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Dose delivered to the lumbosacral plexus from high-dose-rate brachytherapy for cervical cancer

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Introduction

Brachytherapy has a critical role in the definitive treatment of locally advanced cervical cancer.[1] Brachytherapy allows for maximal coverage of gross disease while minimizing radiation exposure to surrounding tissue. [2] Dose and associated toxicity to the vaginal surface, bladder, and rectum are dependent upon choice, technique in placement, and position of applicators. [3] With two-dimensional (2D) imaging, dose to the lumbosacral plexus (LSP) has been visually estimated based on tandem position within the pelvis, measured as the relative distance between the pubic symphysis and the sacral promontory. By convention, the tandem is often adjusted prior to three-dimensional (3D) imaging or 2D treatment planning in an effort to minimize the LSP dose. More recently, a 2010 survey conducted by the American Brachytherapy Society revealed that 70% of respondents use computed tomography (CT) to confirm applicator placement prior to treatment. [4] The increasing use of CT scans allows for more accurate volumetric assessment. Our study investigates the position of the tandem in the pelvis based on 2D imaging and determines the actual LSP dose calculated with 3D treatment planning. In addition, we report our long term toxicity outcomes with regards to radiation induced lumbosacral plexopathy.

Materials and Methods

After institutional review board approval, the treatment records of all women aged greater than 18 years, with FIGO stage IB-IVA cervical cancer treated with CT-based image-guided high-dose-rate (HDR) brachytherapy using a tandem and ring applicator were reviewed. CT images were acquired following instrument placement prior to delivery of each fraction of HDR brachytherapy. The LSP was contoured by a single investigator on CT treatment

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planning scans obtained for the first fraction of brachytherapy in accordance with previously published guidelines.[5] Brachytherapy planning CT images with anterior-posterior (AP) and lateral digitally reconstructed radiograph (DRR) images were reviewed to evaluate the position of tandem relative to the pubic bone and sacral promontory. Dose delivered to the LSP calculated with 3D treatment planning was recorded.

Treatment

HDR brachytherapy was delivered after external beam radiation (EBRT) with concurrent chemotherapy. Conventional EBRT fields were used to deliver 45 Gy to the whole pelvis with or without an additional boost to involved parametria, pelvic, or paraaortic lymph nodes. Boost doses were delivered using standard anterior-posterior/posterior-anterior (AP/PA) fields. Most patients (92%, n=47) received concurrent chemotherapy consisting of weekly cisplatin; 3 patients did not receive chemotherapy and 1 patient received 5-fluorouracil. All patients treated with chemotherapy completed at least 4 cycles and the majority (95%, n=48) completed 6 cycles.

Intracavitary brachytherapy

Tandem and ring applicators were used to deliver intracavitary brachytherapy. Tandem angles were selected based on anatomic positioning of the uterus. One patient (2%) was treated with a 30 degree tandem, 28 patients (55%) were treated with a 45 degree tandem and 22 patients (43%) were treated with a 60 degree tandem. Scout images were obtained prior to CT axial images to evaluate placement of the tandem. Based on clinical experience, instruments were adjusted if the tandem position deviated significantly from midline or was considered less than one third the distance from pubic symphysis to the sacrum on lateral scout image (as shown in Figure 1) at the discretion of the treating physician. HDR brachytherapy with ^{192}Ir was delivered using GammaMed remote after-loading system (Varian Medical Systems, Inc., Palo Alto, CA). All patients received 2400–3000 cGy in 3–5 fractions prescribed to International Commission on Radiation Units and Measurements (ICRU) point A or using CT-based imaged-guided volume optimization that incorporated the high-risk clinical target volume and organ-at-risks including the bladder, rectum and sigmoid colon.[2]

Evaluation of tandem placement

AP and lateral DRRs generated on the treatment planning system (Brachyvision, Varian, Palo Alto, CA) were reviewed to determine position variability of the tandem between patients. Using the lateral DRR, measurements were obtained between the posterior pubic symphysis to the sacral promontory and the tandem to the promontory as shown in Figure 1. The ratio of the distance between the tandem and sacrum over the distance between the pubic symphysis and sacrum was recorded (ST ratio). A ST ratio of 0.50 corresponded to a tandem positioned in the mid-pelvis on lateral DRR projection; patients with a smaller ST ratio had a tandem closer to the sacrum (see Figure 1).

Lumbosacral plexus dose

The LSP was contoured on axial CT images for treatment planning per the LSP atlas previously developed by our group.[5] Using the contours and the generated dose volume histogram from the treatment planning software, the LSP dose was recorded as absolute maximum point dose (cGy), maximum point dose as a percentage of prescribed dose, and maximum dose to 2 cc of the LSP (D2cc). This was then studied as a function of the ST ratio to test the hypothesis that patients with a smaller ST ratio would experience increased LSP dose than patients with a greater ST ratio. The total LSP dose from external beam radiation and brachytherapy was estimated by calculating the biologically equivalent dose delivered in 2 Gy fractions (EQD2). An alpha-beta ratio of 2 for late-responding peripheral nerve tissue was used.[6] Unpaired t-test was utilized to compare the mean D2cc for a single fraction and total EQD2 to the LSP among patients with a ST ratio < 0.33 and ≥ 0.33.

Clinical outcome and toxicity follow up

The electronic medical records of all patients included in the analysis were reviewed to assess for clinical toxicity associated with LSP irradiation. Common Terminology Criteria for Adverse Events version 4.0 was used to identify patients reporting symptoms of peripheral motor or sensory neuropathy. The onset, timing, and duration of symptoms were recorded including any additional medical problems or health events which may have contributed to the pathology.

Statistical analysis

The LSP dose was compared with tandem angles and tumor stages using analysis of variance (ANOVA), and analyzed as a function of tandem position and body mass index (BMI) using linear regression. Multiple regression was used to analyze the joint effects of tandem position, tandem angle, tumor stage, and BMI on dose. All statistical analyses were performed using R, version 2.15.2 (R Core Team, 2012).

Results

From 10/2009 through 11/2012, 55 consecutive women with FIGO stage IB-IVA cervical cancer were definitively treated with CT-based image-guided HDR brachytherapy using a tandem and ring applicator. The images from four patients were excluded from the analysis because the treatment planning scan did not include the sacral promontory superiorly. Patient and tumor characteristics are listed in Table 1. The median age was 52 years (range 27–91). The tumor histology was squamous cell carcinoma for 42 (82%) and adenocarcinoma for 9 (18%) patients. One patient had poorly differentiated carcinoma. The mean BMI of the population was 29 (range 17–47), and 18% of patients had a history of diabetes mellitus. At the time of brachytherapy the position of the uterus was anteverted in 43 (84%) and retroverted in 8 (16%) patients.

The median prescription dose for a single HDR fraction was 600 cGy (range 550–950 cGy). On lateral DRRs, the mean distance between the pubic bone and the sacral promontory was 13 cm (range 10.9–14.6 cm). The distance between the tandem and the sacrum was greater than or equal to 1/3 the distance between the sacral promontory and the pubic symphysis

(ST ratio ≥ 0.33) for 51% (n=26) of patients. The median ST ratio was 0.33 (range 0.16–0.53). Only 2 patients had a ST ratio greater than or equal to 0.50. On AP DRR the tandem was midline for all but one patient, where the tandem was slightly deviated to the right.

The maximum point dose to the LSP for a single fraction ranged from 48–329 cGy with a median of 138.5 cGy. The maximum point dose to the LSP as a percentage of the prescribed dose ranged from 9–47% with a median of 20%. The median D2cc for the LSP was 118 cGy (range 44–287 cGy) for a single HDR fraction. On univariate analyses the absolute max dose and D2cc to the LSP varied significantly with the ST ratio. Dose decreases significantly with increasing ST ratio, with a 2.4 cGy decrease in absolute maximum dose ($P < 0.001$), a 0.4% decrease in maximum dose as percentage of prescribed dose ($P < 0.001$), and a 2.1 cGy decrease in D2cc ($P < 0.001$) for each additional 0.01 increase in ratio. For example, an increase in ST ratio from 0.3 to 0.4 results in a decrease by 24 cGy and 21 cGy of the LSP absolute maximum dose and D2cc, respectively When adjusting for tumor stage, BMI, and tandem angle, the LSP dose decreases significantly with increasing ST ratio. For each additional 0.01 increase in ST ratio, the absolute maximum dose decreases by 2.9 cGy ($P<0.001$) or 0.4% of prescribed dose and the D2cc decreases by 2.5 cGy ($P<0.001$). As illustrated in Figure 2, patients with an ST ratio of < 0.33 had a mean LSP D2cc of 138 cGy (21% of prescribed dose) compared to 99 cGy (16% of prescribed dose) for patients with an ST ratio ≥ 0.33, which was statistically significant ($P <0.0001$).

Total dose to the LSP was estimated by calculating the EQD2 ($\alpha/\beta=2$) point maximum for combined EBRT and brachytherapy, including parametria or pelvic lymph node boost doses. The median prescribed EBRT dose was 4500 cGy (range 4400 cGy-5760 cGy, standard deviation of 426 cGy). The median EQD2 to the LSP was 5855 cGy (range 4575–8158 cGy, standard deviation 626 cGy). There was no significant difference in mean total LSP dose between patients with an ST ratio ≥ 0.33 or < 0.33 (6046 vs 5769 cGy $P=0.13$). However, patients with the lowest total LSP doses were found to have the greatest ST ratios (0.49–0.53).

Tandem angle was also found to significantly impact LSP dose. Post-hoc analysis using the Fisher's Least Significant Difference method showed that the mean of the maximum dose as a percentage of prescribed dose was 4.5% lower with a tandem angle of 60 degrees than with a tandem angle of 45 degrees ($P = 0.010$) and the mean D2cc as a percentage of prescribed dose was 4.0% lower with a tandem angle of 60 degrees than with a tandem angle of 45 degrees ($P = 0.007$). Dose did not change significantly with BMI or tumor stage when adjusting for other variables in the model.

With a median follow up of 14.7 months, 2 patients (4%) have developed symptoms suggestive of lumbosacral peripheral neuropathy. One patient developed right lower extremity weakness and sharp shooting pain radiating from her buttocks to her foot at 18 months post treatment. Her symptoms were intermittent and mild, resolving one month after onset without interruption in activities of daily living. With HDR brachytherapy, the LSP dose was less than 10% of the prescribed dose and the combined EBRT and HDR maximum point EQD2 to the LSP was 4741 cGy. Another patient experienced right lower extremity weakness, numbness, and pain radiating from the lower back to the posterior thigh, 6 months

after completion of chemoradiation. At the time of symptom onset, the patient was also diagnosed with a pathologic fracture of the L1 vertebral body requiring surgical decompression with hardware placement for stabilization. She subsequently experienced compression fractures of the L2 and L3 vertebral bodies following a fall attributed to motor weakness. The patient was treated with palliative radiation to the lumbar spine with 20 Gy in 5 fractions. Ultimately, the she died 9 months post treatment, with progressive weakness and deterioration of overall function.

Discussion

Applicator placement and position influence the dose received by both target tissues and organs at risk, directly impacting clinical outcomes. [7] Modern criteria for optimal instrument positioning described in RTOG protocols include symmetry of ovoids to tandem, displacement of ovoids in relation to the cervical os, position of tandem in mid-pelvis on lateral film, tandem bisecting ovoids on lateral film, and appropriateness of packing.

Common practice includes assessment of instrument positioning with plain film radiographs. On lateral projection, the tandem should be positioned one-third to halfway the distance between the symphysis pubis and the sacrum without lateral deviation. [8–10] In our study, the median distance between the tandem and the sacrum was 4.0 cm, with a median ST ratio of 0.33. Katz et al. retrospectively reviewed 808 intracavitary implants using tandem and ovoids or cylinder performed in 396 patients. The median distance between the tandem and the sacrum was also 4 cm, with a median ratio of 0.50, corresponding to the mid-pelvis. The incidence of RTOG late grade 3 or 4 toxicity was 11%, related to the rectum and bladder, and did not significantly correlate with any parameters of implant geometry.

Our investigation is the first to describe the dose delivered to the LSP using 3D image-guided brachytherapy by contouring the organ at risk on the treatment planning scans. We found that HDR brachytherapy resulted in a median maximum point dose of 138.5 cGy and a median D2cc of 118 cGy, corresponding to 21% and 18% of the prescribed HDR dose for a single fraction, respectively. The dose to the LSP significantly decreased with increasing distance of the tandem from the sacrum. The traditionally recommended position of the tandem at least 1/3 the distance from the sacrum to the pubis on lateral projection was associated with a significant difference in LSP dose for a single HDR fraction, however there was no difference in the total EQD2 combining the EBRT and HDR brachytherapy. This likely reflects the increased dose contribution from external beam radiation compared to brachytherapy, which dilutes the influence of tandem position on the total LSP dose. For all patients, the median total EQD2 point maximum dose to the LSP was 59.0 Gy. Neither BMI, nor uterine position influenced LSP dose.

The LSP dose contribution from HDR brachytherapy was measured solely from the first fraction delivered, which may vary from the dose delivered during each subsequent brachytherapy insertion secondary to changes in tumor size and application positioning. As a result, our determination of the total EQD2 from combined EBRT and HDR brachytherapy may be unduly weighted by the LSP dose delivered on the first fraction. Furthermore, as we transitioned from a prescribing system from point A to an image guided brachytherapy

approach, it is conceivable that manipulating the loading to minimized dose to the upper rectum and sigmoid may also impact dose to the lumbosacral plexus.

Radiation- induced lumbosacral neuropathy has been described for patients with gastrointestinal, lymphoma, genitourinary and gynecologic malignancies. Peripheral nerve injury is a result of delayed radiation injury to mature neural tissue and progressive fibrosis which can cause progressive demyelination. Injury to the LSP may result in pain, numbness, paresthesias, lower extremity weakness, diminished reflexes, and even flaccid paralysis. Although animal studies demonstrate tolerance of the lumbar nerves of up to 80 Gy in 30 fractions, definitive electrophysiologic signs were seen after single doses of 16 Gy.[11] The incidence of neuropathy with conventionally fractioned therapy remains low (0.1–5%) but the true incidence may be obscured by the long latency period (1–24 years) between treatment and toxicity. [12] It is generally held that with conventional fractionation, peripheral nerve injury is rare with doses greater than 60 Gy.[13]

Lower extremity weakness and pain attributed to RILSP following treatment for cervical cancer has been described in the literature, but few examine the dose specifically to the peripheral nerves[14–17] Georgiou et al. reported on 4 cases of RILSP that were diagnosed among 2,140 patients treated with radiation alone for carcinoma of the cervix and endometrium. Using bony landmarks to approximate the position of the LSP, the estimated dose to the sacral plexus ranged from 70–79 Gy. [18] Interestingly, two additional case reports of RILSP were estimated to have occurred with doses of just 57–58 Gy to the LSP. [12, 19] Stryker et al. were among the first to recommend using a posterior block on the lateral whole pelvis external beam fields to minimize dose to the sacral canal and plexus, in response to these results. [12] More recently, Coulombe et al. described 2 cases of lower extremity weakness with paresthesias attributed to radiation plexopathy noted as early as 1 month following completion of definitive chemoradiation for cervical cancer. The authors did not characterize the dose to the LSP specifically, but noted that the nerve roots at L5 for each patient received 2861 and 3718 cGy from EBRT and 190 and 235 cGy from intracavitary brachytherapy. From these reports, it is clear that while rare, the incidence of lumbosacral plexopathy is associated with a wide range of estimated doses (30–79 Gy), making it difficult to define a dose threshold for toxicity. Only two patients in our series developed symptoms of lumbosacral neuropathy: the first patient’s symptoms arose in the setting of pathologic fracture of the spine, and the second was a case of mild transient symptoms. For the latter patient the cumulative LSP maximal EQD2 dose from EBRT and brachytherapy was 47.4 Gy in total, which is much lower than the doses associated with prior reports of RILSP. Interestingly our study is one of the only series to report on patients treated in the era of chemoradiation, where the majority of patients received 6 cycles of weekly cisplatin at 40 mg per square meter. Cisplatin is known to increase the risk of neuropathy, but typically at cumulative doses greater than 300 mg per square meter.[20] As a predisposing comorbidity for peripheral neuropathy, diabetes mellitus was present in 18% of the study population, and was not associated with an increased risk for RILSP.

As described earlier, the published data to date has not identified a convincing dose threshold above which the incidence of RILSP increases. Doses above 55 Gy are consistently reported in association with RILSP, but the reports vary widely from 57–79 Gy.

Our study demonstrates that it is feasible to use the currently published guidelines for LSP contouring to describe the EQD2 dose received during definitive chemoradiation for cervical cancer. Ongoing collection of LSP dose among a much larger population will be necessary to detect any true dose threshold for this late side effect. Efforts to do so remain critical given the improved long term survival that is seen with concurrent chemoradiation and the potentially debilitating impact RILSP may have on quality of life.

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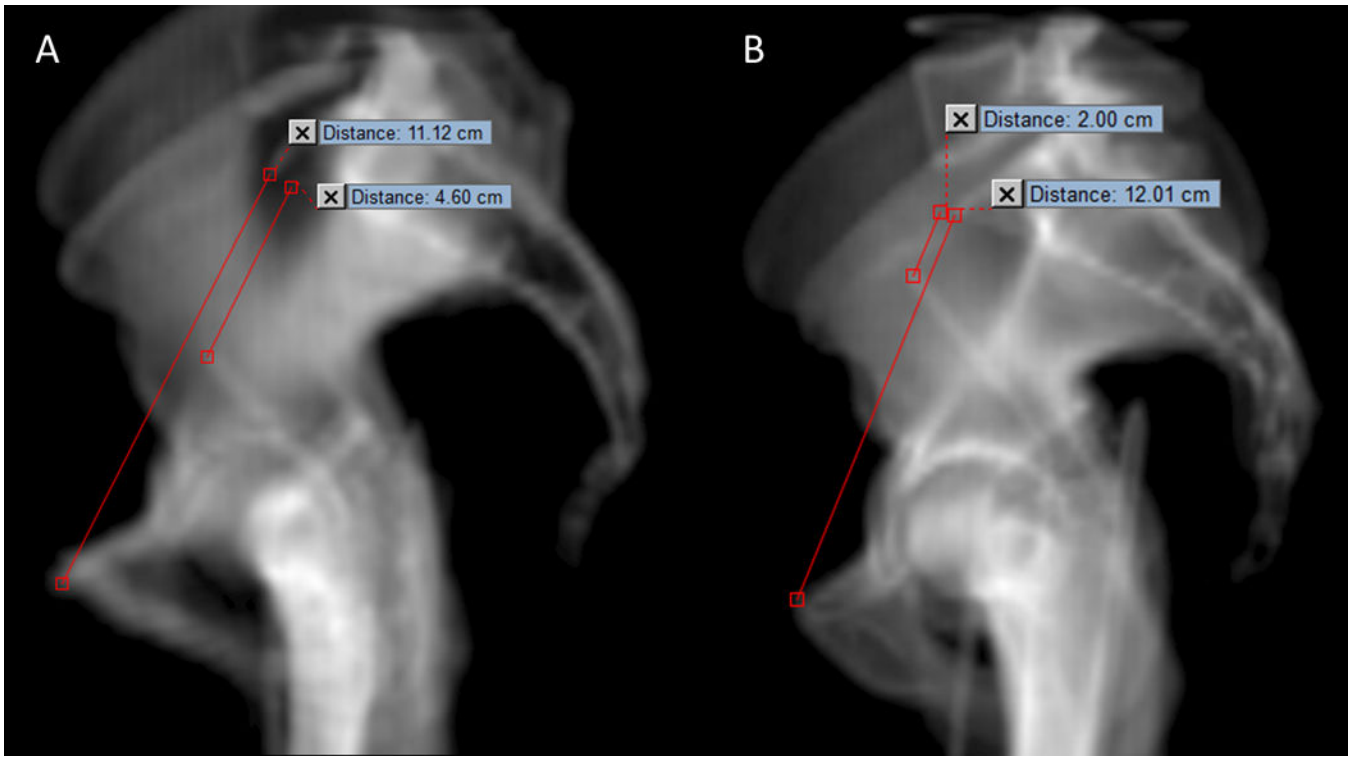

Figure 1. Evaluation of tandem placement and calculation of ST ratio

Variations in tandem placement. Patient A has a ST ratio of 4.60/11.12=0.41 and Patient B has a ST ratio of 2.00/12.01=0.17.

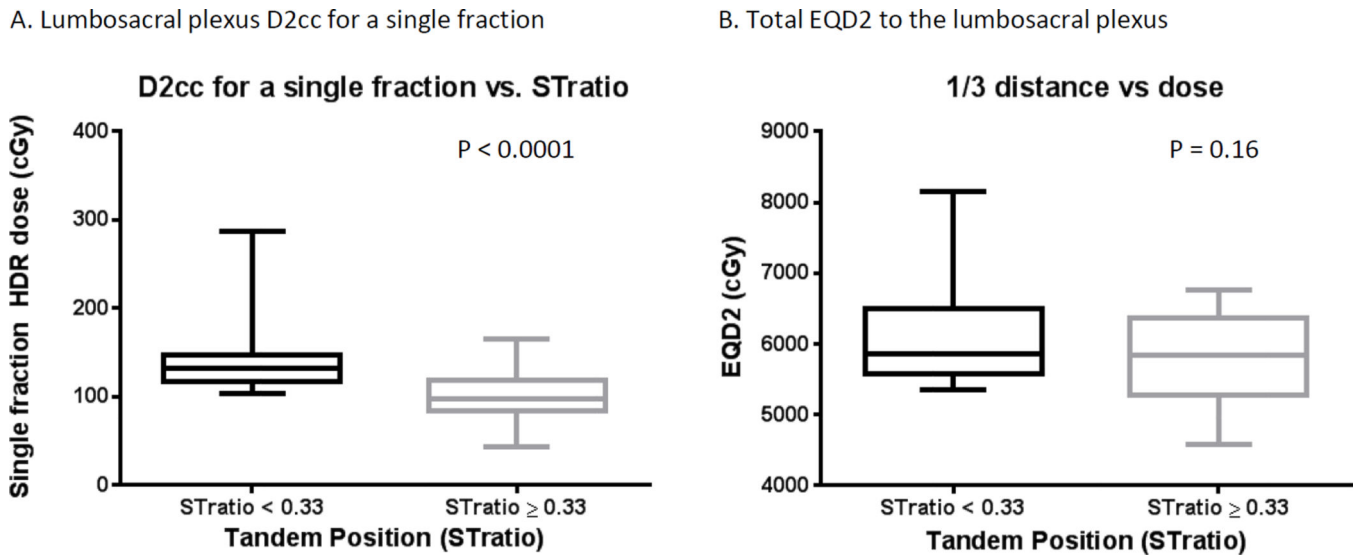

Figure 2. Differences in LSP dose based on tandem position in the pelvis on lateral DRR

Comparison of LSP dose based on changes in ST ratio. A. For a single HDR fraction, the mean D2cc to LSP is significantly less among patients with an ST ratio < 0.33 compared to ≥ 0.33 (P<0.0001). B. Combined external beam and HDR dose to the LSP reported as EQD2 (cGy) does not significantly change with ST ratio less than or greater than 0.33.

Table 1

Patient characteristics

Characteristic	N=51	%
Median age (range)	52 (27–91)	
Histology		
Squamous cell carcinoma	42	82%
Adenocarcinoma	8	16%
Other	1	2%
FIGO stage		
Ib1	6	12%
Ib2	5	10%
IIA	2	4%
IIB	29	56%
IIIB	7	14%
IVA	2	4%
BMI		
<18.5	1	2%
18.5–24.9	14	27%
25–29.9	13	25%
≥ 30	23	45%
Diabetes Mellitis	9	18%
Uterus position		
Anteverted	43	84%
Retroverted	8	16%
Tandem angle		
30 degrees	1	2%
45 degrees	28	55%
60 degrees	22	45%

Abbreviations: FIGO= International Federation of Gynecology and Obstetrics, BMI=body mass index