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Ureteral stent insertion for gynecologic interstitial high-dose-rate brachytherapy


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ABSTRACT PURPOSE: To determine the utility of ureteral stents in interstitial gynecological brachytherapy.

METHODS AND MATERIALS: We reviewed 289 patients with cervix cancer treated with high-dose-rate interstitial brachytherapy who did not have pretreatment hydronephrosis to determine the relative incidence of benign ureteral strictures after treatment. We also did comparative dosimetry analysis in five cases of high-dose-rate brachytherapy. Bilateral ureteral stents were placed during the procedure. Three dosimetry plans were created to determine the impact of modifying clinical target volume (CTV) and applying ureteral dose constraints. In Plan 1, the ureters were contoured and excluded from the CTV and 120% dose constraints were applied. In Plan 2, the ureters were contoured and excluded, but no dose constraints were applied to the ureter. In Plan 3, the CTV was created as if the location of the ureters was unknown and then ureteral dose was determined.

RESULTS: There were 11 ureteral strictures observed in 255 nonstented cases and 0 ureteral strictures in 34 stented cases. Plan 1 reduced the ureter dose (D0.1cc) by a median 22% (7.0–53.8%) compared with Plan 2 and by a median of 30.9% (12.3–65%) compared with Plan 3.

CONCLUSIONS: Placement of stents and ureteral dose constraints facilitates dosimetry and reduces the dose to ureters. Temporary ureteral stents prevent obstruction during interstitial gynecologic brachytherapy and allows the ureters to be addressed as an organ at risk. © 2015 Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: Brachytherapy; High-dose-rate; HDR; Interstitial; Ureteral stent; Ureter; Gynecologic malignancy; Cervix cancer; Endometrial cancer; Stricture

Introduction

Good dosimetry is achieved when the brachytherapy applicator fits the anatomy and encompases the disease. Interstitial (IS) brachytherapy can provide better dosimetry than intracavitary (IC) brachytherapy in properly selected cases, via the insertion of needles or catheters directly into and around the tumor (1–5). The quality of the radiation dosimetry can be further improved by coupling IS brachytherapy with high-dose-rate (HDR) treatment planning by applying dwell time modulation (varying the time the source spends at each location within the catheters).

The ureters often are overlooked as organs at risk (OARs) during radiation treatment planning because they are invisible on noncontrast computed tomography (CT). The literature regarding ureteral injury after low-dose-rate (LDR) IC brachytherapy suggests that clinically apparent radiation damage is relatively uncommon (1–4%) (6–8). The actual incidence, however, may be greater because occult damage or even hydronephrosis and substancial kidney dysfunction can occur before clinical recognition. IS brachytherapy, on the other hand, may pose an even greater risk of ureteral injury because the brachytherapy catheters can be inserted into the parametria immediately adjacent or even penetrate the ureter. The result may be traumatic injury, obstruction, or delivery of excessively high doses of radiation. We incorporated the placement of temporary stents into the IS-HDR procedure to ensure patency during...
the implant and make the ureters are visible on simulation radiography. We believe the placement of stents and the application of dose constraints during treatment planning reduce the risk of ureteral injury. We describe stent placement method, present data on 289 cervical cancer patients without hydronephrosis, and provide dosimetry analysis of five cases treated with IS-HDR.

Methods and materials

First, we reviewed the records of 354 patients from our prospective brachytherapy registry with previously untreated cervical cancer who underwent IS gynecologic template brachytherapy. We analyzed the 289 patients who presented without hydronephrosis and excluded 65 with hydronephrosis whose pathophysiology of disease may have contributed to ureteral injury and therefore could have been a confounding variable. We determined whether the patient had ureteral stenosis or hydronephrosis after radiation therapy by reviewing his or her medical records and imaging reports, interviewing the patient, and contacting his or her other physicians. Ureteral obstruction was assumed to be benign if there was no evidence of recurrent disease (at any site) during the entire period of follow-up (median of 43 months and mean of 60 months). We recognized that strictures can present late in the course of follow-up (benign more likely than malignant), and we believe the duration and nature of the study was sufficient to determine the rate and etiology of ureteral obstruction. Our study methods did not permit (radiologic) identification of subclinical ureteral injury.

Second, five consecutive patients with locally advanced gynecologic cancer treated at University of California, Los Angeles, with IS HDR brachytherapy were selected for dosimetry analysis. These cases were not suitable for IC brachytherapy based on the extent of disease and vaginal anatomy. There were four cases of locally advanced (T3 or T4) cancer with extensive invasion of the parametrium and one case of bulky 1B2 cervical cancer in an elderly patient with a narrow vagina, which was not suitable for an IC device.

Ureteral stent technique

Rigid cystoscopy and placement of the stent was performed at the beginning of the brachytherapy procedure (usually by the radiation oncologist at our institution) to evaluate the condition of bladder and to identify the ureteral orifices. Stent placement takes approximately 5–10% of the total procedure time and constitutes a small fraction of the total cost of the brachytherapy. Size five French open-ended ureteral stents (Pollack–Cook Medical Inc., Bloomington, IN) were placed in each of the ureters with rigid cystoscopy (Fig. 1). Retrograde pyelography was used to confirm stent placement and adjust the position as necessary. The stents exited the urethra along with an 18-French urinary catheter (usually a red Council radio-opaque type), or in the case illustrated in Fig. 1, a clear latex-free urinary catheter (C.R. Bard Inc., Covington, GA). The stents were individually embedded, at the end of the IS implant, into the side of the urinary catheter through tiny staggered incisions in the catheter (11-blade scalpel) 3–5 cm distal to the urethra. This technique is a convenient way to drain the stents without the need for a separate urine collection system. On completion of the IS implant, flexible cystoscopy was performed to adjust or remove any brachytherapy catheters that may have penetrated the bladder lumen. The stents were secured at the urethral meatus by sliding them under a stainless-steel washer (outer diameter 13 mm, inner diameter 7 mm) that was placed on the urinary catheter before its insertion. The stents also were secured to the urinary catheter distal to the washer with one silk drain ties (Fig. 2).

IS brachytherapy

The gynecologic template procedure, described in our previous report, was performed under spinal-epidural block with sedation or general anesthesia (9). It consisted of insertion a tandem, vaginal cylinder, and multiple flexible plastic catheters with metal obturators (Flexiguides; Best Medical International, Inc., Springfield, VA) through a Syed-Neblett template (Alpha-Omega Services, Inc., Bellflower, CA). Transrectal ultrasound, cystoscopy, proctosigmoidoscopy, and fluoroscopy guidance were used. The ureteral stents often were visible on transrectal ultrasound and on fluoroscopy, which was helpful in guidance of the IS implant. Brachytherapy catheters (six) were inserted along the grooves in the outer edge of the vaginal cylinder directly into the cervix and advanced superiorly into the uterus parallel to the tandem. Additional catheters were...
inserted through the perineum lateral to the vagina into the parametria to encompass, where possible, the gross residual disease with a 1- to 2-cm margin. A tandem was used in all cases except the recurrent endometrial cancer; the median number of brachytherapy catheters used in the five dosimetry cases was 26.

Treatment planning

Implant catheter depth was adjusted to final positions during CT simulation. The images were downloaded to a planning computer, where the clinical target volume (CTV) was generated (contoured) from pretreatment clinical examination and scans, the pelvic examination under anesthesia, and the CT simulation images. The contoured OARs were the bladder, urethra, ureters, rectum, sigmoid colon, and small bowel. Only the distal portions of the ureters that were anatomically relevant to brachytherapy were contoured. Treatment planning was performed with Oncentra Masterplan (Nucletron, an Elekta company; Elekta AB, Stockholm, Sweden), which included a first-pass inverse planning simulated annealing. The final dosimetry was a product of review and adjustment of the isodoses and dwell times in the graphical optimization program format. The tandem and flexiguides were equally available as source channels; the tandem was not specifically weighted over other source channels. Instead, each channel was used to achieve the target dose objectives, which are given as percent of prescription dose: $D_{90} (>100\%)$, $V_{100} (>95\%)$, and $V_{150} (25–35\%)$. The $D_{0.1cc}$ dose constraints were bladder wall (<90\%) and urinary catheter balloon, rectum, sigmoid, and small bowel ≤80%. $D_{1cc}$ and $D_{2cc}$ parameters also were calculated for the OARs.

Three separate treatment plans were generated for each patient. For Plan 1 (C/DC), the ureters were contoured (C) and dose constraints (DC) were applied to the ureters. It was the plan used for treatment delivery. The ureters were excluded from the CTV when possible, but they were included when needed to encompass the disease. Plan 1 (C/DC) was optimized to meet the dose constraint objectives to the ureters of 120\% ($D_{0.1cc}$). Two more treatment plans were generated to compare the impact of localizing the ureters and placement of dose constraints on the ureters or not. For Plan 2 (C/no DC) dosimetry, the ureters were contoured the same as Plan 1 (i.e., excluding the ureters from the CTV when possible), but no dose constraints were placed on the ureters. In Plan 3 (no C/no DC), the ureters were neither contoured out of the CTV nor were dose constraints placed on them. Thus, indentations in the contours created in Plan 1 intended to avoid the ureters were made smooth and continuous in an attempt to generate a contour as though ureters were invisible.

Two representative axial CT slices of an implant are shown in Figs. 3a and 3b. In Fig. 3a, the red line represents the CTV used in Plan 1 (C/DC) where the ureters (stents) were excluded from the CTV. The blue line represents the 100% isodose cloud. Fig. 3b represents Plan 3, where the CTV is contoured without regard for the location of the ureters. The bladder, urethra, rectum, sigmoid, and small bowel contours and dose constraints were the same for all three plans. Thus, dose constraints for the ureters were applied in Plan 1 (C/DC), but not in Plan 2 (C/no DC) or Plan 3 (no C/no DC).

Results

In Table 1, 289 cases are categorized according to whether we inserted stents at the time of brachytherapy. There were 255 cases without stents and 34 cases with stents because insertion of stents at the time of brachytherapy was developed later in our experience. We observed
11 of 255 cases of benign ureteral stricture without stents compared with 0 of 34 cases when stents were inserted. It is not possible to demonstrate a statistically significant difference with so few patients in the stented group. There were no infections or other complications attributable to the placement of urinary stents.

The disease characteristics and doses given to the five patients in the dosimetry study are given in Table 2. The median age was 65 years. One patient had recurrent adenocarcinoma of the endometrium (previously treated with hysterectomy without postoperative radiation), and the other four had primary previously untreated squamous cell carcinoma of the cervix.

Plan 1 (C/DC) dosimetry is presented in Table 3, and Fig. 4 is a representative virtual image of target and organ contours. The mean D_{90} was 110% (107–112%), the mean V_{100} was 98% (97–99%), and the mean V_{150} was 26% (19–34%). These same target dose parameters (D_{90}, V_{100}, and V_{150}) were purposely made consistent for all three plans (i.e., target dose prioritized planning). The mean CTV for these five plans was 140 mL (range 60–244 mL). The Plan 2 (C/no DC) and Plan 3 (no C/no DC) target doses were, thus, similar to Plan 1 (C/DC); D_{90} within 6%, V_{100} within 1%, and V_{150} within 4% (p = ns). The D_{0.1cc} doses (surrogate for maximum dose) to the bladder, urethra, rectum, and the right and left ureter for Plan 1 also are specified in Table 3. Apart from the ureters, the normal tissue doses (i.e., bladder, rectum, and urethra) were within 3% of one another for Plans 1, 2, and 3 (p = ns). There was no statistical difference in target coverage (D_{90}, V_{100}, and V_{150}) or OAR dosimetry between the plans except for the ureter.

The mean volume of the ureter contoured as an OAR was 1.36 mL (0.66–2.06 mL). As expected, the dose to the ureters varied according to whether they were within, near, or outside of the CTV. Table 4 shows a comparison of the ureter dosimetry for the six ureters within or adjacent to the CTV. The maximum dose (D_{0.1cc}) to the ureters in Plan 1 (C/DC) ranged from 58% to 116% (maximum allowed 120%). A ureter dose comparison revealed the mean dose to ureters was 22% (7.0–53.8%) lower in Plan 1 (C/DC) than Plan 2 (C/no DC).

For Plan 3 (no C/no DC) the contours were drawn as though the ureters were invisible and the dosimetry run without application of dose constraints. The location of the ureters was then inserted for treatment planning and the ureter doses were calculated. A ureter dose comparison revealed the mean dose to the ureter was 30.9% (12.3–65.4%) lower in Plan 1 (C/DC) than Plan 3 (no C/no DC). Table 5 shows that Plan 1 provided statistically significantly lower D_{0.1cc} doses than Plan 2 or Plan 3. The D_{1cc} doses were not significantly different (Plan 1 vs. Plan 2 or Plan 3). There were no statistically significant differences for D_{0.1cc} or D_{1cc} between Plan 2 vs. Plan 3.

**Discussion**

Recurrent cancer is the most common cause of ureteral obstruction after definitive radiation therapy of cervical cancer, and it usually occurs with in the first 5 years after treatment (6). Radiation therapy also can cause ureteral injury and stricture formation. In studies from the University of South Carolina, Underwood et al. (7) found eight cases from an incomplete review of a 2393 cervical cancer tumor registry and reviewed the literature up to 1977. The review presented a wide range (<1–15%) of incidence of ureteral injury after external beam and LDR brachytherapy. In another study, from Canada, Parliament et al. (8) suggested the rate was 3% (10/328). In a report on 835 patients (approximately 626 treated with external beam radiation therapy (EBRT) and various forms of brachytherapy without surgery) by Lang et al. (10), hydronephrosis

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**Table 1**

Benign stricture after IS brachytherapy (no pretreatment hydronephrosis)

<table>
<thead>
<tr>
<th></th>
<th>Stents placed at the time of brachytherapy</th>
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<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>No stricture</td>
<td>244</td>
</tr>
<tr>
<td>Benign stricture</td>
<td>11</td>
</tr>
</tbody>
</table>

IS = interstitial.
(presumably benign) occurred in approximately 20% of cases. They noted a correlation between greater stage of the disease and greater dose to point A with the occurrence of ureteral injury. According to McIntyre et al. (6), ureteral obstruction due to benign strictures following EBRT and intracavitary LDR brachytherapy (without chemotherapy) for Stage IB cervical cancer occurred in 29/1784 cases or at a rate of about 0.15% per year. When they counted only severe strictures (patients who required surgical intervention, lost the kidney, or died as a result), the incidence at 5 and 10 years was 1.0% and 2.0%, respectively. Malignant obstruction was approximately four times more common than benign, and it was detected at a mean interval of 16 months compared with 45 months for benign structures.

The ureters, which course through the parametrium to enter the bladder in close proximity to the cervix, are at risk for ureteral injury from high-dose radiation therapy. We believe ureteral injury (not necessarily manifest as hydronephrosis) after radiation therapy is probably underrecognized and underreported; our estimate is that after EBRT and IC brachytherapy it occurs within 10 years in 2–10% of cases.

Patients with locally advanced disease and those patients successfully treated with IS brachytherapy have a preventable greater risk of ureteral injury. IS implants are indicated for a variety of reasons, including bulky residual disease after initial treatment or disease extension beyond the cervix, where curative doses may not fully encompass the disease without exceeding bladder and rectal tolerance. IS catheters embedded into the parametrium, however, may come in close proximity, compress, or even penetrate the ureters. Thus, for IS brachytherapy where doses may far exceed the prescription dose, the ureters should be considered an organ at risk. We observed the immediate proximity of IS catheters to the ureters in our IS implant cases while doing CT-based dosimetry in patients who had stents placed before radiation therapy for hydronephrosis. We subsequently began to place stents to protect the ureters during IS brachytherapy regardless of the presence or absence of pretreatment hydronephrosis to prevent obstruction and to mark the ureters as an OAR during dosimetry.

There are few studies published on the occurrence of ureteral injury after IS gynecological brachytherapy. De Crevoisier et al. (11) found a 4% incidence of ureter injury in 91 vaginal cancer patients, which sometimes occurred many years after IC or IS low dose rate (LDR) brachytherapy. Monk et al. (12) reported a 5% incidence of benign ureteral obstruction in 61 patients with Stages II-IVa cervical cancer treated with EBRT and LDR IC or IS brachytherapy. We first reported our results with IS-HDR for cervical cancer in 1999 where, after a median follow-up of 40 months, we had 94% local control and 81% regional control and 6.5% Grade 3/4 complications in 62 patients. Benign ureteral strictures were not observed in that study, but the follow-up was only 3.3 years (9). In the current study, we observed a rate of benign ureteral strictures of 11/244 (4.5%) patients after 5 years. Although this rate not dramatically greater than expected for IC brachytherapy, we thought it prudent to take the relatively simple step of placing stents to prevent injury to the ureters during IS brachytherapy.

The use of scan based simulation and 3D treatment planning has allowed better tumor target definition, scaling of the dose to the tumor dose (low-, intermediate-, and high-risk treatment volumes), and greater monitoring of OARs doses. Although magnetic resonance imaging (MRI) treatment planning for brachytherapy is not universally available, The Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology style image-guided brachytherapy has provided valuable insights and standards

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Plan 1(C/DC) tumor and normal tissue dosimetry (percent prescription dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Rx dose</td>
<td>D90</td>
</tr>
<tr>
<td>Patient 1</td>
<td>110</td>
</tr>
<tr>
<td>Patient 2</td>
<td>109</td>
</tr>
<tr>
<td>Patient 3</td>
<td>112</td>
</tr>
<tr>
<td>Patient 4</td>
<td>111</td>
</tr>
<tr>
<td>Patient 5</td>
<td>107</td>
</tr>
</tbody>
</table>

C = contoured; DC = dose constraints.
for both tumor and normal tissue dosimetry (13). In their report of 156 patients treated with MRI, Potter et al. (14) achieved greater-than-historical local tumor control rates without apparent increases in toxicity (G1-2 36/156 and G3 3/156 bladder toxicity and 14/156 G1-2 and 5/156 G3-4 rectal toxicity). No ureteral complications were described in this group of patients, 44% who were treated with IS and IC brachytherapy. The IS catheters, however, were few in number and confined primarily to the medial parametria via the Utrecht applicator (15).

Our concept of IS brachytherapy is to create a generous matrix of catheters within the endopelvic fascia, which encompasses the original extent of the disease and from which the CTV can be drawn. The available imaging (MRI vs. CT scan) may affect how the CTV is contoured and how the doses are prescribed. We use ultrasound, fluoroscopy, and cystoscopy during the IS implant procedure to guide catheter distribution and to avoid their insertion in the bladder and rectum. Although undesirable, simple puncture of the bladder or rectum has, in our experience and the experience of others, few clinical consequences, so as long as it is recognized during CT simulations and taken into account during dosimetry (16).

Table 4
Plan comparisons ureter dose (percent differences) between plans

<table>
<thead>
<tr>
<th>Patient</th>
<th>Selected ureter</th>
<th>Plan 1 vs. Plan 2</th>
<th>Plan 1 vs. Plan 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0.1cc</td>
<td>D1cc</td>
<td>D0.1cc</td>
</tr>
<tr>
<td>1</td>
<td>Left</td>
<td>53.8</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>28.4</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>15.3</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>17.1</td>
<td>1.7</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>7.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>7.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean</td>
<td>22.2</td>
<td>2.4</td>
<td>30.9</td>
</tr>
</tbody>
</table>

CTV = clinical target volume; n/a = not available.

Until now, the ureters have not been managed as OARs because, unlike the bladder and rectum, they are not readily apparent during the implant procedure or visualized during CT simulation. The stents ensure that the ureter will not be obstructed by the implant catheters and when imaged provide the information needed to apply OAR dose constraints on ureters in or near the CTV (Figs. 3a and 3b and 4). An alternative would be to do a contrast-enhanced CT simulation, but there is no assurance of ureteral patency with contrast and, more importantly, these patients are often volume depleted from chemotherapy and preoperative preparations, which places them at risk for contrast induced acute tubular necrosis.

This dosimetry study focused on the (D0.1) to the ureter because the region and volume of ureter at risk during IS brachytherapy is relatively small (in one case <1 mL of the ureter was relevant to contour.) There is no statistically significant difference for any (p > 0.1) in ureter D1cc. The average volume of contoured ureter volume is 1.4 mL (range: 0.6–2.1 mL). Because the contoured ureter volume is very small and the D1cc is equivalent to D70 (the dose received by 70% of the ureter volume), it is essentially impossible for the D1cc to ureter to represent the hot spot, and it is unlikely to be a meaningful toxicity parameter for such a small volume.

The study design was successful because there are no statistical differences in target coverage (target D90, V100, and V150) and OAR dosimetry between the plans except for the ureter. There is, however, a significant difference (p = 0.024) in ureter D0.1cc for Plan 1 (C/DC) vs. Plan 2 (C/no DC) or Plan 3 (no C/no DC). We have thus shown that knowing the location and placing dose constraints on the ureters significantly reduces the dose (avoids hot spots) during IS brachytherapy by 20–30%. There is no significant difference in ureter D0.1cc for Plan 2 (C/no DC) vs. Plan 3 (no C/no DC), which means excluding the ureters from the CTV does not significantly affect ureter D0.1cc dose, if proper dose constraints are applied.

The evidence presented in this study (4.5% of unprotected ureters vs. 0% in stented cases) suggests there is a clinical benefit to the placement of ureteral stents during IS brachytherapy. The low occurrence rate of strictures and relatively few cases where stents were inserted made it impossible to demonstrate statistical significance. The disadvantages of stents are few. There is a small increase in the duration of the brachytherapy procedure, a slight increase in cost, and additional expertise is needed to do the procedure, which can be obtained by working with an
urologist or learned by the radiation oncologist. We observed no bleeding, infection, perforation, or other complications related to stent placement. Although not mandatory, stent insertions are indicated in cases of IS implantation where the brachytherapy catheters will be in close proximity to the ureters. They include the cases with parametria involvement or other more superior lesions located anywhere along the course of the ureter.

Conclusion

There is a greater potential for traumatic or radiation ureteral injury with IS than IC brachytherapy because IS catheters may come in direct contact with the ureters. Consequently, the radiation dose can be much greater. Insertion of stents during brachytherapy is a low morbidity method to maintain ureteral patency and to be able to visualize the ureters during simulation and to apply ureteral dose constraints during dosimetry. We demonstrated a 20–30% reduction in ureteral D_{0.1cc} dose by the placement of dose constraints. Minor modifications of the clinical target volume contours did not significantly impact the dosimetry. Knowing radiation dose to distal ureter and placing dose constraints of approximately 120% appears to reduce the risk of radiation injury during IS gynecologic brachytherapy.

References