ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Assessment of dose contribution to pelvic lymph nodes in patients undergoing brachytherapy for carcinoma cervix

Deepak Sharma[1], Amrut S Kadam[2], Ramashish Kumar[3], Raghavendra BK[4], Srihari G[5], Perpetua Shruthi A[6], Varun Chandra[7]

[1,3]Senior Resident, Department of Radiation Oncology, Lady Hardinge Medical College, New Delhi, [2]Professor, [7]Junior Resident, Department of Radiation Oncology, Victoria Hospital, Bengaluru Medical College and Research Institute, [6]Registrar, HCG Cancer Centre, KR Road, Bengaluru, [4]Senior Resident, Department of Radiation Oncology, Hassan Institute of Medical Sciences, Sri Chamarajendra District Hospital, Hassan, [5]Senior Resident, Department of Radiation Oncology, Karnataka Medical College and Research Institute, Hubballi (KMC-RI, Hubballi), Karnataka, India

Submission: 20-09-2024 Revision: 30-10-2024 Publication: 01-12-2024

ABSTRACT

Background: The inclusion of pelvic lymph node (PLN) metastasis in the FIGO staging system has impacted disease classification and patient survival. Brachytherapy is a key component in managing carcinoma cervix; however, the dose contribution of brachytherapy to PLNs remains unclear. **Aims and Objectives:** This study aims to quantify the dose contribution of high-dose rate (HDR) brachytherapy to individual pelvic nodal groups. **Materials and Methods:** We included 40 biopsy-proven carcinoma cervix patients, stages IIA to IVA. All patients underwent external beam radiotherapy (EBRT) with concurrent cisplatin chemotherapy, followed by HDR brachytherapy, either intracavitary brachytherapy (ICBT) or interstitial brachytherapy (ISBT). A total dose of 21 Gy in 3 fractions (7 Gy per fraction) was prescribed to the high-risk clinical target volume. **Results:** For ICBT, the mean absolute doses received by the external iliac, internal iliac, and obturator groups were 0.56 Gy, 1.02 Gy, and 1.22 Gy, corresponding to EQD2 ($\alpha/\beta = 10$) values of 0.49 Gy, 0.93 Gy, and 1.14 Gy, respectively. In the ISBT group, the mean absolute doses were 0.49 Gy, 0.86 Gy, and 1.11 Gy, with corresponding EQD2s of 0.43 Gy, 0.85 Gy, and 1.02 Gy. **Conclusion:** PLNs received significant dose contributions from HDR brachytherapy in cervical cancer patients, providing valuable reference data for determining the EBRT boost dose in cases of enlarged PLNs.

Key words: Brachytherapy; Mean absolute dose; Pelvic lymph nodes; Carcinoma cervix

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i12.69957

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Cervical cancer is the most common gynecological cancer after carcinoma breast and the fourth most common malignancy worldwide in women. Over 604,127 (6.5%) women globally develop this tumor as reported in GLOBOCON 2020 and 341,831 (3.4%) die of the disease every year. In India, the incidence of cervical cancer is 9.4% accounting to 123,907 new cases and a total of 77,348 deaths every year.[1] The current standard of treatment for locally advanced cervical cancer includes external beam radiotherapy (EBRT) to pelvis with a dose ranging from 45 to 50.4 Gy in 25–28 fractions with concurrent chemotherapy which is followed by brachytherapy (interstitial or intracavitary) to a dose of 6–9 Gy per fraction in 2–4 fraction to deliver a cumulative equal dose in 2-Gy Fractions (EQD2) of 80–90 Gy to the primary tumor.[2,3]

Previously, uterine cervix carcinoma staged clinically but in the recent times, radiological methods are also used to assign disease stage due to their impact on management.[4] Metastasis to the pelvic lymph nodes (PLNs) also is a common prognostic factors which are included in the FIGO staging.[5] However, there is variation in practice regarding the optimal radiation dose to metastatic PLNs. Dose contribution to PLNs from brachytherapy is not commonly taken into

Address for Correspondence:
Dr. Raghavendra BK, Senior Resident, Department of Radiation Oncology, Hassan Institute of Medical Sciences, Sri Chamarajendra District Hospital, Hassan, Karnataka, India. **Mobile:** +91-8310763324. **E-mail:** raghavendrabk22@gmail.com

consideration in calculating the total dose received by the PLNs as it constitutes a very less yet significant part of the prescribed dose. Considering the fact that positive lymph node status significantly affects the prognosis in carcinoma cervix and upstages the stage to IIIC, determination of dose contribution from brachytherapy to ascertain the total dose delivered to PLNs in carcinoma cervix patients is crucial.

By this study, we aim to quantify brachytherapy dose contribution to the individual pelvic nodal groups, using computed tomography (CT) based 3D planned high-dose rate (HDR) brachytherapy based on Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC ESTRO) guidelines. The dose contribution to the nodal regions in interstitial method of brachytherapy (BT) is underexplored, and hence, we will be including both interstitial as well as intracavitary BT in the study.

Aims and objectives

The aim of this study was to quantify BT dose contribution to the individual pelvic nodal groups using CT-based 3D planned HDR BT based on GEC ESTRO guidelines.

MATERIALS AND METHODS

Case selection

The present study was a prospective single-arm and non-randomized hospital-based study. Forty patients of histologically proven carcinoma cervix were included in the present study in whom definitive Chemoradiotherapy (CTRT) was planned. All patients received definitive chemoradiotherapy (CTRT) with a curative approach. EBRT was administered at a dose of 46–50 Gy across 23–25 fractions, utilizing either a Co-60 Theratron unit at Victoria Hospital, Bangalore or 3D conformal radiotherapy (3D CRT)/intensity-modulated radiation therapy through a LINAC machine done at outside center and referred to Victoria hospital for BT treatment, with concurrent weekly cisplatin at 40 mg/m^2. After completing CTRT, each patient underwent BT, delivered through either intracavitary BT (ICBT) or interstitial BT (ISBT).

Inclusion criteria

1. Histologically confirmed carcinoma of the cervix (e.g., squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma).
2. Patients with FIGO stage IB3 to IVA
3. Patients planned for curative-intent chemoradiotherapy (CTRT) with EBRT followed by BT (either ICBT or ISBT)
4. Patient with Eastern Cooperative Oncology Group Performance Status of 0–2
5. Patients who received concurrent weekly cisplatin chemotherapy during EBRT
6. Patients who provided written informed consent for study participation and data collection.

Exclusion criteria

1. Patients with a history of prior pelvic radiotherapy for any other malignancy
2. Patients with severe renal, hepatic, or cardiac dysfunction that precludes concurrent chemoradiotherapy
3. Patients who did not receive the standard EBRT (46–50 Gy in 23–25 fractions) or who did not complete the planned BT
4. Patients with evidence of distant metastatic disease at the time of diagnosis
5. Pregnant patients, due to potential harm to the fetus
6. Patients who did not consent to participation in the study or who withdrew consent before completion.

Target and organ at risk (OAR) definition

Volume-based prescription and planning, as developed by the GEC-ESTRO working group and detailed in ICRU 89, were followed for target definition and planning. Target delineation included the high-risk clinical target volume (HRCTV) as well as the bladder, rectum, and sigmoid as OARs in accordance with ICRU 89 recommendations. In addition to target volume parameters and OARs, the right and left external iliac (EI), internal iliac (II), and obturator (OB) groups of PLNs were contoured separately on the CT dataset for each patient in the present study, following international consensus guidelines. Treatment planning was conducted on HDR Plus 3.0 planning software, with a dose of 7 Gy per fraction for 3 fractions prescribed to the HRCTV in both ISBT and ICBT cases. The plan was reviewed by two radiation oncologists, who analyzed dose-volume histogram parameters, specifically D90 to the HRCTV and D2cc to the bladder, rectum, and sigmoid.

Dosimetric analysis

Nodal regions were contoured on the planning CT scans following nodal contouring guidelines (reference) (Figures 1 and 2). The average doses received by each nodal group, based on laterality (i.e., left and right), were calculated for all patients. Individual patient results were then calculated and averaged across all patients in the study, within the respective ICBT or ISBT groups. The mean and median absolute doses to each PLN group were recorded. Corresponding EQD2 values (α/β=10) were then calculated for the mean doses.

Statistical analysis

At the end of the study, the data were analyzed statistically using the Statistical Package for the Social Sciences (SPSS) version 22. Mann–Whitney U-test was used. $P<0.05$ was considered as significant.

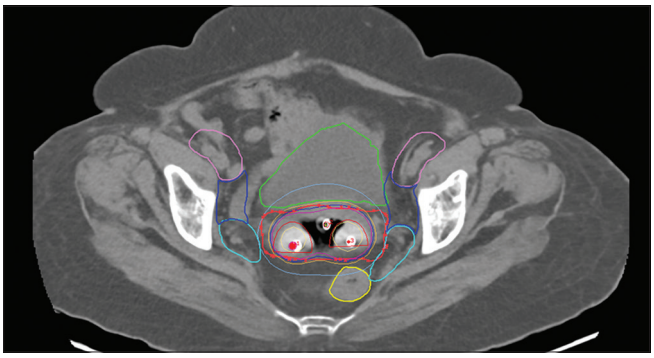

Figure 1: Pelvic lymph node contoured in one of the patients who underwent intracavitary brachytherapy procedure at our center

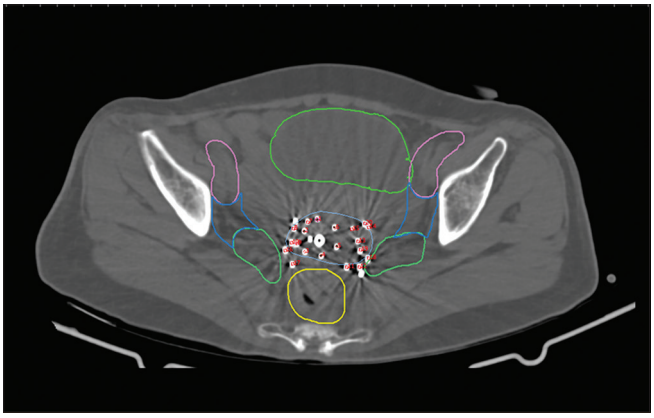

Figure 2: Pelvic lymph node contoured in one of the patients who underwent interstitial brachytherapy procedure at our center

RESULTS

A total of 40 patients of histologically proven carcinoma cervix were included in the present study in which CTRT was carried out. Our study included patients from age group 30 to 70 years. Majority of patients were in the age range of 51–60 years (30%) with mean age of 51 years. The present study included patients from FIGO stage IIA to IVA. Maximum patients were having stage IIB (30%). Majority of patients included in our study received 3D CRT technique accounting to 65%. All the patients included in our study included patients who have received at least five cycles of concurrent cisplatin to a dose of 40 mg/m^2.

On dosimetric analysis, we found per fraction EQD2 dose contribution to EI, II, and OB group of lymph nodes in patients who underwent that ICBT application is 0.5631 Gy, 1.1143 Gy, and 1.2847 Gy, respectively, whereas in patients who underwent that ISBT application is 0.4586 Gy, 0.8653 Gy, and 1.1392 Gy, respectively. Mean dose contribution to the EI, II, and OB group of lymph nodes in patients who underwent ICBT and ISBT are mentioned in Tables 1-3.

DISCUSSION

Cervical cancer is predominantly managed through definitive chemoradiation followed by BT. In recent years, image-guided brachytherapy (BT) has largely replaced the conventional point A-based dosing system previously standard in gynecological BT. Reported PLN metastasis rates vary by FIGO stage: 10–45% in stage IIA, 26–62% in stage IIB, 39–59% in stage IIIA, and 39–88% in stages IIIB/IV. This study aimed to deliver a combined EQD2 dose to the primary tumor (GTV-P and GTV-N) using EBRT followed by BT to a total of 80–90 Gy. Best practices suggest that concurrent chemoradiation with BT should be completed within 8 weeks to avoid treatment breaks, as delays in overall treatment time are linked to poorer outcomes.[11] While the primary tumor dose is well characterized, the dose received by PLNs during BT remains uncertain. Therefore, this study was designed to quantify the dose contribution to PLN groups from HDR BT in patients with cervical cancer.

The previous studies by Chua et al.,[6] Bacorro et al.,[7] Mohamed et al.,[8] Wakatsuki et al.[9] Lee et al.,[10] and have evaluated dose contributions to PLN groups from BT using CT-based planning, with doses prescribed to point A. Chua et al.,[6] reported dose in pelvic group of lymph nodes with the use of two separate dose fractionation schedules (5 and 6 Gy/fraction) on 40 patients. In their study, BT dose of 5Gy was prescribed to point A, mean EQD2 doses received by the EI, II and OB groups were found to be 0.71, 1.04, and 1.27Gy, respectively. Also with BT dose prescription of 6Gy, average EQD2 doses received by the EI, II, and OB groups were 1.08, 1.49, and 1.77Gy, respectively. In the present study, we used volume-based prescription with a dose of 7Gy/fraction to HRCTV, mean EQD2 received by the EI, II, and OB groups in patients who underwent that ICBT was 0.56, 1.14, and 1.28Gy, respectively, but in patents who underwent ISBT, dose received was 0.45, 0.86, and 1.13Gy, respectively.

Lee et al.,[10] reported that the total EQD2 dose to lymph node groups ranged from 4.1 to 9.5% of the prescribed dose, with the OB group receiving the highest dose among the nodal groups. In the present study, using a volume-based prescription, the total mean bilateral EQD2 from BT ranged from 7.4 to 19% of the prescribed dose across all groups.

The results of our study indicate that PLNs received a significant dose contribution from both ICBT and interstitial HDR BT. We found that the average dose received by pelvic nodal groups across the study population ranged from 7.4 to 19% of the prescribed dose, varying by PLN group. According to our hospital protocol, when aggregating the

Table 1: Mean dose contribution to the external iliac group of lymph nodes in patients who underwent ICBT and ISBT

Per fraction brachytherapy dose contribution (Mean absolute dose, (median; IQR) (Gy)	ICBT	ISBT
Right	0.5793 (0.54, 0.387–0.772)	0.4700 (0.445, 0.34–0.56)
Left	0.6793 (0.64, 0.445–0.912)	0.5700 (0.535, 0.40–0.66)
Average of right and left	0.6292 (0.57, 0.43–0.8825)	0.5200 (0.497, 0.36–0.61)
Corresponding EQD2	0.5631 (0.50, 0.37–0.8003)	0.4586 (0.435, 0.31–0.53)
Mean dose (%)	8%	7.4%

ICBT: Intracavitary brachytherapy, ISBT: Interstitial brachytherapy

Table 2: Mean dose contribution to the internal iliac group of lymph nodes in patients who underwent ICBT and ISBT

Per fraction brachytherapy dose contribution (Mean absolute dose, (median; IQR) (Gy)	ICBT	ISBT
Right	1.0900 (0.91, 0.67–1.44)	0.8662 (0.75, 0.61–1.06)
Left	1.2392 (1.08, 0.77–1.56)	1.0057 (0.87, 0.65–1.25)
Average of right and left	1.1646 (0.92, 0.75–1.49)	0.9359 (0.83, 0.65–0.83)
Corresponding EQD2	1.1143 (0.84, 0.67–1.42)	0.8653 (0.75, 0.57–1.11)
Mean dose (%)	16.5%	13.2%

ICBT: Intracavitary brachytherapy, ISBT: Interstitial brachytherapy

Table 3: Mean dose contribution-obturator group of lymphnodes in patients who underwent ICBT and ISBT

Per fraction brachytherapy dose contribution (Mean absolute dose), (median; IQR) (Gy)	ICBT	ISBT
Right	1.2821 (1.24, 0.86–1.85)	1.0392 (0.94, 0.76–1.13)
Left	1.3914 (1.26, 0.99–1.95)	1.3512 (1.33, 0.84–1.52)
Average of right and left	1.3367 (1.16, 0.99–1.95)	1.1990 (1.12, 0.77–1.32)
Corresponding EQD2	1.2847 (1.08, 0.91–1.92)	1.1392 (1.04, 0.69–1.25)
Mean dose (%)	19%	17%

ICBT: Intracavitary brachytherapy, ISBT: Interstitial brachytherapy

doses across three BT fractions, the cumulative EQD2 doses to the EI, II, and OB nodes were 1.68 Gy, 3.33 Gy, and 3.84 Gy, respectively, in patients who underwent the BTICBT procedure. In contrast, patients receiving BTISBT had cumulative EQD2 doses of 1.35 Gy, 2.58 Gy, and 3.39 Gy for the EI, II, and OB nodes, respectively.

Because there is a scarcity of studies assessing the dose contribution to PLNs from BT, these doses are often regarded as negligible in standard practice and typically overlooked in radiotherapy planning. However, in our study, we found these doses to be significant and suggest that they should not be disregarded.

In summary, nodal regions are intricate structures, and dosimetric calculations for specific nodes depend on factors such as location, size, and mobility. In our study, we evaluated the mean doses received by the EI, II, and OB lymph nodes from both ICBT and ISBT. We also examined dose variations within each group and the percentage of HRCTV D90 received by each PLN. This information not only enhances the limited existing data on this topic but also serves as a valuable resource for radiation oncologists, aiding in the estimation of the necessary boost dose during external beam planning based on the specific locations of the PLNs.

Limitations

1. Sample Size: The study may have a limited sample size, which could affect the generalizability of the findings across a broader population
2. Variability in Patient Anatomy: Individual differences in pelvic anatomy, tumor size, and nodal involvement may introduce variability in dose distribution, making it challenging to generalize the results to all patients with carcinoma cervix
3. Imaging and Delineation Uncertainties: Variability in imaging modalities and delineation methods can impact the accuracy of dose quantification to specific lymph node groups, potentially influencing the consistency of dose estimations across patients
4. Limited Follow-Up: The study may lack long-term follow-up data to evaluate the clinical impact of BT doses on PLN control, overall survival, and potential late toxicity

5. EBRT Variability: Differences in EBRT techniques and boost doses across treatment.

CONCLUSION

Our study shows that the PLN groups receive significant doses during BT treatment planning in the definitive management of carcinoma cervix, and these doses should not be overlooked. This dose contribution to the PLNs should be factored in when planning the external beam boost for involved pelvic nodes to ensure a cumulative tumoricidal effect.

ACKNOWLEDGMENT

Authors would like to express their sincere gratitude to the Head of Department at Victoria Hospital, Bangalore, for his invaluable guidance and support throughout this study. We extend our heartfelt thanks to our fellow colleagues for their collaboration and encouragement, which greatly enriched our research.

We also acknowledge the contributions of the medical physicist, whose expertise was essential in planning and executing the dosimetric calculations. In addition, we appreciate the efforts of the operating theater staff and radiation therapy technicians for their assistance and professionalism, which were crucial to the successful completion of this study.

This research would not have been possible without the collective support and dedication of all authors and everyone involved, and we are truly grateful for your contributions.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin. 2021;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004;22(5):872-880. https://doi.org/10.1200/JCO.2004.07.197
3. Guedea F, Venselaar J, Hoskin P, Hellebust TP, Peiffert D, Londres B, et al. Patterns of care for brachytherapy in Europe: Updated results. Radiother Oncol. 2010;97(3):514-520. https://doi.org/10.1016/j.radonc.2010.09.009
4. Pang L, Yang H, Ning Y and Zheng C. Retrospective analysis of clinicopathological features and prognosis of gynecological small-cell carcinoma. Cancer Manag Res. 2021;13:4529-4540. https://doi.org/10.2147/CMAR.S314686
5. Sakuragi N. Up-to-date management of lymph node metastasis and the role of tailored lymphadenectomy in cervical cancer. Int J Clin Oncol. 2007;12(3):165-175. https://doi.org/10.1007/s10147-007-0661-2
6. Chua GW, Foo YW, Tay GH and Tan DB. Assessing dose contribution to pelvic lymph nodes in intracavitary brachytherapy for cervical cancer. J Contemp Brachytherapy. 2017;9(4):345-353. https://doi.org/10.5114/jcb.2017.69237
7. Bacorro W, Dumas I, Levy A, Rivin Del Campo E, Canova CH, Felefly T, et al. Contribution of image-guided adaptive brachytherapy to pelvic nodes treatment in locally advanced cervical cancer. Brachytherapy. 2017;16(2):366-372. https://doi.org/10.1016/j.brachy.2016.11.016
8. Mohamed SM, Aagaard T, Fokdal LU, Pedersen EM, Lindegaard JC and Tanderup K. Assessment of radiation doses to the para-aortic, pelvic, and inguinal lymph nodes delivered by image-guided adaptive brachytherapy in locally advanced cervical cancer. Brachytherapy. 2015;14(1):56-61. https://doi.org/10.1016/j.brachy.2014.07.005
9. Wakatsuki M, Ohno T, Kato S, Ando K, Noda S, Kiyohara H, et al. Impact of boost irradiation on pelvic lymph node control in patients with cervical cancer. J Radiat Res. 2014;55(1):139-145. https://doi.org/10.1093/jrr/rrt097
10. Lee Y, Rash DL and Stern RL. Variation in high-dose-rate brachytherapy dose contribution among pelvic lymph node groups in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2014;90(1):S478. https://doi.org/10.1016/j.ijrobp.2014.05.1482
11. Perez CA, Grigsby PW, Castro-Vita H and Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys. 1995;32(5):1275-1288. https://doi.org/10.1016/0360-3016(95)00220-S

Authors' Contributions:
DS- Definition of intellectual content, prepared first draft of manuscript, editing, and manuscript submission/revision; **ASK-** Concept, design, editing, review manuscript; **RK-** Editing, review manuscript; **RBK-** Editing, manuscript preparation; review manuscript; **SG-** Data collection; review manuscript; **PSA-** Data collection, review manuscript; **VC-** Data collection, review manuscript.

Work attributed to:
Department of Radiation Oncology, Bengaluru Medical College and Research Institute, Bengaluru, India.

Orcid ID:
Dr. Deepak Sharma - https://orcid.org/0009-0004-6971-616X
Dr. Amrut S Kadam - https://orcid.org/0000-0002-7835-5317
Dr. Ramashish Kumar - https://orcid.org/0009-0008-4568-4684
Dr. Raghavendra BK - https://orcid.org/0009-0006-8705-6489
Dr. Srihari G - https://orcid.org/0009-0005-8393-2210
Dr. Perpetua Shruthi A - https://orcid.org/0009-0003-0819-0574
Dr. Varun Chandra - https://orcid.org/0009-0004-2601-3368

Source of Support: Nil, **Conflicts of Interest:** None declared.