

## Original Article



# Prognostic factors of dose-response relationship for nodal control in metastatic lymph nodes of cervical cancer patients undergoing definitive radiotherapy with concurrent chemotherapy

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## ABSTRACT

**Objective:** Regional control is occasionally unsatisfactory in cervical cancer, with the optimal radiation dose for nodal metastases in definitive radiotherapy (RT) with concurrent chemotherapy (CRT) remaining controversial. We investigated dose-response relationship for nodal local control in cervical cancer.

**Methods:** We identified 115 patients with 417 metastatic nodes who received definitive CRT for cervical cancer with nodal metastases. External beam radiation therapy and brachytherapy plans were summated to determine total dose received by each node. Prognostic factors of nodal control and dose-response relationship were investigated using Cox-regression and restricted cubic spline function.

**Results:** The 2-year progression-free survival rate was 69.4%. Among 43 patients with failures, 17 patients (37.5%) had regional failure included in first failure sites of which all except one were in-field only regional failures. Total 30 nodes showed recurrence at initial metastatic site after treatment. Neutrophil-to-lymphocyte ratio (NLR)  $\geq 3.1$ , total radiation dose (minimum dose received by 98% of the target volume in equivalent dose in 2 Gy per fractions), and initial nodal volume  $\geq 5.29$  mL were poor prognostic factors (all  $p < 0.050$ ) of nodal local control. Restricted cubic spline functions revealed strongest dose-response relationship in high NLR (NLR  $\geq 3.1$ ) and initial nodal volume  $\geq 5.29$  mL subgroup.

**Conclusion:** Initial nodal volume, radiation dose, and NLR were significant factors of nodal local control in cervical cancer; a stronger dose-response relationship was seen in bulky nodes with high NLR. Clinicians may consider these factors when determining the RT dose and the need for boost to nodal metastases in cervical cancer.

**Keywords:** Cervical Cancer; Radiotherapy; Brachytherapy; Dose; Lymph Node; Nodal Control

### Presentation

This study was presented in poster presentation in 2019 American Society for Radiation Oncology annual meeting.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

Conceptualization: L.W.H., K.G.E., K.Y.B.; Data curation: L.W.H.; Formal analysis: L.W.H.; Investigation: L.W.H.; Methodology: K.G.E., K.Y.B.; Project administration: K.G.E., K.Y.B.; Supervision: K.G.E., K.Y.B.; Writing - original draft: L.W.H.; Writing - review & editing: L.W.H., K.G.E., K.Y.B.

### Synopsis

One-third of cervical cancer with nodal metastases had regional failure as first failure, mostly in-field failures. Neutrophil-to-lymphocyte ratio (NLR)  $\geq 3.1$ , radiation dose, and initial nodal volume  $\geq 5.29$  mL were significant factors of nodal control. The strongest radiation dose-response was found in bulky nodes with a high NLR.

## INTRODUCTION

The standard treatment for locally advanced cervical cancer is definitive radiotherapy (RT) with concurrent chemotherapy (CRT). In total, 20%–47% of cervical cancer patients are diagnosed with positive metastatic lymph nodes [1,2]. Consensus on radiation dose for cervical tumor and advances in treatment techniques have resulted in outstanding local control rates, but radiation to metastatic lymph nodes lacks consensus concerning the appropriate dose or technique, occasionally resulting in unsatisfactory treatment outcomes [3-7].

The optimal radiation dose for metastatic lymph node in cervical cancer remains not fully understood. Only few studies proposed the minimal dose level for nodes smaller than a specific volume or diameter [8,9]. Other studies have reported the relationship between nodal control and standardized uptake value (SUV) using positron emission tomography (PET) imaging [6,10,11]. Bacorro et al. [12] demonstrated the effect of nodal dose-volume on nodal control probability with greater benefit of additional doses to larger nodes. Meanwhile, no studies have investigated the relationship between neutrophil-to-lymphocyte ratio (NLR) and nodal control. High NLR has been reported as a factor associated with shifting the systemic immune response towards promoting the radioresistance and rapid tumor growth, thus resulting in poor local control and survival outcomes in cervical cancer [13,14]. Nodal control of cervical cancer is likely to be multifactorial, involving all the above factors simultaneously.

In this study, we investigated the dose-response relationship for metastatic lymph nodes in uterine cervical cancer with the prognostic factors of nodal control rate and attempted to propose the optimal dose for a specific metastatic node.

## MATERIALS AND METHODS

### 1. Patient selection

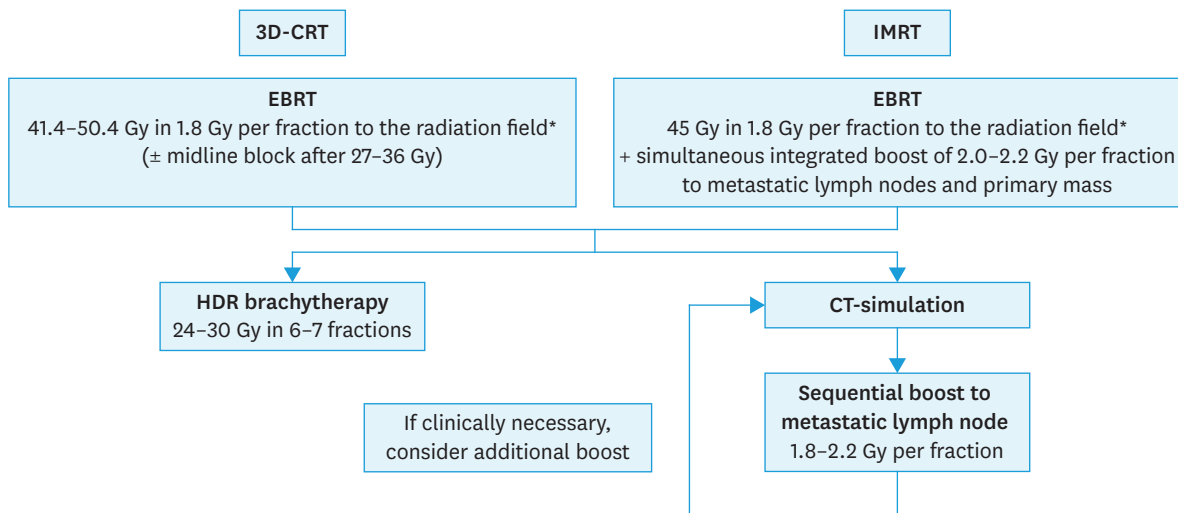
Patients who received definitive CRT for histologically confirmed cervical cancer between January 2013 and September 2017 at our institution were identified (n=275). Patients without nodal metastases (n=133), who received neoadjuvant chemotherapy before RT (n=12), patients without their first follow-up visit after treatment (n=7), and those who did not finish the planned treatment (n=8) were excluded. Finally, 115 patients with 417 nodal metastases were included. The need for informed consent was waived due to the study's retrospective nature. The Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea approved this study (approval number: 4-2020-1005).

### 2. Pre-treatment evaluation and treatment protocols

All patients diagnosed with cervical cancer underwent abdomino-pelvic magnetic resonance imaging (MRI), and PET-computed tomography (CT), with baseline studies consisting of pelvic

examination, chest X-ray, intravenous pyelogram, cystography, sigmoidoscopy, and blood test for staging. The NLR was calculated based on complete blood cell counts performed at baseline study. The 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system was used. Metastatic nodes were defined by radiologists based on significant PET uptake, short-axis diameter of  $\geq 10$  mm, round shape, and/or heterogeneous enhancement.

Patients diagnosed with FIGO stage bulky IB, or FIGO stage IIB or higher received definitive CRT. A flowchart of the treatment for locally advanced cervical cancer in patients receiving definitive CRT in our institution is shown in **Fig. 1**. Detailed indications and treatment schemes for external beam radiation therapy (EBRT) and high-dose rate (HDR)-intracavitary brachytherapy (ICBT) are described elsewhere [15,16]. EBRT was performed using Elekta Infinity linear accelerator and Versa HD (Elekta AB, Stockholm, Sweden) for 3-dimensional conformal radiation therapy (3D-CRT) while TomoTherapy (Accuray Inc., Madison, WI, USA) was used for intensity-modulated radiation therapy (IMRT). For EBRT planning, Pinnacle (version 9.10; Philips Radiation Oncology Systems, Milpitas, CA, USA) and TomoHD radiation treatment planning system (version 5.1.6.1; Accuray Inc.) was used for 3D-CRT and TomoTherapy, respectively. For the treatment planning of HDR-ICBT, a CT-based treatment plan was used. HDR-ICBT was performed using Afterloading MultiSource (version 4.15.1; Eckert & Ziegler BEBIG, Berlin, Germany) with HDR plus (version 3.0; Eckert & Ziegler BEBIG) for treatment planning. On nearing the completion of HDR-ICBT and initial EBRT, CT-simulation was performed to consider boosts to metastatic nodes. Sequential boost (SEB) to the gross metastatic nodes was administered to patients receiving 1.8–2.2 Gy per fraction, followed by another CT-simulation. Based on the physician’s discretion, additional boost was administered if necessary. After the introduction of IMRT, simultaneous-integrated boost was given followed by SEB when nodal response was insufficient after initial EBRT. Planning target volume or nodal boost was defined as the nodal gross tumor volume with a 3–5-mm margin. The boost volume was reduced according to the latest CT-simulation whenever nodal boost was performed.



**Fig. 1.** Flowchart of the treatment selection for locally advanced cervical cancer in patients receiving definitive radiotherapy with concurrent chemotherapy. CT, computed tomography; EBRT, external beam radiation therapy; HDR, high-dose rate; IMRT, intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy.  
\*Semi-extended field for nodal involvement below or at common iliac nodes, extended-field for nodal involvement higher than common iliac nodes, whole-pelvis field with boost to gross nodal volume only considered for patients with 5-fluorouracil/cisplatin chemotherapy.

### 3. Follow-up after treatment

One month after the initial treatment, cervical cancer patients underwent follow-up examinations every 3 months for the first 2 years and once per year thereafter. Patients underwent pelvic examination, tumor marker evaluation, and imaging by CT and/or MRI. PET-CT was performed when findings suggestive of recurrence were noted on CT and/or MRI or tumor marker elevation occurred without evidence of recurrence on CT and/or MRI. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Late toxicities were defined as those occurring 3 months post-treatment.

### 4. Assessment of nodal characteristics

All CT and PET-CT data of each patient were imported into MIM software (MIM Software Inc., Cleveland, OH, USA). All metastatic nodes were separately contoured on MIM software. The volume (in mL) of each node was assessed using both initial CT-simulation and first boost CT-simulation. The ratio of the nodal volume at initial CT-simulation to that at first boost CT-simulation was calculated. The maximum and mean PET SUV values of each node were measured by fusing PET-CT and CT-simulation. The mean dose and the minimum dose received by 98% of the target volume ( $D_{98\%}$ ) to each nodal planning target volume was measured in biologically equivalent dose in 2 Gy per fractions (EQD2) with an  $\alpha/\beta$  value of 10 Gy. The summation of radiation dose was performed using MIM software after importing and summing all EBRT and HDR-ICBT plans for each patient, as both treatment plans were based on CT.

### 5. Statistical analysis

The Kaplan-Meier method and log-rank test were used to estimate and compare ever-nodal recurrence-free rates, progression-free survival (PFS) and overall survival (OS). Ever-nodal recurrence-free interval was measured from the diagnosis date to the date of ever-recurrence in the identical node, considering each node as an independent entity. In case of patient death or salvage surgery, the node was censored. If a viable tumor was found after salvage surgery, then the node was considered to recur at the time of surgery. The Cox-regression model was used to identify factors associated with ever-recurrence in a single node. Regarding the patterns of first failures, regional failure was defined as recurrence in regional lymph node nodes including parametrial, obturator, internal and external iliac, sacral, presacral, common iliac and para-aortic lymph node. Distant failure was defined as any recurrence except local and regional failure. For evaluating NLR and initial nodal volume, the optimal cutoff points for time to ever-nodal recurrence were calculated according to the Contal and O'Quigely's method. Significant factors ( $p < 0.050$ ) in univariate analysis with Cox-regression were entered into the multivariate analysis. For dose-response analysis, patients were grouped into NLR-low and NLR-high groups. Restricted cubic spline function was implemented to examine the non-linear relationship of the ever-nodal recurrence hazard ratio (HR) against nodal PTV  $D_{98\%}$  in EQD2 which remained significant after multivariate Cox-regression analysis. Restricted cubic spline function, a form of regression analysis, was used because not only it can decipher a non-linear relationship between associated factors, but also can take time factor into account which allows to reveal the relationship between HR and a certain clinical factor. Statistical analyses were performed using SPSS software (version 25.0; IBM Inc., Armonk, NY, USA) and R version 4.0.2 (R Foundation, Vienna, Austria; <https://www.R-project.org/>). The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines were followed in the analysis for this study [17].

## RESULTS

Patient and treatment characteristics of the 115 patients are listed in **Table 1**. Most patients were squamous cell carcinoma (97 patients, 84.3%). HDR-ICBT was performed in all patients except 3 patients whose tumor response was poor after EBRT. The nodal and treatment characteristics of all 417 individual nodes are listed in **Table 2**, where 411 nodes (98.6%) received any form of boost, and 98 nodes (23.5%) were classified as para-aortic nodes.

The median follow-up duration for all patients was 44.5 months (range, 8.6–97.6). The 2-year and 5-year OS rates were 95.4% and 85.8%, respectively. The 2-year and 5-year PFS rates were 69.4% and 62.1%, respectively. Forty-three patients (37.4%) experienced any form of failure. The most common form of first failure was distant only failure (20 patients, 46.5%), followed by regional and distant failure (9 patients, 20.0%), and regional only failure (5 patients, 11.6%) (**Table S1**). Among patients who had regional failure included in first failure site (17 patients, 39.5%), recurred regional nodes were in-field only regional failures in 16 patients, and 1 patient had both in-field and out-field regional failures. Patients who had regional failure included in first failure site showed 5-year OS rate of 37.2% (vs. 91.8% in all

**Table 1.** Patient and treatment characteristics

Characteristic	Value
Age (yr)	51 (28–79)
Pathology	
Squamous cell carcinoma	97 (84.3)
Adenocarcinoma	13 (11.3)
Others	5 (4.3)
FIGO stage	
IA	3 (2.6)
IB	19 (16.5)
IIA	4 (3.5)
IIB	66 (57.4)
IIIA	2 (1.7)
IIIB	15 (13.0)
IVA	6 (5.2)
No. of positive nodes	2 (1–15)
RT technique	
3D-CRT	76 (66.1)
IMRT	31 (27.0)
Combined	8 (7.0)
RT field	
Whole pelvis	21 (18.3)
Semi-extended field	45 (39.1)
Extended field	49 (42.6)
Whole-pelvis dose	
45 Gy/25 fractions	102 (88.7)
41.4 Gy/23 fractions	3 (2.6)
50.4 Gy/28 fractions	10 (8.7)
HDR-ICBT dose per fraction (Gy)	5.0 (2.0–6.0)
HDR-ICBT fractions	6 (5–10)
Chemotherapy regimen	
Cisplatin	82 (71.3)
5-Fluorouracil/cisplatin	28 (24.3)
Others	5 (4.4)
NLR	2.7 (0.9–9.7)

Values are presented as number (%) or median (range).

FIGO, International Federation of Gynecology and Obstetrics; HDR, high-dose rate; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiation therapy; NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiation therapy.

**Table 2.** Nodal characteristics

Characteristic	Value
<b>Pathology</b>	
Squamous cell carcinoma	344 (82.5)
Adenocarcinoma	64 (15.3)
Others	9 (2.2)
<b>Location</b>	
Parametrial	6 (1.4)
Obturator	114 (27.3)
Internal iliac	22 (5.3)
External iliac	94 (22.5)
Common iliac	82 (19.7)
Presacral	1 (0.2)
Para-aortic	98 (23.5)
Initial nodal volume (mL)	2.24 (0.22–112.06)
Nodal volume before boost (mL)	0.95 (0.00–39.02)
Ratio of initial nodal volume to nodal volume before boost	0.57 (0.01–3.98)
Nodal max SUV	4.20 (0.20–20.70)
Nodal mean SUV	2.20 (0.10–11.10)
<b>Type of nodal boost</b>	
SEB	286 (68.6)
SIB only	16 (3.8)
SIB followed by SEB	109 (26.1)
No boost	6 (1.4)
Prescribed radiation dose, Gy <sub>EQD2</sub> *	53.10 (40.71–71.92)
EBRT D <sub>98%</sub> of nodal PTV, Gy <sub>EQD2</sub> *	53.44 (31.33–70.75)
EBRT D <sub>mean</sub> of nodal PTV, Gy <sub>EQD2</sub> *	54.40 (35.28–73.70)
HDR-ICBT D <sub>98%</sub> of nodal PTV, Gy <sub>EQD2</sub> *	2.43 (0.00–17.74)
HDR-ICBT D <sub>mean</sub> of nodal PTV, Gy <sub>EQD2</sub> *	2.95 (0.00–25.21)
Total (EBRT+ HDR-ICBT) D <sub>98%</sub> of nodal PTV, Gy <sub>EQD2</sub> *	56.87 (31.33–79.22)
Total (EBRT+ HDR-ICBT) D <sub>mean</sub> of nodal PTV, Gy <sub>EQD2</sub> *	58.36 (35.28–85.08)

Values are presented as number (%) or median (range).

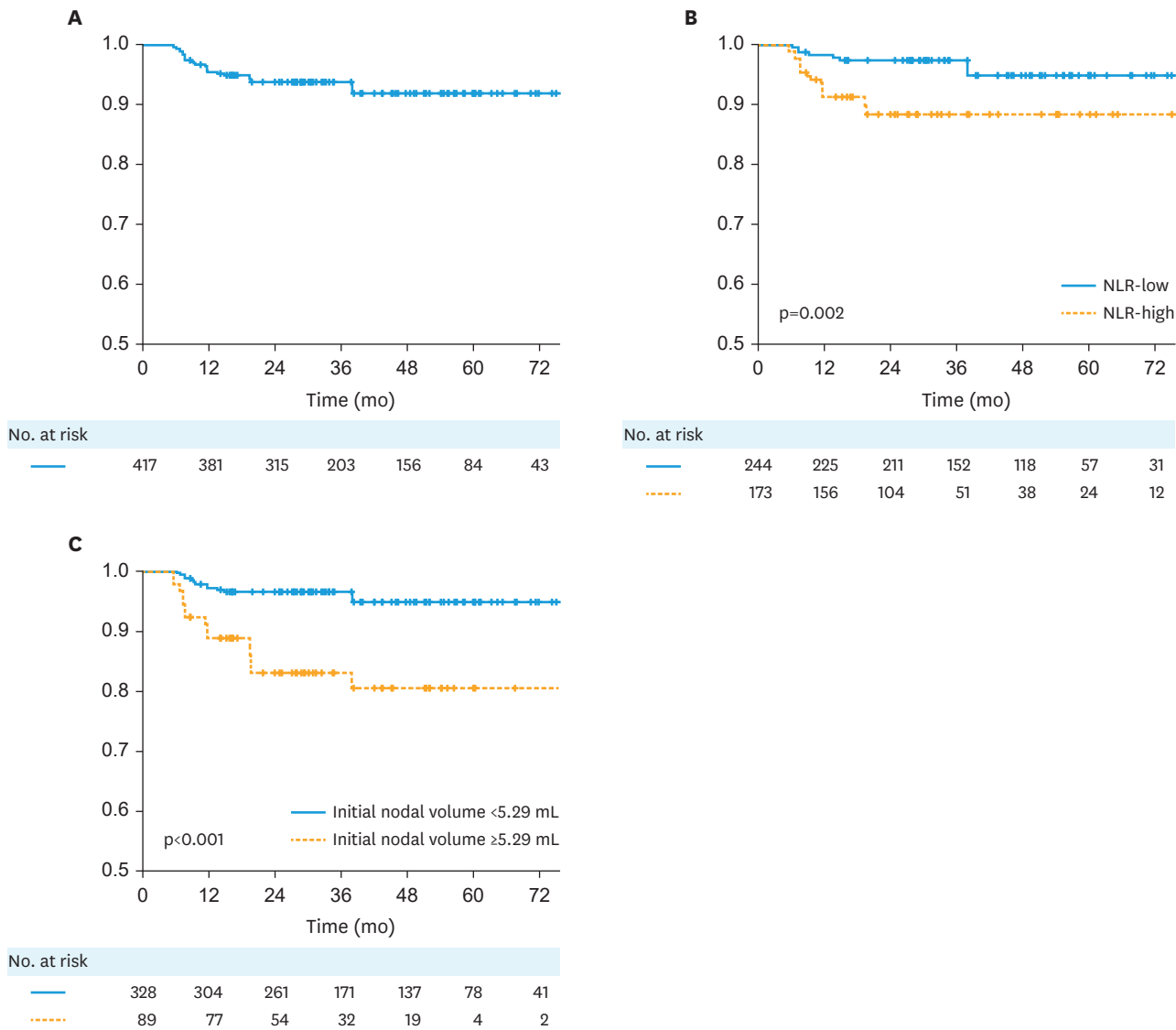
D<sub>mean</sub>, mean dose; D<sub>98%</sub>, minimum dose received by 98% of the target volume; EBRT, external beam radiation therapy; EQD2, equivalent dose in 2 Gy per fractions; HDR, high-dose rate; ICBT, intracavitary brachytherapy; SIB, simultaneous integrated boost; SEB, sequential target boost; SUV, standardized uptake value; PTV, planning target volume.

\*Equivalent dose at fractionation of 2 Gy ( $\alpha/\beta=10$  Gy).

other patients,  $p < 0.001$ , **Fig. S1**). In multivariate analysis of OS, pathology of adenocarcinoma (vs. squamous cell carcinoma), higher FIGO stage, and primary mass size were significant factors (**Table S2**) whereas pathology of adenocarcinoma (vs. squamous cell carcinoma), higher FIGO stage, and NLR  $\geq 3.1$  (vs.  $< 3.1$ ) were significant factors regarding PFS (**Table S3**). The 1-year and 2-year PFS rates for NLR  $\geq 3.1$  (vs.  $< 3.1$ ) patients were 53.8% (vs. 90.8%) and 48.5% (vs. 80.2%), respectively ( $p = 0.002$ , **Fig. S2**). Among all patients, 14 experienced grade  $\geq 3$  treatment-related toxicities (**Table S4**). For all patients with grade 3 or higher toxicities, RT plans were reviewed in search for those related to lymph node boosts. Plan reviews revealed one patient with grade 4 duodenum ulcer perforation that occurred 4 months after definitive CRT with boost to metastatic para-aortic node to 57.25 Gy<sub>EQD2</sub>.

The median follow-up duration for total nodes was 34.7 months (range, 5.6–95.2). In total, 30 nodes showed recurrence at the initial site. The 1-year and 2-year ever-nodal recurrence-free rates were 95.4% and 93.7%, respectively (**Fig. 2A**). **Table 3** shows the results of Cox-regression analysis for ever-nodal recurrence of each node. An NLR of 3.1 and an initial nodal volume of 5.29 mL were found to be the optimal cutoff values. In multivariate analysis, NLR  $\geq 3.1$  (vs.  $< 3.1$ ), initial nodal volume  $\geq 5.29$  mL ( $< 5.29$  mL), and total (EBRT+HDR-ICBT) D<sub>98%</sub> of nodal PTV in EQD2 (all  $p < 0.050$ ) were significant prognostic factors for ever-nodal recurrence. In the NLR-low (NLR  $< 3.1$ ) and NLR-high (NLR  $\geq 3.1$ ) groups, the 2-year ever-

**Dose-response of node metastasis in cervix cancer**



**Fig. 2.** Kaplan-Meier curves of ever-nodal recurrence-free rate in total patients (A), according to NLR-low (<3.1) and NLR-high (≥3.1) group (B), and according to initial nodal volume (<5.29 mL vs. ≥5.29 mL) (C). NLR, neutrophil-to-lymphocyte ratio.

nodal recurrence rates were 97.5% and 88.4%, respectively (p=0.002) (**Fig. 2B**). In nodes with initial volume <5.29 mL and ≥5.29 mL, the 2-year ever-nodal recurrence-free rates were 96.5% and 83.0%, respectively (p<0.001) (**Fig. 2C**).

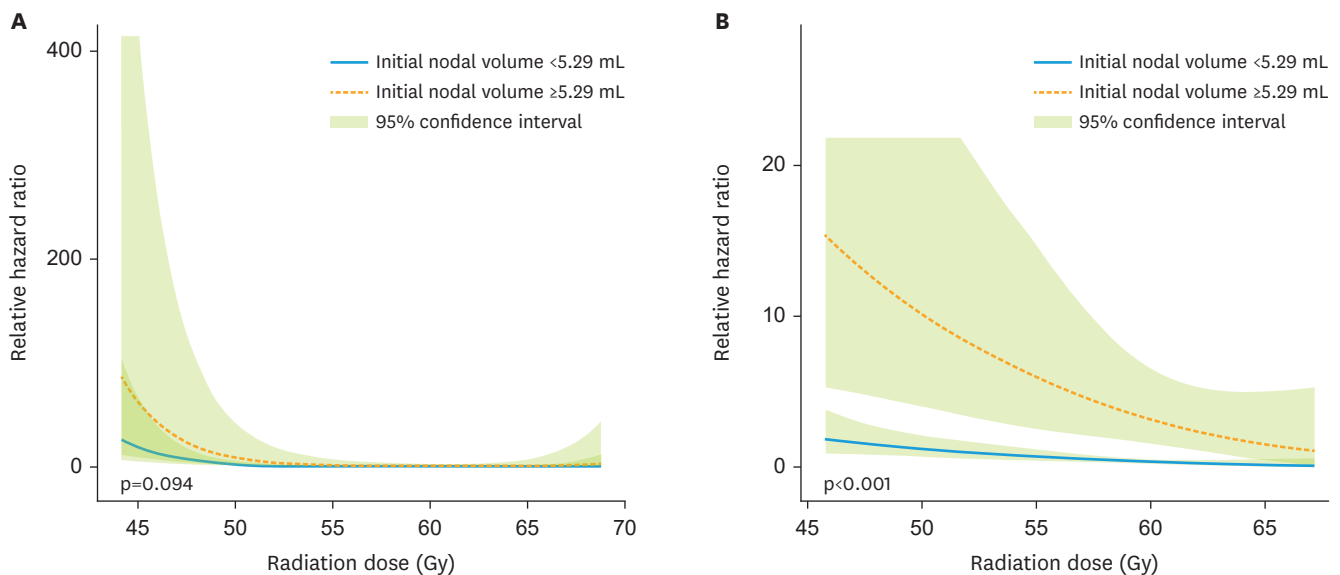
For further analysis of dose-response relationship depending on risk factors, total nodes were stratified into NLR-high and NLR-low groups. **Fig. 3** shows a relationship between radiation dose and relative HR of ever-nodal recurrence using restricted cubic spline function for the NLR-low and NLR-high groups, respectively. In the NLR-low group, the relative HR of ever-nodal recurrence showed much weaker relationship with the radiation dose in any dose range than that in the NLR-high group regardless of nodal volume. For 50 Gy<sub>EQD2</sub> and 60 Gy<sub>EQD2</sub>, the respective relative HRs in NLR-low group were approximately 2.68 (95% confidence interval [CI]=1.21–5.93) and 0.30 (95% CI=0.17–0.52) for an initial nodal volume of <5.29 mL and 9.25 (95% CI=1.98–43.24) and 0.99 (95% CI=0.31–3.13) for an initial nodal volume of ≥5.29

**Dose-response of node metastasis in cervix cancer**

**Table 3.** Cox regression model for ever-nodal recurrence

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
<b>Pathology</b>				
Squamous cell carcinoma	Reference value	0.863		
Adenocarcinoma	1.31 (0.50–3.43)	0.588		
Others	NA	0.980		
NLR ( $\geq 3.1$ vs. $< 3.1$ )	3.10 (1.43–6.72)	0.004	2.52 (1.15–5.53)	0.021
RT modality (IMRT vs. 3D-CRT)	0.35 (0.12–1.02)	0.156		
<b>RT field</b>				
Whole pelvis	Reference value	0.273		
Semi-extended field	0.75 (0.14–4.09)	0.739		
Extended field	1.70 (0.40–7.22)	0.472		
No. of positive nodes	1.04 (0.95–1.14)	0.353		
Location (para-aortic or common iliac vs. pelvic)	2.82 (1.28–6.20)	0.010		
Total (EBRT+ HDR-ICBT) $D_{98\%}$ of nodal PTV (per 1 Gy <sub>EQD2</sub> *)	0.87 (0.83–0.92)	<0.001	0.86 (0.82–0.90)	<0.001
Total (EBRT+HDR-ICBT) $D_{mean}$ of nodal PTV (per 1 Gy <sub>EQD2</sub> *)	0.89 (0.84–0.94)	<0.001		
Initial nodal volume ( $\geq 5.29$ mL vs. $< 5.29$ mL)	3.99 (1.95–8.18)	<0.001	5.72 (2.74–11.95)	<0.001
Ratio of nodal volume before EBRT to that after EBRT (per 1)	1.52 (0.69–3.37)	0.298		
Nodal max SUV	1.06 (0.98–1.15)	0.118		
Nodal mean SUV	1.13 (0.92–1.39)	0.263		

CI, confidence interval; NA, not applicable;  $D_{mean}$ , mean dose received by target volume;  $D_{98\%}$ , minimum dose received by 98% of the target volume; EBRT, external beam radiation therapy; HDR, high-dose rate; HR, hazard ratio; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiation therapy; NLR, neutrophil-to-lymphocyte ratio; PTV, planning target volume; RT, radiotherapy; SUV, standardized uptake value; 3D-CRT, 3-dimensional conformal radiation therapy.  
\*Equivalent dose at fractionation of 2 Gy ( $\alpha/\beta=10$  Gy).



**Fig. 3.** Restricted cubic spline functions for radiation equivalent dose in a fraction of 2 Gy according to initial nodal volume in NLR-low ( $< 3.1$ ) (A) and NLR-high ( $\geq 3.1$ ) (B) groups.  
NLR, neutrophil-to-lymphocyte ratio.

mL. The initial nodal volume did not significantly affect the dose-response relationship in the NLR-low group ( $p=0.094$ ). For 50 Gy<sub>EQD2</sub> and 60 Gy<sub>EQD2</sub> in NLR-high group, the relative HRs were 1.25 (95% CI=0.73–2.14) and 0.39 (95% CI=0.27–0.57) for an initial nodal volume of  $< 5.29$  mL and 10.20 (95% CI=3.97–26.17) and 3.21 (95% CI=1.57–6.56) for an initial nodal volume of  $\geq 5.29$  mL. In the NLR-high group, nodes with an initial nodal volume of  $\geq 5.29$  mL showed a significantly higher relative HR than nodes with an initial volume of  $< 5.29$  mL ( $p<0.001$ ), showing the most vivid relationship between relative HR of ever-nodal recurrence and radiation dose.



## DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the dose-response relationship combining the above factors to suggest nodal subgroups for boost and target doses for a specific metastatic lymph node in cervical cancer. Our study demonstrated the radiation dose-response relationship in metastatic lymph nodes in cervical cancer and prognostic factors of nodal control rate. NLR, a recently known key prognostic factor in cervical cancer was revealed as a novel nodal response prognostic factor. A stronger dose-response relationship was noted in the NLR-high group compared to that in the NLR-low group, especially in bulky nodes.

With the image-guided brachytherapy, local control rate in cervical cancer has significantly improved, but this has not been the case for regional control [3-5]. The recently revised 2018 FIGO staging system for cervical cancer now directly stages any cervical tumor with nodal metastases to FIGO stage IIIC, as they have poorer survival compared to those without nodal metastases [18]. Recently published EMBRACE-I study also underlines the significance of nodal control, as para-aortic nodal failures occur frequently along with total nodal failure rate of 16% in node-positive patients [19,20]. Our study showed that 17 (14.8%) of the 115 cervical cancer patients had any form of regional failure as first failure (**Table S1**). More importantly, these patients had remarkably poor survival outcomes compared to other patients. Notably, all these patients had in-field regional failures, suggesting the importance of specifying the high-risk metastatic nodes and giving sufficient radiation dose to improve survival outcomes in these patients. To improve nodal control, some studies have proposed threshold doses for metastatic nodes with certain sizes [9,21,22], while others suggested nodal SUV as a prognostic factor for nodal control as well [11,23]. Nevertheless, these studies lacked comprehension of the multifactorial process of nodal control. Here, not only radiation dose and volume but also nodal SUV, hematologic factors, and interim volume response were all combined to identify the most significant prognostic factors of nodal control.

Recent study demonstrated a continuous dose-volume relationship, without taking time factor into account [12]. Moving further, our study is the first to report the dose-response relationship with taking time factor into account. To accurately determine the radiation dose-response relationship, we incorporated all EBRT and HDR-ICBT plans to precisely measure the affected dose in each node. As a result, location of nodes which was significant factor in univariate Cox-regression for ever-nodal recurrence, were not significant after multivariate analysis. Brachytherapy is known to affect pelvic cavity nodes at the dose of 2–4 Gy<sub>EQD2</sub>, in accordance with our results [24-26]. It is reasonable to understand that the lower nodal recurrence rate of pelvic nodes compared to para-aortic nodes is partly due to the additional scattered dose from HDR-ICBT.

Pre-existing high NLR and tumor-related leukocytosis are significantly related to poor tumor response, decreased OS and PFS in cervical cancer although the exact mechanism remains unknown [13,27,28]. Studies have found that pre-existing high NLR and tumor-related leukocytosis are consequences of systemic inflammatory response related to carcinogenesis and tumor progression [29]. Moreover, granulocyte colony-stimulating factor released by the tumor could increase neutrophil counts along with myeloid-derived suppressor cells, which cause rapid progression and radioresistance [14]. Therefore, we believed NLR, a factor that reflects the systemic inflammatory response and tumor microenvironment, could be used to predict nodal response as well. In this study, NLR was significantly associated with poor nodal control as well as decreased PFS. This study is the first to identify NLR as

an independent factor affecting nodal control, emphasizing that radiation dose should be individualized according to the patient's immuno-oncologic characteristics.

Here, PET SUV did not appear to be a significant factor of nodal recurrence, in contrast to previous studies [10,11]. Limited analysis upon interim metabolic response because of the lack of interim PET in our patients might have caused this discrepancy, as some studies suggested that metabolic response is related to survival outcomes and nodal control [6,10]. It is well-known that metastatic nodes undergo substantial volume change during RT [30]. However, interim volume response was not significant factor of nodal recurrence, contrary to the finding of a previous study [31]. However, Bacorro et al. [12] suggested that interim radiologic response might not be a reliable indicator of nodal control, in line with our results. Incorporating other significant factors such as NLR might have also contributed to the dilution of the significance of nodal SUV or interim volume response.

Restricted cubic spline functions demonstrated the strongest dose-response relationship in the NLR-high and initial nodal volume  $\geq 5.29$  mL subgroup. This provides valuable information as it could suggest the nodal subgroup where boost should be considered along with possible target doses. The positive dose-response relationship in high NLR, initial nodal volume  $\geq 5.29$  mL subgroup stretched beyond 60 Gy<sub>EQD2</sub>. In this group, nodal boost beyond 60 Gy<sub>EQD2</sub> seems a considerable option to achieve maximal nodal control. Yet, the risk-benefit of nodal boost should be carefully weighted, although only one  $\geq G3$  toxicity related to nodal boost was noted. It is uncertain whether the benefit of nodal control outweighs the risk of boost even in these nodes. Considering the excellent absolute control rate in nodes with low NLR and initial nodal volume of  $< 5.29$  mL, 50–55 Gy using simultaneous integrated boost without additional SEB seems to be a reasonable option. By omitting unnecessary boost, the risk of radiation-related toxicity can be reduced along with overall treatment time, a well-known factor related to treatment outcomes in cervical cancer [32–34].

There are several limitations in this study. The metastatic nodes were not pathologically confirmed, but clinically diagnosed based on suspicious findings from imaging studies. This was a retrospective study performed at a single institution with a limited number of patients. The value of risk groups based on NLR should also be interpreted carefully, because validation using an independent dataset is necessary to solidify the results from this study. Dose-response relationship regarding nodal subgroups warrant caution also. Number of nodes per subgroups are limited, resulting in some widely varying CIs. Nonetheless, there are some apparent strengths of our study. For the first time, it investigated the multifactorial process in nodal response and identified NLR as a novel factor affecting nodal control. We demonstrated the dose-response relationship as a continuous function of radiation dose incorporating both EBRT and HDR-ICBT dose in different clinical risk groups, suggesting optimal subgroup where nodal boost would most likely come with the largest clinical benefit.

In conclusion, we identified initial nodal volume, radiation dose, and NLR as significant nodal control factors. A strong dose-response relationship was noted in the NLR-high and initial nodal volume  $\geq 5.29$  mL subgroup beyond 60 Gy<sub>EQD2</sub>. Clinicians may consider these prognostic factors and give boosts to bulky nodes in high NLR patients wherein the dose-response benefit is greatest, while carefully weighing the risk-benefit ratio. Further validation is necessary to clarify the oncologic outcomes of individualized nodal boosts in cervical cancer patients receiving definitive CRT.

## SUPPLEMENTARY MATERIALS

### Table S1

Pattern of first failures

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### Table S2

Cox regression model for overall survival

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### Table S3

Cox regression model for progression-free survival

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### Table S4

Grade  $\geq 3$  treatment-related toxicities

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### Fig. S1

Kaplan-Meier curves of overall survival in total patients according to regional nodal failure as first failure.

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### Fig. S2

Kaplan-Meier curves of progression-free survival in total patients according to NLR.

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