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Urethral dosimetry and toxicity with high-dose-rate interstitial brachytherapy for vaginal cancer

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ABSTRACT

PURPOSE: The tolerance and complication rates of the urethra are unknown for the interstitial high-dose-rate brachytherapy (HDR-BT) for vaginal cancer.

METHODS AND MATERIALS: Patients with vaginal cancer near/involving the urethra who were treated with HDR-BT between 2008 and 2011 were included. Patients received mean external beam dose of 48.0 Gy followed by mean HDR-BT dose of 4.5 Gy/fraction for five fractions. With CT-based planning, the urethra was contoured from the bladder neck to the meatus. Doses were converted to the biologically equivalent dose in 2 Gy/fraction (EQD_2).

RESULTS: A total of 16 patients were included, and the EQD_2 D_{90} was 74.9 Gy. The urethral volume was 1.31 cm^3, and the EQD_2 to 0.1 and 1 cm^3 were 76.2 and 48.9 Gy, respectively. Two of the 6 patients with urethral involvement developed urethral necrosis. The D_{90} for these 2 patients was 76.8 Gy, and the urethral doses to 0.1 and 1 cm^3 were 95.1 and 45.8, respectively. Those who developed severe urethral toxicity had a trend to urethral EQD_2 (95.1 Gy vs. 73.4 Gy, $p = 0.1$) and significantly higher dose per fraction of HDR-BT to 0.1 cm^3 of the urethra (5.7 Gy vs. 3.7 Gy, $p = 0.02$) when compared with those who did not develop severe urethral toxicity.

CONCLUSIONS: This study is among the first to assess urethral dosimetry for patients treated with HDR-BT for vaginal cancer. Patients who received five fractions of higher than 5 Gy/fraction to 0.1 cm^3 of urethra (estimated EQD_2 of 85 Gy) are at increased risk of severe urethral toxicity.

Keywords: Interstitial brachytherapy; Urethra; Dosimetry; Vaginal cancer; Urethral

Introduction

Primary or recurrent disease in the vagina is an uncommon entity (1). Often organ-sparing surgical resection is not feasible because of the proximity of tumor to structures, including rectum, bladder, and urethra (2). Consequently, radiation therapy has emerged as the mainstay of treatment. This may be delivered by external beam radiation therapy (EBRT), brachytherapy (BT), or a combination of the two.

Multiple reports have described the value of BT in the treatment of primary or secondary vaginal cancer (3–7). Although many of the published series have reported on low-dose-rate BT (LDR-BT), high-dose-rate BT (HDR-BT) has several advantages. HDR-BT with remote afterloading systems minimizes radiation exposure to clinical staff and visitors, and affords the opportunity for dose optimization (3). Single-institution series have been reported on three-dimensional (3D)–based planning for HDR-BT, which can allow for conformal dose delivery (8, 9). However, there remains discrepancy on the optimal dose and fractionation schedule. The American Brachytherapy Society recently published consensus guidelines for interstitial BT on vaginal cancer, which emphasized the importance of image-guided target delineation and sparing of critical structures (10).

Potential side effects of treatment include toxicity to the rectum, bladder, vagina, or urethra. Urethral toxicity, in particular, has been poorly studied. Specifically, the tolerance of the urethra and complication rates remain relative unknown, and consequently no tolerance dose is suggested for the urethra in the current American Brachytherapy Society guideline. This study sought to further characterize urethral toxicity and identify doses that increase the risk for late urethral toxicity.

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Methods and materials

Patient population

Patients with primary or recurrent vaginal cancer with a lesion involving the anterior, mid, or distal vaginal wall, in proximity to the urethra or involving the urethra who were treated with interstitial HDR-BT from 2008 to 2011 were included. This study was conducted under a formal Institutional Review Board–approved protocol.

Radiation therapy

Patients received mean EBRT dose of 48.0 Gy (range, 45–54 Gy) delivered to the whole pelvis including bilateral inguinal region with 3D or intensity-modulated radiation therapy technique. One patient had an extended field to cover a para-aortic lymph node. This was followed by HDR interstitial BT using the Syed–Neblett template. Our technique has been previously described and will be summarized here (8). Fifteen-gauge titanium–zirconium needles were placed under general anesthesia, and an epidural catheter was placed for analgesia. After placement, a CT scan was performed to confirm placement and for treatment planning. Diluted contrast of 40–60 cm^3 was placed in the rectum and sigmoid as well as the bladder to facilitate contouring. A urinary catheter was placed and also facilitated contouring of the urethra.

Nucletron PLATO Brachytherapy planning system (Versions 14.2-3; Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) was used for 3D planning. CT-based planning was used for all patients to delineate the clinical target volume (CTV) and critical structures (rectum, bladder, sigmoid colon, and urethra). The urethra was defined based on the urethral catheter and was contoured from the bladder neck to the meatus. The CTV was defined based on the integration of multiple sources, including pretreatment MRI, positron emission tomography/CT, and physical examination findings.

Based on the tumor position and extent of disease at the time of BT, the dose prescribed to the target volume was usually between 70 and 85 Gy. The mean HDR-BT dose prescribed to the CTV was 4.5 Gy/fraction (range, 4.0–5.0 Gy) for five fractions, delivered twice daily. For all patients, the goal was to constrain the point dose to the urethra to lower than 100% of the prescription dose. When the urethra was directly involved by disease, the goal was to keep the maximal point dose to the urethra to lower than 125% of the prescription dose.

Statistical methods

For analysis, all doses were converted to the biologically equivalent dose in 2-Gy per fraction (EQD_2), applying the linear–quadratic model ($\alpha/\beta = 10$ for tumor; $\alpha/\beta = 3$ for organs at risk). Continuous variables were compared using a two-sided Student's t test.

Results

Patient characteristics

A total of 16 patients met the inclusion criteria and were available for analysis. Average age was 68.4 years (range, 44–86). Approximately 43.8% ($n = 7$) of the patients had primary vaginal cancer, and the remainder had recurrent or metastatic disease. Most of the metastatic/recurrent cases had an endometrial primary malignancy ($n = 5/9$); the remainder of these cases were from a vulvar, cervical, or unknown primary etiology. Histology was squamous cell carcinoma in eight cases, adenocarcinoma in seven cases, and carcinosarcoma in one case (Table 1).

Treatment planning

All patients underwent EBRT during treatment course before HDR-BT. The mean dose was 48.0 Gy (range, 45.0–54.0 Gy). After EBRT, all patients were treated with HDR-BT. The EQD_2 D_{90} to the CTV was 74.9 Gy (range, 64.0–83.0 Gy). For all patients, critical structures, including the rectum, bladder, sigmoid, colon, and urethra, were contoured and monitored.

Urethral dosimetry

The volume of the urethra was 1.31 cm^3 (range, 0.4–2.9 cm^3). The EQD_2 urethral dose to 0.1 and 1 cm^3 was on average 76.2 Gy (range, 49.4–111.2 Gy) and 48.9 Gy (range, 43.2–68.1 Gy), respectively. The HDR-BT dose per fraction to 0.1 and 1 cm^3 of the urethra was on average 3.9 Gy (range, 1.4–6.9 Gy) and 0.60 Gy (0.0–3.2 Gy), respectively.

Urethral toxicities

Six of the sixteen patients in the study had disease involving the urethra as determined by the clinical and/or radiographic assessment (Table 2). Two of these patients developed urethral necrosis after HDR-BT. The D_{90} for these 2 patients was 76.8 Gy (range, 70.7–83.0 Gy). The D_{90} for these 2 patients differed because of the response to EBRT at the time of BT. One patient had a good response to EBRT, and consequently the D_{90} was 70.7, whereas the other had extensive residual disease necessitating a higher

Table 1
Disease characteristics

Disease characteristics	n (%)
Disease type	
Primary: stage II	3 (18.8)
Primary: stage III	4 (25.0)
Recurrent/metastatic	9 (56.3)
Histology	
Squamous	8 (50.0)
Adenocarcinoma	7 (43.8)
Sarcoma	1 (6.3)