An exploratory study of the dose correlation between point B and metastatic lymph nodes in three-dimensional high-dose-rate brachytherapy for cervical cancer

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Abstract
Objective: To determine the dose correlation between point B and metastatic lymph nodes in cervical cancer treated with three-dimensional (3D) high-dose-rate (HDR) brachytherapy.

Methods: A retrospective study was conducted involving 30 cervical cancer patients with lymph node metastases who completed 3D HDR brachytherapy at Liaoning Cancer Hospital and Institute from May 2019 to November 2020. Brachytherapy was performed with a Fletcher applicator at a prescribed dose of 28 Gy/4 f. Computed tomography images of the external irradiation target were fused with delineated images of the brachytherapy target on the MIM system. The minimum dose received by 90% of the volume (D90) was read on the MIM system for all metastatic lymph nodes and the point B dose was read for the brachytherapy target area. In total, 78 metastatic lymph nodes from 30 patients with cervical cancer were included in this study, including para-aortic, common iliac, external iliac, internal iliac, obturator, and inguinal lymph nodes. Paired t-tests and Pearson correlation coefficient analyses were performed to examine the difference in the equivalent dose between each group of metastatic lymph nodes and point B.

Results: The mean equivalent point B dose was 6.69 ± 1.08 Gy. There were significant differences in dose between point B and the para-aortic, common iliac, external iliac, internal iliac, and inguinal lymph nodes (p < 0.05), with a weak positive correlation (r < 0.4). There was no statistically significant difference in dose between obturator lymph nodes and point B (p = 0.3999), with a positive correlation (r = 0.65).

Conclusion: 3D HDR brachytherapy contributed significantly to pelvic lymph node doses in cervical cancer patients with lymph node metastasis, but less to para-aortic and inguinal lymph node doses. The dose at point B grossly overestimated the mean dose to pelvic lymph nodes; only the dose to obturator lymph nodes was similar to that of point B, with a slightly positive correlation.

Keywords
3D brachytherapy, cervical cancer, high-dose-rate, metastatic lymph nodes, point B
INTRODUCTION

More than 50% of patients with locally advanced cervical cancer have lymph node metastases. Effective treatment of metastatic lymph nodes is one of the most important factors affecting these patients’ prognosis. Researchers have suggested that the number of lymph node metastases should be included in cervical cancer staging. The most common lymph node metastasis sites for cervical cancer include the para-aortic, pelvic, and inguinal lymph nodes. The current primary treatment regimen utilizes a simultaneous or sequential boost method of external irradiation to the pelvic lymph nodes, combined with brachytherapy and concurrent chemotherapy.

The Manchester system, one of the standard dose systems that emerged in the 1930s, defines intersection point A at 2 cm from the mucosa of the uterine axial hole on the central side of the uterine tube, and intersection point B at 2 cm above the lateral fornix and 5 cm beyond the uterine axial opening. Point B dosage was utilized as the standard value for radiation supplied to the pelvic lymph node area until the introduction of image-guided brachytherapy methods. External irradiation dose calculations are reasonably precise; however, there is no standard calculation technique for the brachytherapy dosage to metastatic lymph nodes. The purpose of this study was to determine the dose distribution of three-dimensional (3D) high-dose-rate (HDR) brachytherapy to common metastatic lymph nodes in cervical cancer patients with lymph node metastases, as well as the relationship between point B dosage and dose distribution.

METHODS

2.1 Clinical data

Thirty patients with cervical cancer with lymph node metastases who received radiotherapy at Liaoning Cancer Hospital and Institute from May 2019 to November 2020 were selected and their data retrospectively analyzed. According to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging criteria for cervical cancer, all patients were staged as IIIC1r, IIIC2r, IVA, and IVB with lymph node metastases, and were pathologically diagnosed with squamous cell carcinoma, adenocarcinoma, and others.

| Item                           | N  | (%) |
|-------------------------------|----|-----|
| Pathologic type               |    |     |
| Squamous cell carcinoma       | 24 | 80.0|
| Adenocarcinoma                | 5  | 16.7|
| Other                         | 1  | 3.3 |
| FIGO staging                  |    |     |
| IIIC1r                        | 14 | 46.7|
| IIIC2r                        | 8  | 26.7|
| IVA                           | 5  | 16.6|
| IVB                           | 3  | 10.0|
| Metastatic lymph nodes site   |    |     |
| Para-aortic lymph nodes       | 8  | 10.3|
| Common iliac lymph nodes      | 5  | 6.4 |
| External iliac lymph nodes    | 23 | 29.5|
| Internal iliac lymph nodes    | 21 | 26.9|
| Obturator lymph nodes         | 12 | 15.4|
| Inguinal lymph nodes          | 9  | 11.5|

A short diameter >8 mm was consistent with metastatic lymph nodes according to imaging data from patients before treatment: a total of 78 lymph nodes were included in the study. The age range of the patients was 35–72 years, and the mean age was 55.5 years. The fundamental clinical features of the 30 patients are shown in Table 1.

2.2 External radiation therapy

All 30 patients received pelvic external beam intensity-modulated radiotherapy (IMRT) with 6 MV energy X-rays. The primary lesion and lymphatic drainage area received a total dose of 45–50 Gy in the planned target area. For suspected metastatic lymph nodes based on medical imaging, a synchronous boost or a sequential boost of 5–15 Gy was given. The 30 patients, who were in the supine position, underwent computed tomography (CT) simulated positioning scanning; the CT images were transmitted to the Pinnacle 9.10 treatment planning system. The planned target area included the vaginal stump, vaginal part, and lymph node drainage area. The structures at risk included the small intestine, rectum, bladder, left and right femoral head, and bone marrow. The radiotherapy plan adopted coplanar double arc clockwise and counterclockwise rotation irradiation.

2.3 3D HDR brachytherapy

Thirty patients received 192Ir 3D HDR brachytherapy after completion of external irradiation using the Fletcher applicator. Patients were treated in the lithotomy position with the cervix exposed using a vaginal dilator. The uterine cavity tube and left and right ovoids were successively standardized and fixed. The vagina was packed with gauze to stabilize the applicator while allowing air in the vagina to be discharged; the gauze also served a hemostatic role. Each patient received oral small bowel contrast, and 100 ml of contrast medium was injected into the bladder through a urinary catheter before CT positioning. The patient was positioned and scanned with a Siemens large-bore CT ranging from the upper edge of the first lumbar vertebra to the middle of the femur with a slice thickness of 3 mm. The CT images were then transmitted to the Oncentra planning system. The prescribed dose for radiotherapy was 7 Gy/f, and the treatment was given twice a week for four sessions in total.
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2.4 | Delineation of the target area and brachytherapy plan design

According to the imaging data and the patient’s gynecologic status, the physician determined the clinical target volume (CTV) range of the clinical target area and delineated the organs at risk, such as the small intestine, colorectum, and bladder, using the target definition criteria recommended by the European Society of Radiation Oncology Working Group (GEC-ESTRO). As illustrated in Figure 1, metastatic lymph nodes were identified using imaging data from the patient at the start of therapy, CT positioning, external beam planning, and the MIM software fusion approach. The physicist reconstructed the Fletcher applicator according to its anatomic position and used graphical optimization (GO) combined with manual forward optimization methods to optimize the dose, resulting in a nearly flat, pear-shaped dose distribution.7

2.5 | Metastatic lymph node dose and B-site dose assessment

The dose received by 90% of the volume (D90) of the metastatic para-aortic, common iliac, external iliac, internal iliac, obturator, and inguinal lymph nodes were correlated and compared with the point B dose of the Manchester system. The metastatic lymph node dose was converted to the equivalent dose in 2 Gy (EQD2), equivalent to the dose of 2 Gy fractions in conventional fractionation. This conversion was based on the following equation: EQD2 = Nd[1 + d/(α/β)]/(1 + 2d/α/β), where the α/β of the CTV and metastatic lymph nodes in the clinical target area was taken as 10.9

2.6 | Statistical methods

Statistical analysis was performed with SPSS 20.0, and measurement data were analyzed using the mean ± standard deviation (SD). A paired t-test was performed for metastatic lymph node and point B doses. A p value below 0.05 was considered statistically significant. The Pearson correlation coefficient was calculated between the metastatic lymph node and point B doses. The two variables were considered strongly correlated at an r ≥ 0.7, moderately correlated at an r of 0.4 to < 0.7, weakly correlated at an r of 0.2 to < 0.4, and not correlated at an r < 0.2.10

3 | RESULTS

3.1 | Metastatic lymph node dose

After 30 patients received 3D HDR brachytherapy with a prescribed dose of 28 Gy/4 f, the EQD2 of the CTV D90 in the clinical target area was 39.5 ± 2.67 Gy, including a 6.69 ± 1.08 Gy dose at point B and 5.05 ± 1.39 Gy at the pelvic metastatic lymph node D90, with a range interval of 2.05–8.37 Gy, and a proportion of total brachytherapy dose on D90 of the para-aortic, common iliac, external iliac, internal iliac, obturator, and inguinal lymph nodes (Table 2).

Except for the inguinal lymph nodes, the minimum, 25%, median, 75%, maximum, and mean values for the para-aortic, common iliac, external iliac internal iliac lymph nodes, and point B dose showed an increasing trend (Figure 2).

3.2 | Comparison of EQD2 and point B dose difference of metastatic lymph node D90

The EQD2 in the para-aortic, common iliac, external iliac, internal iliac, and inguinal lymph nodes were significantly different between the D90 and point B doses (p < 0.0001), whereas the difference in EQD2 between the D90 and point B doses in the obturator lymph nodes was not (p = 0.3999; Table 2).
TABLE 2 Comparison of EQD2 dose to metastatic lymph nodes and Manchester point B dose

| Item                      | D90 (Gy, EQD2) | Total brachytherapy dose (%) | t-test  | r     | p value for r |
|---------------------------|----------------|-----------------------------|---------|-------|---------------|
|                           | Mean ± SD      | Range interval              |         |       |               |
| Para-aortic lymph nodes   | 0.53 ± 0.17    | 0.36–0.87                   | 1.3     | <0.0001 | 0.16          | <0.0001       |
| Common iliac lymph nodes  | 3.08 ± 0.59    | 2.05–3.85                   | 7.8     | <0.0001 | 0.19          | <0.0001       |
| External iliac lymph nodes| 4.63 ± 1.12    | 2.96–6.67                   | 11.7    | <0.0001 | 0.28          | 0.0015        |
| Internal iliac lymph nodes| 5.22 ± 1.05    | 3.16–7.20                   | 13.1    | <0.0001 | 0.32          | 0.0031        |
| Obturator lymph nodes     | 6.35 ± 1.26    | 4.37–8.37                   | 16.0    | 0.3999  | 0.65          | 0.0255        |
| Inguinal lymph nodes      | 1.78 ± 0.77    | 0.82–3.10                   | 4.5     | <0.0001 | 0.31          | <0.0001       |
| Point B                   | 6.69 ± 1.08    | 4.23–8.67                   | 16.9    |         |               |               |

r: Pearson correlation coefficient.

FIGURE 2 Descriptive distribution diagram of calculated doses at D90 and point B in different lymph node regions. PA, para-aortic lymph nodes; CI, common iliac lymph nodes; EI, external iliac lymph nodes; II, internal iliac lymph nodes; OB, obturator lymph nodes; ING, inguinal lymph nodes. The boxplot numbers are the minimum, 25%, median, 75%, and maximum values from the bottom up. × indicates the mean value.

3.3 Dose-correlation between the EQD2 of the metastatic lymph node D90 and point B

The EQD2 of the para-aortic, external iliac, internal iliac, and inguinal lymph node D90 had a weak correlation with the dose at point B (r = 0.2-0.4, p < 0.05). The EQD2 of the obturator lymph node D90 had a moderate correlation with the dose at point B (r = 0.65, p = 0.0255; Figures 2 and 3).

4 DISCUSSION

Point B in the Manchester system is frequently used to estimate the dose to pelvic lymph nodes when cervical cancer is treated with conventional 2D brachytherapy. Some studies have reported a considerable discrepancy between the dosage to point B and the actual dose to pelvic lymph nodes since the introduction of image-guided 3D brachytherapy systems.

In this study, we delivered 3D HDR brachytherapy with the Fletcher applicator to 30 cervical cancer patients with lymph node metastases and showed that the Point B dose significantly overestimated the pelvic lymph node dose. The mean EQD2 of the metastatic pelvic lymph node D90 in 30 patients was 5.05 ± 1.39 Gy, 24.5% lower compared with the point B dose of 6.69 ± 1.08 Gy. There was a weak or no correlation between the lymph node and point B doses for the metastatic lymph nodes included in the study, except for 12 obturator lymph nodes that had a moderate correlation with the point B dose.

It is not difficult to find point B when making a brachytherapy plan for patients with cervical cancer. The point B and lymph node dose follow the inverse square law: the closer to the target, the greater the dose. We estimated the relationship between point B and the pelvic metastatic lymph node doses based on the sample data in this paper. These relationships are as follows: the dose of obturator lymph nodes is equivalent to that of point B, the dose of internal iliac metastatic lymph nodes is about 78% of the dose of point B; the dose of external iliac metastatic lymph nodes is about 70% of the dose of point B; the dose of the common iliac metastatic lymph nodes is about half of the dose of point B. The dose of para-aortic and inguinal metastatic lymph nodes is less affected by brachytherapy and can be ignored. Due to the small sample size included in this study, these estimates warrant further clinical study and verification. However, the dose of point B is affected by many factors, such as the size of the patient’s uterus, the anatomical structure of patient, size of the target volume drawn by the doctor, standard position of the applicators, accuracy of the location of the radiation source, and time of exposure. Due to the nature of brachytherapy, the position and dose of point B are affected by the uterus and cervix position, which often changes greatly during each treatment. Current 3D brachytherapy can only provide the relative position of the target area and organs and lacks image guidance and dose verification during the treatment process. This posed a challenge for us in estimating the dose of individual metastatic lymph nodes, but we were able to estimate a rough dose range (Table 2). Using these estimates, the dose of external irradiation of metastatic lymph nodes in patients with cervical cancer can be adjusted accordingly.
to the brachytherapy dose. External irradiation can increase the dose of para-aorta and inguinal lymph nodes and reduce the dose of pelvic metastatic lymph nodes. Using these estimates, the dose of at-risk organs can be minimized while still meeting the clinical dose for treatment of metastatic lymph nodes, thus reducing toxicity and adverse reactions after radiotherapy and improving patients' quality of life.

In this investigation, outlining metastatic lymph nodes during 3D brachytherapy in 30 patients proved difficult. Specifically, the volumes of numerous metastatic lymph nodes were greatly reduced following external irradiation and concomitant chemotherapy, so it was difficult to accurately outline them on brachytherapy CT positioning. Furthermore, the pre-treatment magnetic resonance (MR), positron emission tomography-computed tomography (PET-CT), and external irradiation plan did not account for the patient's body position during brachytherapy, and MIM software fusion technology-facilitated delineation of metastatic lymph nodes. An error of ±2 mm is expected in the 3D space of the lymph nodes outlined after fusion, as the scanning slice thickness differed between the fusion reference image and the CT positioning of brachytherapy when the metastatic lymph node images were fused using the auxiliary frame of MIM software fusion technology and the deformation fusion technology. This led to an overestimation of the volume of the metastatic lymph nodes and an underestimation of the dose required.

The data presented herein are largely in agreement with the data reported in the literature in recent years (Table 3). For example, Van den Bos et al. treated 27 patients with cervical cancer with 3D HDR brachytherapy, delineated 57 pelvic metastatic lymph nodes treated in fractions of 5–6 Gy/f, and found an increasing trend in the dose to the common iliac, external iliac, internal iliac, and obturator lymph nodes. McKeever et al. reported that the dose to the internal iliac metastatic lymph nodes within the sacroiliac joint was 61.8% higher than the internal iliac metastatic lymph nodes outside the sacroiliac joint in 29 patients with cervical cancer who underwent HDR brachytherapy. In 21 patients with cervical cancer, Lee et al. designated 45 metastatic lymph nodes for brachytherapy and showed that the EQD2 dosage to the pelvic metastatic lymph nodes accounted for 4.1–9.5% of the prescribed brachytherapy dose. Bacorro et al. concluded that the mean dose of brachytherapy for external iliac, internal iliac, and obturated metastatic lymph nodes in cervical cancer is approximately twice that of the total metastatic lymph nodes, similar to the findings of the present study.

According to Van den Bos et al., the contribution of brachytherapy for cervical cancer to a single metastatic lymph node varies substantially depending on patient and treatment parameters. If an individual metastatic node cannot be accurately identified, the dose to the individual metastatic node may be estimated by evaluating the dose range to the nodal region. This finding identifies another method of delineating the lymph nodes in brachytherapy for cervical cancer, that is, delineating the overall lymph node area. Matsukawa et al. reported that among 49 patients with cervical cancer treated with brachytherapy, the obturator lymph node group dose was 53% of the point B dose, the internal iliac lymph node group was 22% of the point B dose, and there was a strong dose correlation between the D50 in obturator lymph node group and point B.

Lee et al. performed 70 HDR brachytherapy sessions in 14 patients with cervical cancer. Before each radiotherapy session, the patients' external iliac, internal iliac, and obturator lymph node groups were delineated. The dose-volume histogram (DVH) doses (D100, D90, D50, D2cc, D1cc, and D0.1cc) were compared with the point B dose using t-tests and correlation studies. It was concluded that the point B dose

**FIGURE 3** Correlation between the EQD2 of metastatic obturator lymph nodes D90 and dose at point B \( r = 0.65, p = 0.02 \)
was a poor surrogate for specific metastatic lymph node group doses and that there was a statistical difference between the highest doses of brachytherapy in other pelvic lymph node groups and the obturator lymph node group. These results mirror the findings of this study.

In a study of 25 patients with cervical cancer, Mohamed et al.18 identified the dose of the para-aortic, common iliac, external iliac, internal iliac, presacral, and obturator lymph node groups, and found that brachytherapy significantly contributed to the dose of the pelvic lymph nodes. The dose contribution of brachytherapy to the pelvic lymph node group of patients with cervical cancer is clear, but the correlation between doses to point B and doses to any other lymph node group is modest.19 This perspective is similar to that of the current study. Data obtained by delineating the overall lymph node group often tend to underestimate the dose to individual metastatic lymph nodes. As such, these data are of little significance in estimating the dose to individual metastatic lymph nodes, although they may guide the approximate dose to the entire lymph node group.

In cervical cancer patients with lymph node metastases, 3D HDR brachytherapy contributes significantly to the pelvic lymph node dose, but less to the para-aortic and inguinal lymph node doses. The average dose to the pelvic lymph nodes was greatly overestimated by point B. Only the dose to the obturator lymph nodes was similar to the point B dose, with some positive correlation.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

ETHICS STATEMENT
Our institution does not require ethical approval because it does not involve human subjects during the study.

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How to cite this article: Yang D, Gao Y. An exploratory study of the dose correlation between point B and metastatic lymph nodes in three-dimensional high-dose-rate brachytherapy for cervical cancer. Prec Radiat Oncol. 2022;6:209–215. https://doi.org/10.1002/pro6.1168