre-treatment magnetic resonance imaging (MRI) findings of the cervix and external urethral orifice. Sagittal T2-weighted image of the cervix (A) and axial diffusion-weighted image (DWI) of the cervix (B) show tumor extended from the cervix along the mucosal surface of the vagina. Dynamic enhanced sagittal T1-weighted image (C) shows contrast effect in the external urethral orifice (yellow arrowhead). Axial DWI of the external urethral orifice (D) found slightly diffusion restriction (red arrowhead).

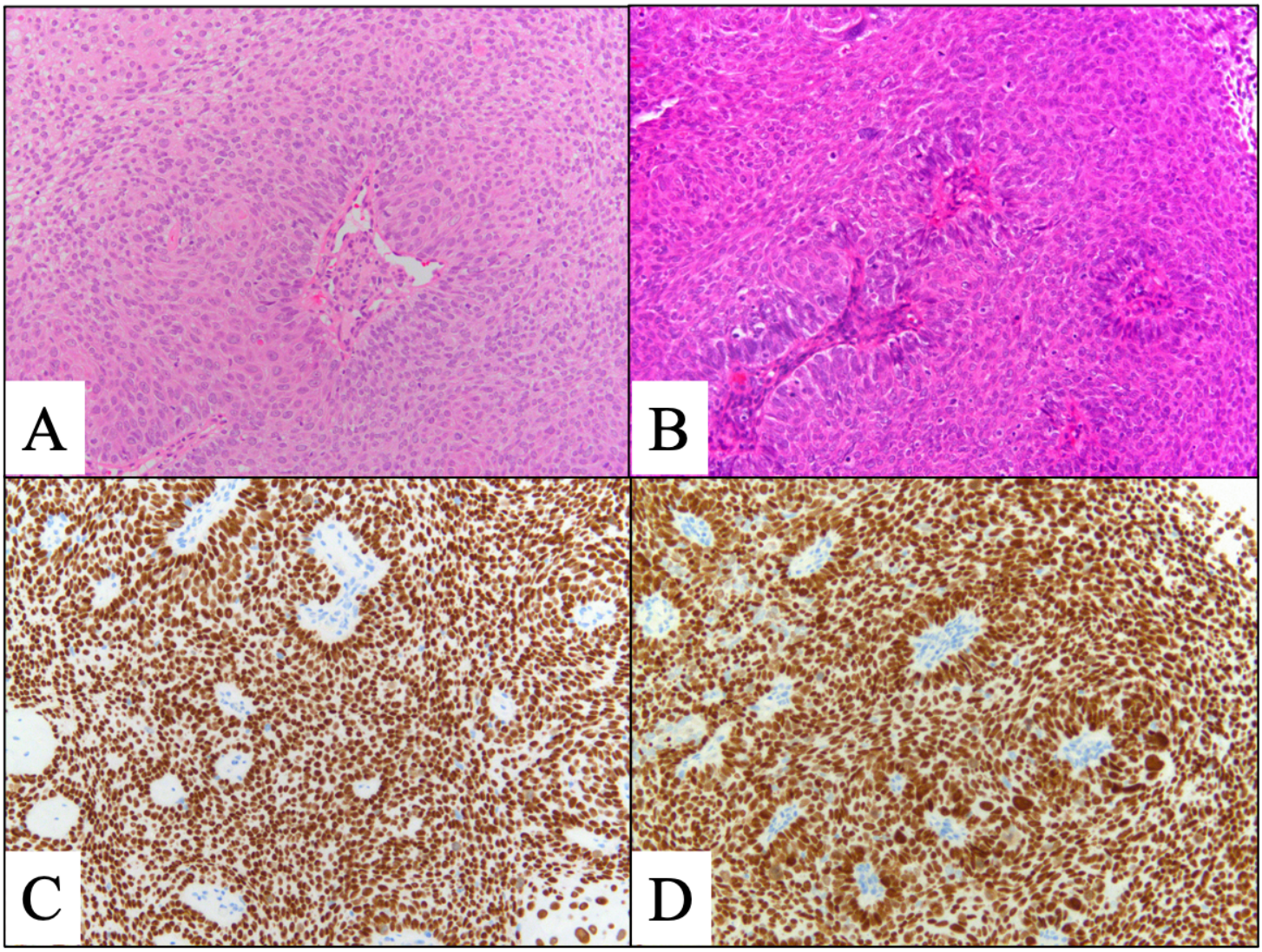

Figure 3

Hematoxylin and eosin-stained sections at 20× magnification of the cervical tumor (A) and the external urethral orifice tumor (B) showing atypical cells with rounded swollen nuclei proliferating in alveolar habits. Cervical tumor indicating squamous cell carcinoma and external urethral orifice tumor suggesting metastatic squamous cell carcinoma. P40 immunostaining of specimens at 20× magnification of the cervix (C) and the external urethral orifice (D) are positive and have similar staining pattern.

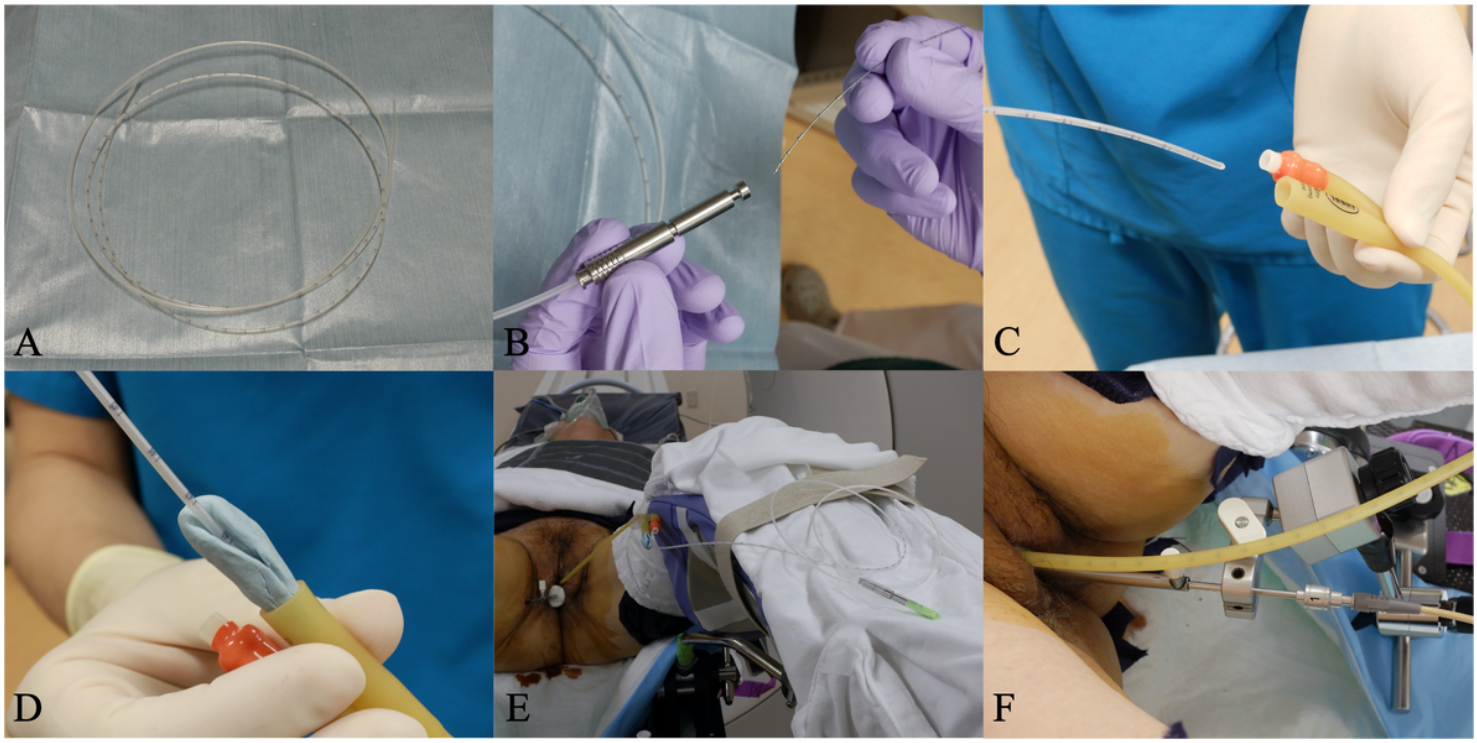

Figure 4

Photograph of the procedure of intraluminal urethral brachytherapy (BT). (A) Overall image of the Lumencath applicator. (B) Dummy source inserted into Lumencath applicator. (C) Lumencath applicator with dummy source inserted into 16-French Foley catheter. (D) Image of the hollow cap made of the dental vinyl silicone impression material. (E, F) Photograph of the applicator insertion and immobilization during BT.

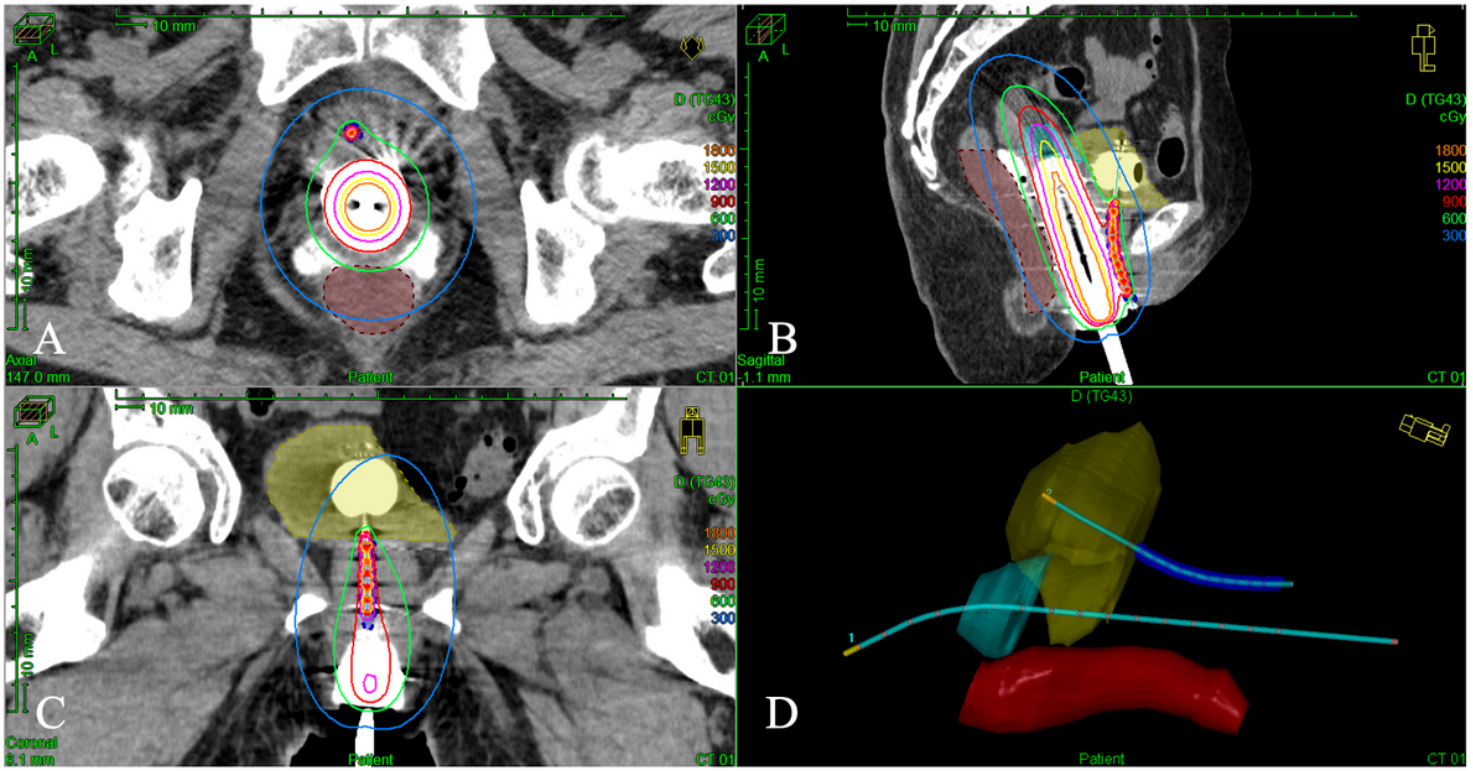

Figure 5

Dose distribution and applicator reconstruction of computed tomography (CT)-based image-guided brachytherapy. (A) Axial view, (B) sagittal view, and (C) coronal view of treatment planning. (D) Three-dimensional image of the applicator reconstruction. Light blue shade; clinical target volume of cervix, yellow shade; bladder, brown shade; rectum, blue shade; urethra. Green line represents 100% (6 Gy) isodose line. Red line represents 150% (9 Gy) isodose line.

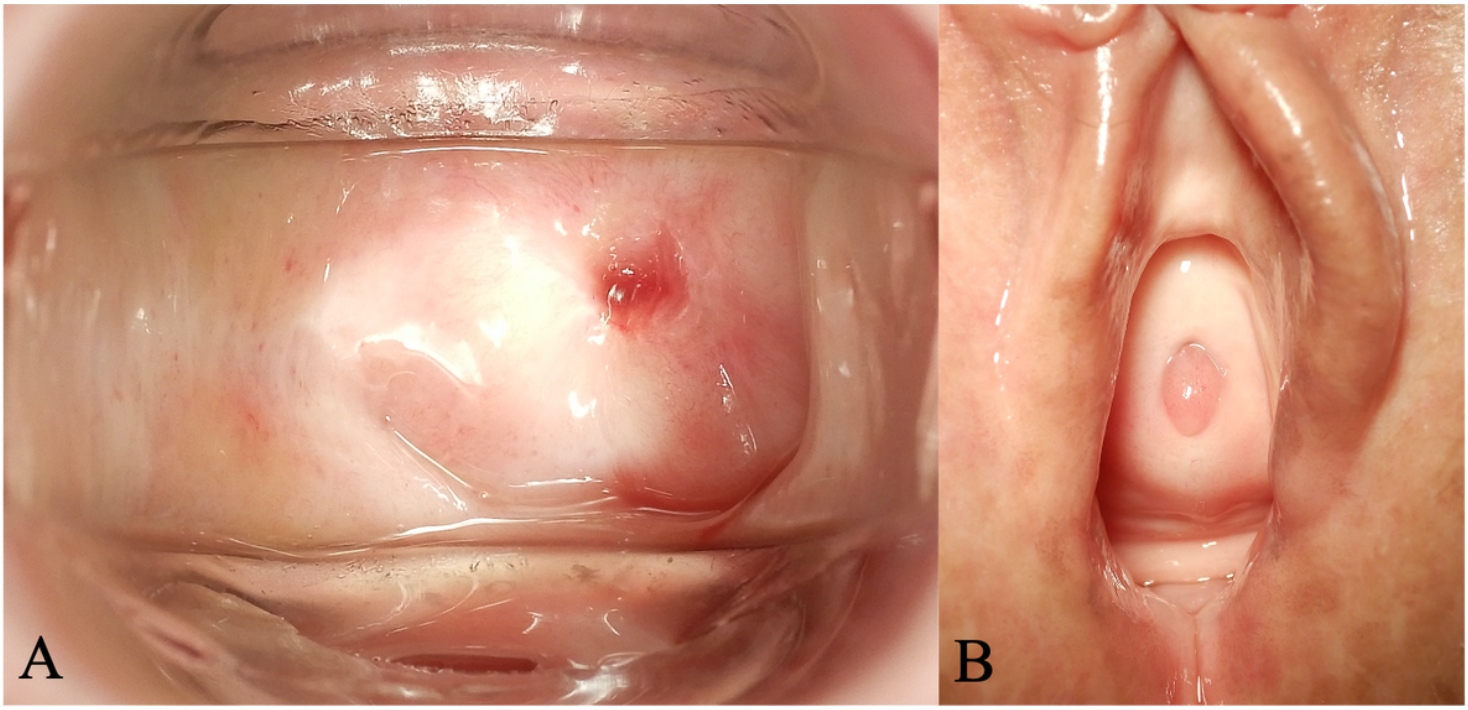

Figure 6

Post-treatment gross findings of the cervix (A) and the external urethral orifice (B) at 9 months after chemoradiotherapy. Tumors in the cervix, vagina, and external urethral orifice completely disappear.