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Assessment of radiation doses to the para-aortic, pelvic, and inguinal lymph nodes delivered by image-guided adaptive brachytherapy in locally advanced cervical cancer

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ABSTRACT

PURPOSE: This study evaluated the dose delivered to lymph nodes (LNs) by brachytherapy (BT) and the effect of BT image–guided optimization on the LN dose.

METHODS AND MATERIALS: Twenty-five patients with locally advanced cervical cancer were retrospectively analyzed, 16 patients of them had LN involvement. The patients received whole pelvis intensity-modulated radiation therapy (45–50 Gy/25–30 fx) to whole pelvis and two fractions of MRI pulsed-dose-rate BT. The delineated LN groups were para-aortic, inguinal, common iliac (CI), external iliac, internal iliac, obturator, and presacral. For each LN group, $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ (the dose that covers 98%, 50%, and 2% of the volume, respectively) were evaluated for optimized and standard BT plans. The correlation between total reference air kerma (TRAK) and $D_{50\%}$ of the LN groups was evaluated.

RESULTS: BT contributed considerable dose (mean $D_{50\%}$ was 3.8–6.2 Gy equivalent total dose in 2-Gy fractions) to the pelvic LN (external iliac, internal iliac, obturator, and presacral) in optimized plans, whereas less-dose contribution to CI, para-aortic, and inguinal (mean $D_{50\%}$ was 0.5–1.9 Gy equivalent total dose in 2-Gy fractions) was observed. Optimized plans delivered less dose to the LNs as compared with standard plans, although differences only amounted to a mean of 0.2–0.9 Gy ($D_{50\%}$). TRAK showed a significant correlation with LN $D_{50\%}$ for all LN groups except CI, although only 19–38% of the dose variation could be explained by the TRAK.

CONCLUSIONS: BT contributes considerable dose to pelvic LNs and should be considered in the evaluation of total LN doses.

Keywords: Cervical cancer; Brachytherapy; MRI guided; Radiation dose; Para-aortic lymph node; Pelvic lymph node; Inguinal lymph node

Introduction

The uterine cervix has a rich lymphatic supply. Draining lymph node (LN) groups are mainly the internal iliac (II), external iliac (EI), common iliac (CI), and para-aortic (PA) LNs (1). Although the International Federation of Gynecology and Obstetrics staging does not include LN involvement as a criterion for cervical cancer staging, yet LN is one of the negative prognostic factors, and usually it is considered in the general treatment strategy along with other factors both in radical and adjuvant settings (2–4). Pathologically enlarged LNs can be treated by surgical debulking (5) or external beam radiotherapy (EBRT) boosting (3, 6) using simultaneous integrated boost or sequential boost after completion of elective whole pelvic irradiation.

In a study by Beadle *et al.* (7), patterns of regional recurrence after definitive radiotherapy for cervical cancer were

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evaluated. In their series, patients with regional recurrences (iliac, inguinal [ING], or PA) were divided into infield only, infield plus marginal, and marginal only. They reported a 5-year overall survival rate of 0% for patients with a component of infield recurrences and 8% for patients with isolated recurrence above the field (7). Infield recurrences had a higher tendency to have initial positive LNs (7).

Infield LN recurrences may be because of the delivery of a suboptimal dose. However, there is currently no broad consensus on the radiation boost dose needed for LN control. The prerequisite for adequate assessment of dose–response relations for involved LNs is to accurately assess and report the total dose delivered to the investigated region. Although the EBRT dose to LNs is usually planned, the dose contribution from brachytherapy (BT) is most often not reported, and hence its impact on LN control has not been assessed. Although most doses are delivered by EBRT, even a limited additional dose from BT could be important for nodal control. Studying regional LN control requires accurate reporting of the total dose delivered to the LN from EBRT plus BT. This will improve the possibilities to prescribe an evidence-based dose to pathological nodes and improve regional control of the pelvis.

This study was designed to evaluate the BT dose contribution to different LN groups and create its atlas as well as compare doses to LNs from standard nonoptimized with optimized three-dimensional (3D) MRI-guided pulsed-dose-rate (PDR) BT.

Methods and materials

Twenty-five consecutive patients with locally advanced cervical cancer who underwent pelvic–abdominal CT scanning for EBRT planning were included. Patients were treated at Aarhus University Hospital between June 2010 and April 2012. Sixteen of the 25 patients had positive LN enlargement. Patients received whole pelvis intensity-modulated radiation therapy (45–50 Gy in 25 or 30 fractions) with concomitant weekly cisplatin, followed by two fractions of 3D MRI-guided PDR-BT delivered 1 week apart, and each fraction was 20-hourly pulses. Pathologically involved LN was boosted to a dose level of 60 Gy in 30 fractions. A description of the PDR-BT application and MRI technique has been previously published (8). Briefly, patients underwent MRI with applicator *in situ* for each BT fraction. BT imaging, contouring, reconstruction, and reporting were done according to the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology guidelines (9–12). For each BT fraction, a standard and nonoptimized BT plan was first created with Point A dose normalization to 85 Gy total equivalent total dose in 2-Gy fractions (EQD2). Manual optimization was then performed to adapt the dose to the target and organs at risk. A description of the BT standard and optimized plans has been previously reported (13). The BT plan optimization aimed to deliver a total EQD2 (EBRT plus BT) of at least 85 Gy to the high-risk clinical target volume (HR CTV) D_{90} (the dose that covers 90% of the HR CTV), and to keep the D_{2cc} (the dose that covers an absolute 2 cm^3 of the volume) for the bladder below 90 Gy, and the D_{2cc} for the rectum, sigmoid, and bowel below 70–75 Gy.

In all patients, CT scanning of the abdomen and pelvis was performed for planning of EBRT. The following LN groups were delineated on the planning CT: PA, ING, CI, EI, II, obturator (OB), and presacral (PS). Figure 1 shows PA, CI, EI, II, OB, and PS LN group delineation. Delineation was done bilaterally on the planning CT images according to the published guidelines (14). The CT images were coregistered (bony registration) to the MRI of the first BT fraction, and the BT dose distribution was transferred to the planning CT scan. Thus, we had both the LN contours and the BT dose distribution on the same image. For each group, and for bilateral sides, $D_{98\%}$ (the dose that covers 98% of the volume), which is the near minimum dose, $D_{50\%}$ (the dose that covers 50% of the volume), which is the median dose, and $D_{2\%}$ (the dose that covers 2% of the volume), which is the near maximum dose for the optimized BT plan, were recorded and compared with those of the standard BT plan. Physical doses delivered to the LNs during BT were recalculated into EQD2 using linear quadratic model (α/β = 10 Gy, T1/2 = 1.5 h). EQD2 doses from the first BT fraction were multiplied by two to estimate the total BT dose contribution from two fraction treatments. To test if our results were applicable to high-dose rate (HDR) BT, we also renormalized the plans to HDR schedule of four fractions of 7 Gy each.

Pairwise *t* test was performed to compare the optimized plan with the standard nonoptimized BT plan, and a *p*-value below 0.05 was considered statistically significant. Regression analysis of the total reference air kerma (TRAK) and the $D_{50\%}$ to each of the LN groups was performed for the optimized BT plan by using STATA statistical software, version 12.1 (StataCorp LP, USA).

Results

Clinical characteristics of the included patients are presented in Table 1. The mean ± standard deviation (SD) HR CTV volume at the first fraction of BT was 39.5 ± 15 cc with a range of 19–67 cc. Total mean ± SD HR CTV D_{90} was 90.4 ± 3.6 Gy of EQD2 for the optimized plan. Table 2 shows a summary of EQD2 in Gy delivered by BT to the various LN groups for the standard vs. the optimized BT plans. For the optimized plan, the mean $D_{50\%}$ delivered by BT to the pelvic LNs (EI, II, OB, and PS) was 3.8–6.2 Gy. Less dose contribution was seen in PA, CI, and ING LNs with mean $D_{50\%}$ of 0.5, 1.9, and 1.5 Gy, respectively. Interpatient variations for $D_{50\%}$ were seen with SDs of up to 2.6 Gy. For standard plans, the mean $D_{50\%}$ ranged from 4.1 to 6.4 Gy in the four pelvic LN groups. For PA, CI, and ING, $D_{50\%}$ ranged from 0.6 to