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# An analysis of simulation for adjuvant intracavitary high-dose-rate brachytherapy in early-stage endometrial cancer

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**ABSTRACT**

**PURPOSE:** The utility of serial simulations in vaginal vault irradiation is controversial. Our primary endpoint was to assess the significance of simulation in women who received adjuvant intracavitary high-dose-rate brachytherapy (HDR-BT) for early-stage endometrial adenocarcinoma. Secondary endpoints included assessment of acute and late treatment toxicity, medication requirements, and charges related to the HDR-BT simulation and procedure.

**METHODS AND MATERIALS:** Twenty-four consecutive women with early-stage endometrial cancer treated with adjuvant HDR-BT were evaluated. Descriptive statistical analyses were performed on the ratio of calculated to prescription BT dose at predefined dosimetric points. Data on acute and late toxicities, medication usage, and simulation charges were evaluated and compared.

**RESULTS:** The intravaginal cylinder was placed three times over 10–14 days (median 6.5 Gy prescribed to 5 mm). No substantial deviation in the means of the calculated ratios was observed except at the bladder point (mean $0.77 \pm 0.23$). Early toxicity was found to be no greater than Grade 1 ($n = 5$). Serious late toxicities were uncommon; one woman developed a Grade 3 gastrointestinal toxicity. Half of the women required prescription medication incident to simulation. The average simulation charge was $1252.80.

**CONCLUSIONS:** Despite the broad range of doses calculated at the bladder point, genitourinary toxicity was minimal. Simulation proved useful in recording dose and represented a small, yet important portion of the total treatment charge but did not alter treatment in this series. The necessity of simulation for intracavitary high-dose-rate vaginal brachytherapy remains unclear. 

*Keywords:* Endometrial cancer; High dose rate; Brachytherapy; Planning

## Introduction

Endometrial cancer remains the most common gynecologic cancer in the United States. The American Cancer Society estimates 41,200 new cases of cancer of the uterus will be diagnosed in 2006 (1). Seven thousand three hundred fifty women are projected to die due to uterine cancer in 2006 (1).

The current treatment standard for early-stage endometrial carcinoma is total abdominal hysterectomy with bilateral salpingo-oopherectomy with lymph node dissection. Postoperative or adjuvant radiation therapy is advocated according to disease characteristics that predict for local failure (2–10). In the postoperative setting, practitioners may advocate external beam radiation, brachytherapy (BT), or a combination depending upon the pathologic characteristics of the disease. When postoperative BT is indicated, high-dose-rate brachytherapy (HDR-BT) is gradually becoming the mainstay due to convenience of the treatment technique. A recent survey of radiation oncologists in the United States by the American Brachytherapy Society showed that 69% of respondents were using HDR-BT, whereas 60% were using low-dose-rate BT (11). Despite the absence of data from a completed Phase III trial, HDR-BT is becoming preferred over pelvic external beam radiation because of the relatively few side effects, relative ease of administration, and the favorable therapeutic ratio associated with HDR-BT (12).

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It is a common practice to plan HDR-BT with simulation before each treatment for cervical cancer even though the utility and significance of treatment planning for vaginal vault irradiation with a vaginal cylinder is debatable (13, 14). The purpose of this analysis was to evaluate the clinical significance of simulation in women receiving adjuvant intracavitary HDR-BT for early-stage endometrial carcinoma. The analysis consists of a comparison of the calculated dose at various predefined points to the prescription dose for each treatment. In addition, data regarding simulation-associated morbidities and charges were collected and evaluated.

## Methods and materials

For the years 1998–2003, 24 women with early-stage (International Federation of Gynecology and Obstetrics [FIGO] IA–IIA) endometrial adenocarcinoma treated with postoperative intracavitary HDR-BT alone were identified. Our institution's treatment policy is to deliver HDR to women with eligible stage and grade who have undergone total abdominal hysterectomy with bilateral salpingo-oopherectomy with lymph node staging. In addition to adequate staging and resection, these 24 women had followup of greater than 1 year and did not have tumors of serous papillary or clear-cell histology. Women who received adjuvant chemotherapy were excluded. Information regarding clinical and pathologic disease characteristics, medication usage, and treatment data were retrospectively collected from patient records.

Before treatment, 2-D simulation was completed and consisted of placing a foley catheter as per International Commission on Radiation Units (ICRU) 38 (15), insertion of the vaginal cylinder, and the obtaining of orthogonal x-rays. Our standard is to not prescribe medication before urinary catheterization and placement of the cylinder. However, patients were administered oral anxiolytics, narcotics, or other medications as needed for discomfort or anxiety at the time of or immediately after the simulation procedure.

The HDR-BT details are summarized in Table 1. Postoperative vaginal-cuff BT was delivered using a single-channel vaginal cylinder in three ($n = 23$) or six ($n = 1$) treatments over 10–14 days with a vaginal cylinder as an outpatient procedure. In general, women were fitted with the largest diameter cylinder possible. The median cylinder diameter was 3 cm with a median number of 10 dwell positions at 5-mm spacing. The median dose prescribed per fraction was 650 cGy (range, 550–700) to a depth of 0.5 cm ($n = 23$) or to the cylinder surface ($n = 1$). The length of vaginal tissue treated consisted of the proximal vaginal mucosa (median length, 5.0 cm; range, 4.0–7.5 cm).

Figure 1 illustrates the relationship of seven predefined dosimetry points to the HDR-BT vaginal applicator. The bladder point and rectal points were defined per the ICRU 38 (15), and the remaining points have been selected based on clinical experience at our institution and are consistently evaluated in all cases. These points were designated on the orthogonal x-rays or within the digitized computer plan.

Table 1
High-dose-rate brachytherapy details

| | |
|---|---|
| Total dose (cGy) | *n* |
| 1,800 | 9 |
| 1,950 | 13 |
| 2,100 | 1 |
| 3,300 | 1 |
| Dose/fraction (cGy) | |
| 550 | 1 |
| 600 | 9 |
| 650 | 13 |
| 700 | 1 |
| Applicator diameter (cm) | |
| 2.5 | 5 |
| 3 | 8 |
| 3.5 | 11 |
| Applicator dwell positions | |
| 8 | 2 |
| 9 | 7 |
| 10 | 9 |
| 11 | 5 |
| 15 | 1 |

The orthogonal plain films from simulation were digitized into the treatment planning system after which doses to all points were calculated using Nucletron Plato BPS v13.5-14.2.3 software. A ratio of calculated dose to prescription dose was then determined for each point for all simulations. These ratios were compared across the cohort to assess for significant variation for each woman's treatment. Descriptive statistical analyses were performed, calculating the central tendency and standard deviation of the data. Information regarding medication usage incident to simulation was retrospectively collected to characterize procedure-related morbidity. Charges resulting directly from simulation were collected from hospital accounting services and were used to determine the percentage of each patient's total charges related to the simulation.

Routine followup included a baseline examination of 4–8 weeks after completion of BT. Thereafter, women were routinely followed every 3–4 months for 2 years, then twice annually until year 5, then annually thereafter. Hematologic and radiographic examinations were obtained when clinically indicated. Information regarding acute and late treatment-related toxicities was retrospectively gathered from treatment charts, treatment summaries, and weekly on-treatment visit notes. Those toxicities that occurred at the time of or after simulation that did not predate the procedure were recorded and graded as acute toxicities while any late toxicity within the treatment record was recorded. Toxicity was scored according to the National Cancer Institute Common Toxicity Criteria version 3.

## Results

Twenty-four women were included in this analysis. With a median followup of 24 months (range, 12–66), two

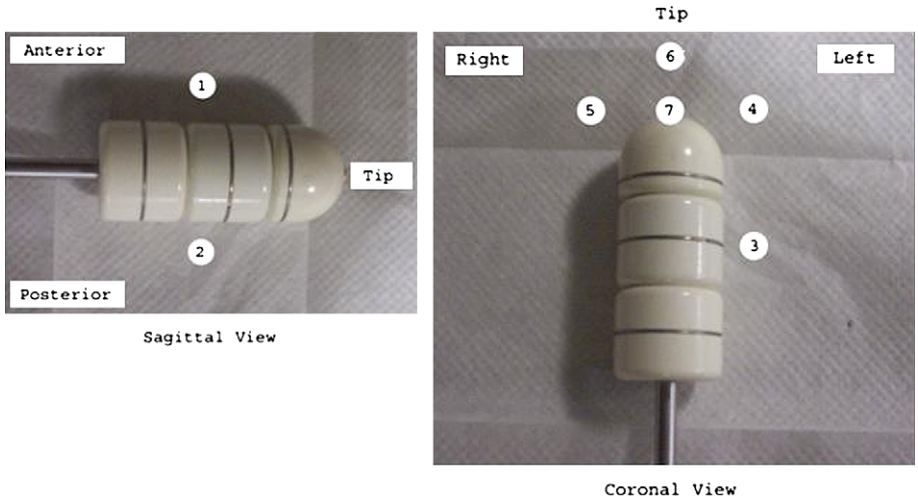


Fig. 1. Vaginal applicator diagram showing predefined dosimetry points (approximations): (1) bladder; (2) rectum; (3) 5 mm lateral to applicator; (4) 5 mm left of applicator tip; (5) 5 mm right of applicator tip; (6) 5 mm from applicator tip midline; and (7) applicator tip.

women had developed distant metastatic disease. No local recurrences have occurred.

The descriptive statistical analyses of the dose ratios for all points are shown in Table 2.

The HDR-BT procedure was well tolerated by most women (Table 3). One woman experienced Grade 3 gastrointestinal toxicity (she developed a small bowel obstruction 6 months after HDR-BT). Five of 24 women (21%) experienced early toxicity. Eleven women (46%) experienced late toxicity, all were Grade 1, except for the late Grade 3 mentioned above.

Twelve of 24 women requested or required medications at the time of or immediately after simulation (Table 3). In all, 21 total prescriptions were written. The most common drug classes prescribed were antifungals ($n = 5$), analgesics ($n = 5$), and antibiotics ($n = 4$). Benzodiazapenes and an antispasmodic were also prescribed.

The average charge for simulation was $1252.80. This equated to an average 9.8% of a patient's total treatment charge. The percentage of simulation charges as it relates to total charges for each patient is listed in Table 3.

## Discussion

In this retrospective analysis of 24 women with early-stage endometrial cancer, the ratio of calculated dose to prescribed dose was statistically similar for all women across the entire cohort at all analyzed points save the bladder point (Table 2). Commonly referenced data on treating early-stage endometrial cancer with adjuvant HDR-BT have been summarized in Table 4 (16–28). Despite endometrial carcinoma being the most common gynecologic malignancy in the United States, there is a relative paucity of literature reporting HDR-BT bladder and rectal doses. Of the studies that included information on doses to the bladder and rectum, few indicate doses lower than we report, some of which may be due to prescription to the vaginal mucosal surface.

The largest variation in the ratio of calculated dose to prescription dose in this study occurred at the bladder point. The current literature is laden with examples of various techniques that have been used to adjust the dose to the bladder during intracavitary radiation for gynecologic cancers (29–32). Eisbruch *et al.* suggest that using interstitial implants aided by laparotomy for cervical cancer may be the best way to minimize bladder dose (29). Another study suggested the use of ultrasound to define bladder dose (30). More recently, three-dimensional imaging has been offered as a way to minimize bladder dose in the treatment of cervical cancer (31). Bladder distention by use of a balloon inflated inside the bladder has also been used to standardize bladder volume in the treatment of cervical cancer (32). Despite the significant difference in simulated dose to the bladder across all analyzed plans in our study, genitourinary toxicity remained minimal and there were no other clinical

Table 2
Descriptive statistics of calculated-to-prescription dose for each dosimetry point in all women

| | Points from applicator tip | | | | | | |
|---|---|---|---|---|---|---|---|
| | Bladder (1) | Rectal (2) | 5 mm Laterally (3) | At tip (7) | 5 mm Superior (6) | 5 mm Right (5) | 5 mm Left (4) |
| Mean | 0.77 | 0.95 | 0.96 | 2.1 | 0.92 | 0.96 | 0.99 |
| Range | 0.22–1.2 | 0.68–1.1 | 0.64–1.1 | 1.5–2.5 | 0.69–1.2 | 0.91–0.99 | 0.83–1.1 |
| SD | 0.23 | 0.08 | 0.11 | 0.3 | 0.13 | 0.03 | 0.06 |

Numbers in parentheses following dosimetry points correspond to Fig. 1 points.

Table 3
Acute and late toxicities, simulation medication usage, and charges for each patient

| | Acute toxicity | | Late toxicity | | | Simulation charges |
|---|---|---|---|---|---|---|
| Patient | Type | Grade | Type | Grade | Medication(s) used | Percentage of total cost |
| 1 | None | | HB | 1 | None | 9.6 |
| 2 | None | | GI | 1 | Antifungal | 8.2 |
| 3 | GI | 1 | SRF | 1 | Anxiolytic, analgesic | 8.7 |
| 4 | None | | None | | None | 14 |
| 5 | GU | 1 | None | | Anxiolytic, antibiotic | NA |
| 6 | None | | None | | None | 8 |
| 7 | None | | None | | None | 9.4 |
| 8 | None | | SRF | 1 | Antibiotic | 9.8 |
| 9 | GI | 1 | GU | 1 | None | 12 |
| 10 | None | | None | | None | 6.9 |
| 11 | None | | SRF | 1 | None | 8 |
| 12 | None | | None | | None | 12 |
| 13 | GI | 1 | SRF | 1 | Antifungal, opioid | 12 |
| 14 | None | | None | | Analgesic | 9.6 |
| 15 | None | | SRF | 1 | None | 11 |
| 16 | SRF | 1 | SRF | 1 | Antifungal, analgesic, opioid | 12 |
| 17 | None | | None | | Anxiolytic | 8.1 |
| 18 | None | | GI | 3 | Antispasmodic | 8 |
| 19 | None | | None | | None | 8.5 |
| 20 | None | | None | | Antifungal, analgesic, antibiotic | 12 |
| 21 | None | | None | | Antibiotic | 10 |
| 22 | None | | None | | None | 10 |
| 23 | None | | None | | None | 7 |
| 24 | None | | HB | 1 | Opioid, antifungal, analgesic | 11 |

GU = renal/genitourinary; GI = gastrointestinal; SRF = sexual/reproductive, function; HB = hemorrhage/bleeding; NA = not available.

manifestations of genitourinary sequelae, suggesting that this finding may not be clinically relevant in this subset of women treated with this specific BT technique. Although we observed a consistent calculated rectal dose across the cohort, gastrointestinal toxicities were more common overall than genitourinary toxicities, which may reflect the lower radiation tolerance of bowel tissue compared to bladder tissue (33, 34) and the lower mean dose ratio to the bladder compared to the rectal points, 0.77 vs. 0.95, respectively.

The relative number of patients experiencing toxicity as a result of HDR-BT, either long term or short term, in our study is higher than many reported studies (Table 4). This may be due to a number of reasons. For example, many

Table 4
Summary of the available literature regarding women who received adjuvant HDR-BT in endometrial cancer

| | | | Dose (cGy unless otherwise specified) | | | Toxicity | | Recurrence[a] | |
|---|---|---|---|---|---|---|---|---|---|
| Study | *N* | Prescription point | Prescribed | Bladder | Rectal | Mild | Severe | % | Months |
| Horowitz | 164 | 0.5 cm AS | 700 × 3 | nr | nr | nr | 0 | 8.5 | 65 |
| Solhjem | 100 | 0.8 cm AT | 700 × 3 | 1,593 | 1,725 | 104 | 0 | 3 | 23 |
| Kucera | 354 | 2.0 cm from axis | 700 × 4 | nr | nr | nr | nr | 0.6 | 6–96 |
| Hong | 44 | 0.5 cm AS | 700 × 3 | nr | nr | 5 | 0 | 14 | 60 |
| Sorbe | 404 | 1.0 cm AS | 450–600 × 5–6 | 93% of PD | 124% of PD | 189 | nr | 3.7 | 44 |
| Chen | 23 | 0.5 cm AS | 1,000 × 3 | nr | nr | nr | 0 | nr | nr |
| Pellizzon | 70 | VMS | 600–1,000 × 4–5 | 115–600/treatment | 306–640/treatment | 28 | 3 | 2.9 | 15 |
| Weiss | 122 | VMS | 700 × 3 | 670 | 820 | 22 | 0 | 9.8 | 48 |
| Petereit | 191 | VMS | 1,620 × 2 | nr | nr | 20% | 1 | 1.6 | 38 |
| Anderson | 102 | 0.5 cm AS | 500 × 3 | nr | nr | 19 | 0 | 6.9 | 49 |
| MacLeod | 143 | VMS | 850 × 4 | nr | nr | 38 | 0 | 3.5 | 83 |
| Noyes | 63 | VMS | 1,620 × 2 | ?2592 | ?2592 | 17 | 0 | 1.6 | 19 |
| Fanning | 60 | 0.5 cm AS | 700 × 3 | nr | nr | 4 | 0 | 1.7 | 36 |
| Onsrud | 217 | 0.5 cm AS | 550 × 4 | Standard: 1,800<br>Individualized: 1,400 | Standard: 2,200<br>Individualized: 1,700 | 71 | 0 | 1.8 | 84 |
| This study | 24 | 0.5 cm AS | 626 × 3 | 1,446 | 1,785 | 11 | 1 | 8.3 | 24 |

HDR-BT = high-dose-rate bachytherapy; AS = from applicator surface; VMS = from vaginal mucosal surface; AT = from applicator tip; nr = not reported; PD = prescription dose, toxicity; Mild = Grades 1–2; Severe = >Grade 3.

[a] Includes local and distant recurrences.

studies report only acute (17, 18) or long-term toxicities (23) or had short followup (21, 26). Additionally, there is a lack of consistency within the literature in reported toxicity as some studies report toxicity as the number of patients affected while others report toxicities without regard to the number of patients. Finally, our study reports toxicity using the National Cancer Institute Common Toxicity Criteria version 3, whereas the others have not consistently used the same criteria. In the largest reported study of postoperative vaginal irradiation with HDR for endometrial carcinoma, Sorbe *et al.* reported that 189 of 404 total women experienced some form of radiation toxicity. One hundred twenty five patients experienced early toxicities, a majority of which were mild. Late reactions occurred in 64 women. In all, 36 women experienced toxicities Grade 2 or higher, 8 of which were early reactions and 28 of which were late reactions. Intestinal toxicity was more common than bladder toxicity for both early and late toxicities. When considering the Sorbe *et al.* study, the rate of toxicity we report compares favorably, in that 5 of 24 patients experienced acute toxicities and 11 developed late effects (though 10 were Grade 1). Furthermore, it should be noted that although these acute toxicities were graded on a temporal relationship to radiotherapy, late toxicities were recognized and graded on their presence but cannot with great confidence be relegated only to radiation treatment as these women also had undergone surgical resection.

One of the potential advantages of intracavitary HDR-BT is that it is relatively minimally invasive and does not require hospitalization. Half of the women in this analysis required medications incident to the simulation process. Eleven of the 21 prescriptions were analgesics or anxiolytics, indicating that simulation caused some form of physical or emotional discomfort in a fraction of the women in this series. We were unable to find current literature that addresses this subject, and the findings in this study suggest that the invasiveness of the procedure is relative to the perspective and experience of the patient. Although severe drug interactions or toxicities are uncommon, those drugs prescribed for these women have the potential for iatrogenic morbidity.

As the cost of the delivery of health care attracts greater scrutiny, it is noteworthy that on average 10% of these patients' treatment charges were incurred with the simulation procedure. On the basis of recorded data, the calculations associated with the simulation did not alter or delay the treatment in any of the 24 women. Once again, there is no data available in the current literature that addresses the cost effectiveness of simulation before HDR-BT for endometrial cancer. This investigation is by no means a rigorous cost–benefit analysis, but these preliminary findings suggest the need for further review of current practices with possible modifications that could minimize patient morbidity and risk while optimizing the financial impact.

The previously referenced American Brachytherapy Society survey (11) reported that a little more than 78% and 80% of responding U.S. radiation oncologists recorded the doses delivered to the bladder and rectum, respectively. The survey also showed that 66.1% of physicians recorded maximal doses using radiographs with contrast imaging, 18.2% used CT scans, and 1.2% used *in vivo* measurements. Just over 69% of respondents who used localization films for each fraction stated they adjusted the applicator position, whereas 12.3% did not adjust the applicator position and 19.9% did not obtain localization films for each application. Standard approach at our institution was revised to obtain imaging before the first treatment of every patient. However, this current data suggest that even this exercise may be unnecessary. Although the results of this study indicate that in this particular group of women, simulation did not result in a change of applicator position nor alter the treatment course, we recognized that these findings are exploratory and not definitive in nature. It should also be noted that these findings would only be applicable to single-channel vaginal applicators and not for multichannel cylinders at relatively modest doses. Our hope is that this study can add to ongoing research protocols that will further optimize cancer care for individual patients while minimizing the side effects, potential iatrogenic morbidities, and costs associated with treatment.

## Conclusion

Despite the broad range of doses calculated at the bladder point, genitourinary toxicity was minimal. Simulation proved useful in recording dose and represented a small, yet important portion of the total treatment charge but did not alter treatment in this series. The necessity of simulation for intracavitary high-dose-rate vaginal BT remains unclear.

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