Observational Study

Medicine®

OPEN

Clinical impact of boost irradiation to pelvic lymph node in uterine cervical cancer treated with definitive chemoradiotherapy

Kyu Hye Choi, MD[a], Ji Yoon Kim, MD[a], Dong Soo Lee, MD, PhD[b], Yun Hee Lee, MD[c], Sea-Won Lee, MD[a], SooYoon Sung, MD[a], Hee Hyun Park, MD[a], Sei-Chul Yoon, MD, PhD[d], Soo Young Hur, MD, PhD[e], Jong-Sup Park, MD, PhD[e], Yeon Sil Kim, MD, PhD[a,*]

Abstract

The aim of this study was to analyze tumor control and clinical outcomes of patients with uterine cervical cancer treated by chemoradiotherapy according to pelvic lymph node (PLN) positivity and boost irradiation to PLN and to determine toxicities associated with boost irradiation.

We retrospectively reviewed patients with uterine cervical cancer treated with chemoradiotherapy between March 2000 and April 2015. Clinical characteristics, failure pattern, and survival outcomes of patients with or without PLN metastasis and those with or without boost irradiation were analyzed.

A total of 80 cases were PLN-negative and 46 were PLN-positive. A total of 11 patients underwent PLN boost irradiation. The 2-year and 5-year overall survival (OS) rates showed significant difference between the PLN-positive and PLN-negative groups ($P = .010$). The 2-year and 5-year progression-free survival (PFS) rates showed significant difference between the 2 groups ($P = .032$). The 2-year and 5-year OS rates of the no-boost irradiation group were 82.9% and 58.3%, respectively, whereas all patients in the boost irradiation group were alive at the time of analysis ($P = .065$). There was no recurrence in the boost irradiation group. The difference in PFS was significant between the boost and the no-boost irradiation groups ($P = .023$). The 2-year and 5-year pelvic-recurrence free survival (PRFS) did not show significant difference but the tendency of increased risk of pelvic recurrence in no-boost group (boost vs no-boost; 81.9% and 70.2% vs 100% and 100% in 2-year and 5-year PRFS, respectively, $P = .156$). Boost irradiation to PLN could improve locoregional control especially in large pelvic LN (≥1.5 cm). Our results showed that only 1 acute and late toxicity of higher than grade 3 occurred.

PLN metastasis was significant prognostic factor in cervix cancer treated by chemoradiotherapy. In the boost irradiation group, there was no recurrence or death with significantly better PFS. Boost irradiation to PLN is expected to improve locoregional control, but further follow-up and assessment are needed.

Abbreviations: CI = confidence interval, CR = complete response, CT = computed tomography, EBRT = external beam radiotherapy, ECOG = Eastern Cooperative Oncology Group, EFRT = extended field radiotherapy, FIGO = International Federation of Gynecology and Obstetrics, GI = gastrointestinal, GU = genitourinary, Hb = hemoglobin, HDR-ICR = high-dose-rate intracavitary brachytherapy, HR = hazard ratio, IMRT = intensity modulated radiation therapy, IRB = Institutional review board, LN = lymph node, MRI = magnetic resonance imaging, NA = not available, OS = overall survival, PC = pelvic control, PFS = progression free survival, PLN = pelvic lymph node, PR = partial response, PRFS = pelvic-recurrence free survival, RECIST = Response Evaluation Criteria in Solid Tumors, RTOG = Radiation Therapy Oncology Group, SCC = squamous cell carcinoma, SCC Ag = squamous cell carcinoma antigen, SD = stable disease, SUVmax = maximum standard uptake value.

Keywords: boost irradiation, cervix cancer, chemoradiotherapy, pelvic lymph node, radiotherapy dosage

Editor: Maohua Xie.

The authors report no conflicts of interest.

[a] Department of Radiation Oncology, Seoul St. Mary's Hospital, [b] Department of Radiation Oncology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [c] Department of Radiation Oncology, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju-si, Gyeongsangnam-do, [d] Department of Radiation Oncology, Bucheon St. Mary's Hospital, [e] Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

[*] Correspondence: Yeon Sil Kim, Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea (e-mail: yeonkim7@catholic.ac.kr).

Medicine (2018) 97:16(e0517)

Received: 30 August 2017 / Received in final form: 31 January 2018 / Accepted: 28 March 2018

http://dx.doi.org/10.1097/MD.0000000000010517

1. Introduction

Uterine cervical cancer is the fourth common female malignancy. A total of 528,000 new cases were diagnosed worldwide in 2012.[1] According to the statistics in Republic of Korea, 3633 new cases of uterine cervical cancer were diagnosed (7th common female cancer prevalence) and 892 cancer deaths (9th common female mortality rate) were reported in 2013.[2] Treatment of locally advanced cervical cancer has been changed from hysterectomy and lymphadenectomy to concurrent chemoradiation as a curative treatment. With improvement in treatment modality, cancer mortality rate is decreasing over time.

It has been reported that lymph node (LN) positivity is the most significant prognostic factor for recurrence and death of patients with cervical cancer, followed by the size of primary mass.[3] A study has reported that the 5-year survival rate is reduced from 85% to 90% to 30% to 50% in patients with positive pelvic lymph nodes (PLNs).[4] Before the era of concurrent chemoradiation, surgical resection of metastatic LNs was the mainstay of treatment. Incidence of LN involvement in uterine cervical cancer after hysterectomy has been reported to be more than 11.4% in stage IB and 21.5% in stage IIB disease.[5] Furthermore, positive PLNs frequently lead to para-aortic nodal spread and systemic dissemination of the disease. Therefore, many studies have been conducted on prophylactic irradiation of the para-aortic nodal area.[6–9]

In many facilities, boost irradiation is used empirically if LNs are involved. However, few reports have clearly demonstrated the benefit of boost irradiation on the involved LNs or the adequate dose of boost irradiation.[10,11] Some studies have expressed concern that giving high-dose boost irradiation to pelvic nodes might increase the risk of acute or late genitourinary (GU) and gastrointestinal (GI) toxicities. Therefore, the objective of this study was to examine tumor control and clinical outcomes according to PLN positivity and boost irradiation to PLNs. We also determined the toxicities associated with boost irradiation.

2. Methods

2.1. Patients

Between March 2000 and April 2015, a total of 222 patients with uterine cervical cancer received concurrent chemoradiation therapy on the pelvis with curative intent in the Department of Radiation Oncology at Seoul St. Mary's Hospital and Uijeongbu St. Mary's Hospital. Of these patients, 87 patients who did not have pelvic magnetic resonance imaging (MRI) or computed tomography (CT), so that PLN positivity cannot be determined, 4 patients who received neoadjuvant chemotherapy, 1 patient who was diagnosed of microinvasive carcinoma in biopsy, and 4 patients who had follow-up loss were excluded. The remaining 126 patients were analyzed in this study. The following inclusion criteria were used: International Federation of Gynecology and Obstetrics (FIGO) stage IB–IVA without para-aortic node involvement or distant metastasis at initial diagnosis. Patients were initially evaluated by taking medical history, performing pelvic and physical examination by experienced gynecologists, and acquiring routine hematologic and serum chemistry results including squamous cell carcinoma antigen (SCC Ag). All patients underwent pathologic diagnosis by biopsy. Imaging studies included abdominal and pelvic CT, MRI, or ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan before treatment. A positive LN was defined when a short axis length was greater than 1 cm on CT and/or MRI or a maximum standard uptake value (SUVmax) was higher than the background blood pool activity measured in the thoracic aorta or normal liver parenchymal activity. This study was approved by the institutional review board (Seoul St. Mary's Hospital and Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, reference number: XC16RIMI0079K, XC16RIMI0079U) and informed consent was waived.

2.2. Radiotherapy

Patients were treated with external beam radiotherapy (EBRT) followed by high-dose rate intracavitary brachytherapy (HDR-ICR). All 126 patients received external irradiation to the whole pelvis with 15-MV photons. They underwent CT simulation using an immobilization device for RT planning. All EBRT was planned using Pinnacle treatment planning system (Philips, Amsterdam, The Netherlands). Primary tumor mass, enlarged LNs, the entire uterus, adequate vagina, parametrium, internal, and external iliac lymphatic chain were included in the whole pelvic field. The 4-box technique was used with parallel-opposed anteroposterior-posteroanterior and 90° and 270 ° lateral ports. EBRT was delivered at a total dose up to 50.4 Gy in 28 fractions over 5 to 6 weeks. Initial 45 Gy was delivered to the whole pelvis. Then, 5.4 Gy was administered with a midline block. For patients of enlarged PLN in pretreatment CT/MRI or metabolically active nodes in FDG-PET, boost irradiation was delivered using 4-field box technique. Planning target volumes were defined 1 to 1.5 cm expansions of gross enlarged nodes.

High-dose rate intracavitary radiotherapy was applied in 119 patients using Ir-192 source after EBRT. HDR brachytherapy treatment plan was calculated with Nucletron's PLATO and Oncentra MasterPlan treatment planning systems (Nucletron BV, Veenendaal, The Netherlands). A total dose of 20 to 35 Gy in 4 to 6 fractions (median, 30 Gy in 6 fractions) prescribed to A-points was delivered with HDR-ICR. In this study, the delivered dose with brachytherapy was not considered in the analysis of the total dose to the LNs because brachytherapy was performed with 2D plan in these cases.

2.3. Chemotherapy

Concurrent chemotherapy was administered to all patients. Ninety-nine patients were treated with 5 to 6 cycles of weekly cisplatin (40 mg/m^2) or tri-weekly cisplatin (40 mg/m^2) with etoposide (60 mg/m^2). Twenty-seven patients received 2 or 3 cycles of carboplatin (area-under-the-curve 5) with etoposide or paclitaxel (175 mg/m^2) every 3 weeks.

2.4. Follow-up and evaluation criteria

Patients were evaluated every 3 months for 2 years after completion of treatment. Then, they were then evaluated every 6 months for 3 years. Each time they visited, medical history, physical examination, and pelvic examination were performed. Additional follow-up imaging studies such as abdomen and pelvic CT and/or MRI for response evaluation were done between 3 and 6 months after completion of treatment. Treatment failures were classified as local recurrence, regional PLN recurrence, and distant metastasis. Clinical response was determined using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria based on the follow-up abdomino-pelvic CT and/or MR.[12]

Toxicity was objectively scored according to the Common Terminology Criteria for Adverse Events version 4.0.[13] In this study, toxicities of higher than grade 3 were recorded. Acute toxicities were defined as radiation-induced complication occurring within 3 months after the beginning of radiation therapy. Late toxicities were defined as those occurring after 3 months.

Time to recurrence or progression was measured from the date of pathologic diagnosis to the date of documented event. Overall survival (OS) was defined as the time from pathologic diagnosis of cervix cancer to the date of death of any cause or the date of the last follow-up. Progression-free survival (PFS) was defined as the time from pathologic diagnosis to the date of first failure at any site or the date of the last follow-up or death. Pelvic control (PC) was defined as primary and pelvic nodal control, and pelvic-recurrence free survival (PRFS) was defined the time from pathologic diagnosis to the date of first pelvic-recurrence or the date of the last follow-up or death.

2.5. Statistical analysis

Survival proportions were estimated using the Kaplan–Meier method. To identify prognostic factors independently associated with survival and to estimate hazard ratios (HR), log-rank test and Cox proportional hazards model were applied. Chi-square test and Fisher exact test, Cochran–Armitage trend test or *t* test were used for statistical analysis to determine the correlation between categorical variables. All tests were 2-sided. A *P* value of less than .05 was considered as statistically significant. All statistical analyses were performed using the Statistical Analysis System (SAS) software package version 9.2 for Windows (SAS Institute Inc., Cary, NC). The statistical consultation was supported by a Catholic Medical College Cinical Research Coordinating Center (CMC CRCC).

3. Results

3.1. Tumor and patient characteristics

Among the 126 patients, 80 were PLN-negative while 46 were PLN-positive. Median follow-up duration was 43.1 months (range; 3.5–183.9 months). Age and performance status (Eastern Cooperative Oncology Group or ECOG) at the time of diagnosis, FIGO stage, pathologic diagnosis, initial primary tumor size, parametrial invasion, hemoglobin, and SCC Ag levels before treatment were compared between the 2 groups. There was no significant difference in tumor or patient characteristics between the 2 groups except age and pretreatment SCC Ag levels. After whole pelvic irradiation, 11 out of the 46 PLN-positive patients received additional radiation boosts of 5.4 to 14.4 Gy (median, 5.4 Gy) in 3 to 8 fractions to the enlarged LNs. CT and/or MRI was done once again after the completion of EBRT and before the initiation of intracavitary brachytherapy. The determination of boost was based on the size of the initial LN and follow-up imaging studies were used for boost planning and intracavitary radiation. Tumor and patient characteristics of all patients are summarized in Table 1. Age was significantly different in PLN-negative and positive groups (median, 63 vs 56; $P \leq .0001$). Those of patients with positive PLN are summarized in Table 2.

3.2. Treatment outcomes

Initial clinical response was evaluable for 124 patients after the treatment (median; 43 days, range; 35–81 days). Complete response (CR) and partial response (PR) were identified in 102 and 22 patients, respectively, in the entire patients.

Among the 11 patients who received pelvic node boost irradiation, 8 (72.7%) and 3 (27.2%) had CR and PR, respectively, for primary tumor. Of the 35 patients who did not receive pelvic nodal boost, 26 patients (73.7%) and 8 patients (22.9%) had CR and PR, respectively, and 1 patient did not have

Table 1

Clinical characteristics in patients according to pelvic lymph node (PLN) positivity.

		Entire patients (n = 126)	No LN involvement (n = 80)	LN involvement (n = 46)	*P*
Age, y	Median (range)	60.5 (27–85)	63 (43–85)	56 (27–83)	<.0001
ECOG (%)	≤1	93 (73.8)	55 (68.8)	38 (82.6)	.089
		33 (26.2)	25 (31.3)	8 (17.4)	
FIGO stage (%)	IB	4 (3.2)	4 (5)	0	.16
	IIA	3 (2.4)	1 (1.3)	2 (4.4)	
	IIB	92 (73.0)	59 (73.8)	33 (71.7)	
	IIIA	10 (7.9)	8 (10)	2 (4.4)	
	IIIB	10 (7.9)	5 (6.3)	5 (10.9)	
	IVA	7 (5.6)	3 (3.8)	4 (8.7)	
Histology (%)	SCC	117 (92.9)	74 (92.5)	43 (93.5)	.839
	Adenocarcinoma	7 (5.6)	5 (6.3)	2 (4.4)	
	Others	2 (1.6)	1 (1.3)	1 (2.2)	
Primary tumor size, cm	Median (range)	4.1 (1.2–8.5)	4 (1.2–8.5)	4.3 (2.1–8.0)	.134
Parametrial invasion	Present	119 (94.4)	75 (93.8)	44 (95.7)	1
(%)	Absent	7 (5.6)	5 (6.3)	2 (4.4)	
Pretreatment Hb,	Median (range)	11.9	12.1	11.5	.065
g/dL		(6.7–14.6)	(6.7–14.5)	(8.5–14.6)	
Pretreatment SCC Ag,	Median (range)	4.7	3.9	10.1	.053
ng/mL		(0.20–102.13)	(0.20–102.13)	(1.09–62.83)	

Datas are presented as n (%) for categorical variables and median (min-max) for continuous variables.

P values are calculated using Chi-square test, Fisher exact test, Cochran–Armitage trend test, or *t* test.

ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, Hb = hemoglobin, LN = lymph node, NA = not available, PLN = pelvic lymph node, SCC Ag = squamous cell carcinoma antigen, SCC = squamous cell carcinoma.

Table 2

Clinical characteristics in patients according to lymph node boost.

		No LN boost (n = 35)	LN boost (n = 11)	*P*
Age, y	Median (range)	57 (27–83)	53 (34–70)	.958
ECOG (%)	≤1	27 (77.1)	11 (100)	.169
	>2	8 (22.9)	0	
FIGO stage (%)	IB	0	0	.451
	IIA	2 (5.7)	0	
	IIB	23 (65.7)	10 (90.9)	
	IIIA	2 (5.7)	0	
	IIIB	5 (14.3)	0	
	IVA	3 (8.6)	1 (9.1)	
Histology (%)	SCC	32 (91.4)	11 (100)	.604
	Adenocarcinoma	2 (5.7)	0	
	Others	1 (2.9)	0	
Number of node(s)	1	20 (58.8)	4 (44.4)	.1
	2	14 (41.2)	3 (33.3)	
	3	0	2 (22.2)	
Size of node(s), cm	Median (range)	1.35 (0.8–5.0)	2.8 (0.8–9.2)	.448
Primary tumor size, cm	Median (range)	4.1 (2.2–7.2)	4.5 (2.1–8.0)	.134
	>4	19 (54.3)	9 (81.8)	.16
Parametrial invasion (%)	Present	33 (94.3)	11 (100)	1
	Absent	2 (5.7)	0	
Pretreatment Hb, g/dL	Median (range)	11.4 (8.5–14.6)	11.7 (9.2–13.5)	.845
Pretreatment SCC Ag, ng/mL	Median (range)	9.28 (1.09–62.83)	12.94 (1.56–22.79)	.724

Datas are presented as n (%) for categorical variables and median (min-max) for continuous variables.

P values are calculated using Chi-square test, Fisher exact test, Cochran–Armitage trend test, or *t* test.

ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, Hb = hemoglobin, LN = lymph node, NA = not available, SCC Ag = squamous cell carcinoma antigen, SCC = squamous cell carcinoma.

information available. The response for pelvic nodes in the boost group was CR in 9 patients (81.8%) and PR in 2 patients (18.2%). Among the 35 patients who did not receive a boost, 28 (79.3%), 5 (14.3%), and 1 (2.9%) had CR, PR, and stable disease (SD), respectively, and 1 patient did not have information available.

3.3. Survival outcomes

3.3.1. Effect of PLN status on OS and PFS. Thirty-three (26.2%) patients had expired at the time of analysis. The number of cancer-specific death was 25 (75.8% of total death). Nineteen of them died of recurrence of the disease and other 6 of cancer-specific death were the patients with persistent disease after chemoradiation and death without disease progression or recurrence. The number of initial recurrence was 24 patients, which were 14 in local recurrence, 2 in regional recurrence, and 14 in distant recurrence, including overlapping. In all patients, the 2-year and 5-year OS rates were 90.8% and 76.1%, respectively. The 2-year and 5-year PFS rates were 77.7% and 67.7%, respectively.

We performed Kaplan–Meier survival analysis to analyze OS and PFS according to PLN positivity. Results are shown in Fig. 1. A significant difference in 2-year and 5-year OS rates was observed between the two groups (2-year and 5-year OS; 86.8% and 63.6%, respectively, in the group with positive node vs. 92.5% and 81.0%, respectively, in the node negative group, $P = .010$). The 2-year and 5-year PFS rates were 64.6% and 61.0%, respectively, in the LN-positive group, and 85.1% and 71.4%, respectively, in the LN-negative group. There was significant difference ($P = .032$) in PFS between the 2 groups.

3.3.2. Initial pattern of failure according to PLN status. Among 80 PLN-negative patients, local recurrence occurred in 7 patients. One patient had a regional recurrence in both iliac and both inguinal nodal chains. Therefore, the patient underwent reirradiation using intensity-modulated radiotherapy (IMRT). There were 7 patients with distant failure. All these patients had their disease spread to distant organs such as liver, lung, and ovary except 1 who had a left para-aortic nodal recurrence.

Among 46 PLN-positive patients, 7 patients had local recurrence in the primary mass and 1 patient had nodal recurrence in right obturator. Seven cases of distant failure were observed with metastases to the lung and ovary in 3 patients. In the other 4 patients, distant failure was confined to nodal areas such as supraclavicular, axillary, retroperitoneal, and para-aortic nodes. There was no recurrence or failure in the boost irradiation group.

We also analyzed node size for pelvic nodal control in the PLN-positive patients. Twenty-one patients with nodes sized ≥1.5 cm and 22 patients nodes sized <1.5 cm were compared. In the group with nodes size ≥1.5 cm, initial response of LN was significantly worse than that in group with nodes size less than 1.5 cm ($P = .007$). However, there was no significant difference in regional control, OS, or PFS ($P = .365$, $P = .459$, and $P = .4$, respectively).

3.3.3. Effect of PLN boost irradiation on OS and PFS, and PRFS. We compared the 2-year and 5-year PFS and OS between the boost irradiation group and the no-boost group. The ranges of follow-up period for the pelvic boost group and the no-boost group were 6.22 to 160.95 months (median; 18.65 months) and 7.14 to 183.88 months (median; 44.11 months), respectively. The 2-year and 5-year OS rates in the no-boost group were 82.9% and 58.3%, respectively, whereas all patients in the boost irradiation group were alive at the time of analysis ($P = .065$). The 2-year and 5-year PFS were 55.9% and 52.4%, respectively, in the no-boost group. On the contrary, there was no recurrence in the boost group with significant difference ($P = .023$). Survival curves in boost and no-boost group are shown in Fig. 2.

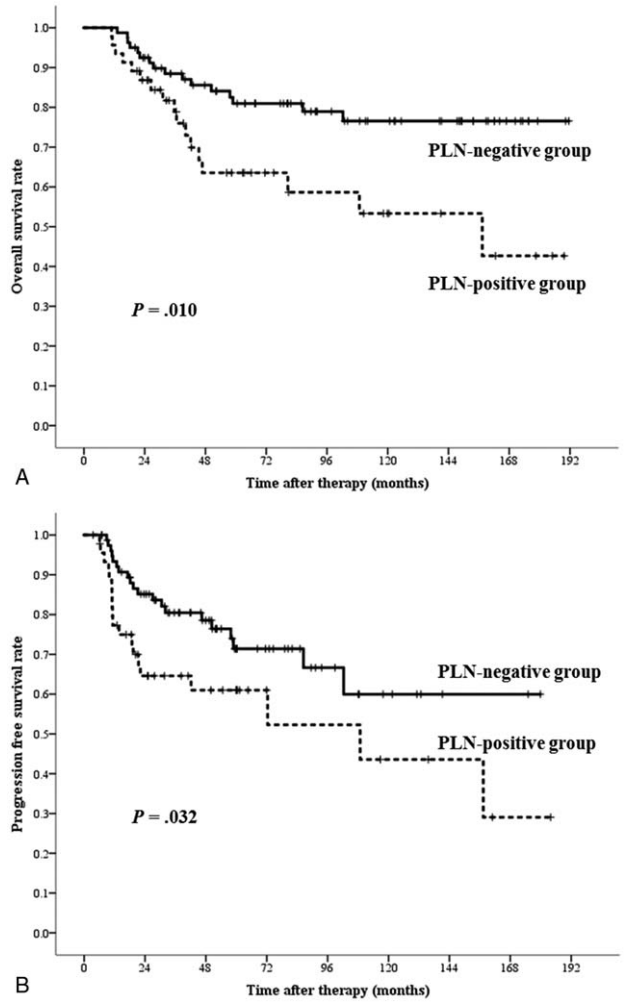

Figure 1. Kaplan–Meier curves for (A) OS, (B) PFS in PLN-positive and PLN-negative group. OS = overall survival, PFS = progression-free survival, PLN = pelvic lymph node.

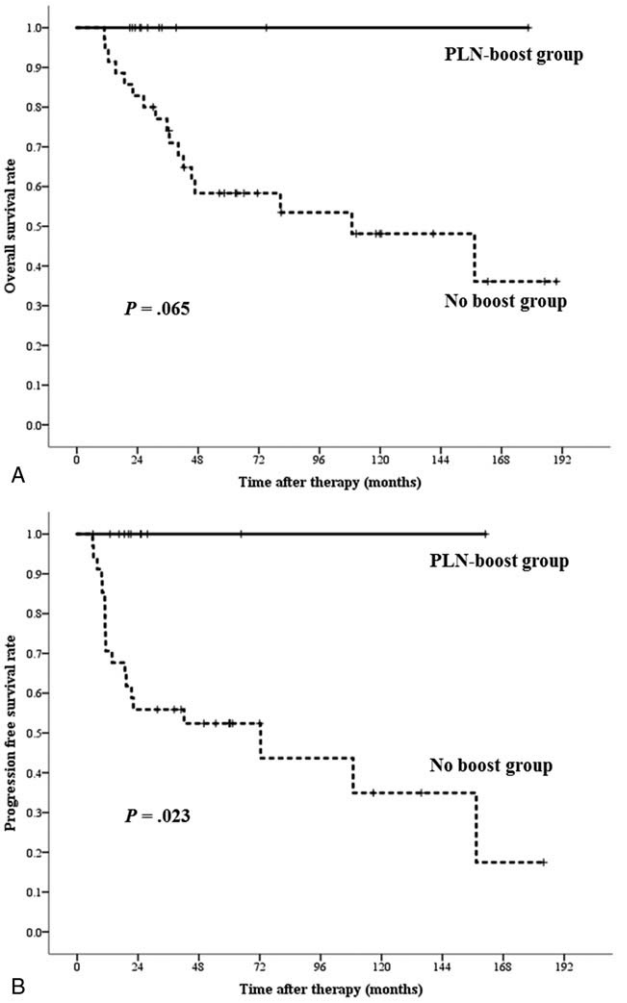

Figure 2. Kaplan–Meier curves for (A) OS, (B) PFS in PLN-boost and no-boost group. OS = overall survival, PFS = progression-free survival, PLN = pelvic lymph node.

In analysis of PC between boost and no-boost group, 2-year and 5-year PRFS did not show significant difference but a tendency of increased risk of pelvic recurrence in no-boost group (boost vs no-boost; 81.9% and 70.2% vs 100% and 100% in 2-year and 5-year PRFS, respectively, $P = .156$). Results are shown in Fig. 3.

3.3.4. Multivariate analysis of prognostic factors for OS and PFS. The prognostic factors for OS and PFS were analyzed in all cohorts. In univariate analysis, the presence of PLN involvement ($P = .010$) and the response of the primary mass after radiation therapy ($P < .001$) were significantly associated with OS rate. In multivariate analysis of OS, the response of the primary mass showed significant difference [$P < .001$, HR 4.447; 95% confidence interval (95% CI), 2.150–9.197]. The significant factors associated with PFS were ECOG ($P = .025$), PLN involvement ($P = .032$), and treatment response of the primary mass after RT ($P < .001$) in both univariate and multivariate analyses. Additional details are summarized in Table 3. In univariate and multivariate analysis of OS and PFS in LN-positive patients, there was no significant prognostic factor, summarized in Table 4.

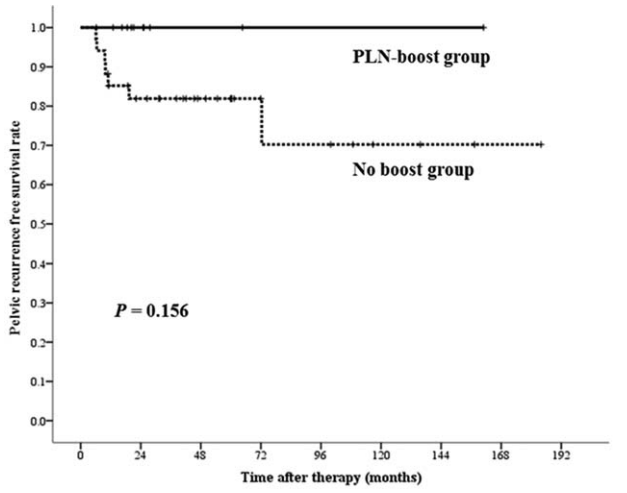

Figure 3. Kaplan–Meier curves for PRFS in PLN-boost and no-boost group. PLN = pelvic lymph node, PRFS = pelvic-recurrence free survival.

Table 3

Univariate and multivariate analysis for OS and PFS in entire patients.

Variable	No. of patients	UVA for OS	MVA for OS		UVA for PFS	MVA for PFS	
		P	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)
ECOG							
0–1	93	.119			.025	.012	1
2	33						2.732 (1.246–5.992)
FIGO							
IB	4	.494			.433		
IIA	3						
IIB	92						
IIIA	10						
IIIB	10						
IVA	7						
Parametrial invasion							
Present	119	.146			.184		
Absent	7						
Pretreatment Hb, g/dL*							
≤10	17	.250			.672		
> 10	105						
Pretreatment SCC Ag, ng/mL*							
≤ 2	36	.667			.901		
> 2	86						
Primary mass size, cm							
≤ 4	61	.969			.784		
> 4	65						
Pelvic LN status							
Absent	80	.010	.059	1	.032	.037	1
Present	46			1.959 (0.974–3.938)			2.179 (1.048–4.529)
Initial response of primary mass†							
CR	102	< .001	< .001	1	<.001	< .001	1
PR	22			4.447 (2.150–9.197)			4.047 (1.976–8.291)

CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, Hb = hemoglobin, HR = hazard ratio, LN = lymph node, MVA = multivariate analysis, OS = overall survival, PFS = progression free survival, PR = partial response, SCC Ag = squamous cell carcinoma antigen, UVA = univariate analysis.

* Exclude 4 patients for whom no information was available.

† Exclude 2 patients for whom no information was available.

3.4. Toxicity

There were 5 and 6 events of acute and chronic complications, respectively, in GI tract among all patients (Table 5). In GU tract, 7 patients experienced chronic complications and none experienced acute complication. Acute GI toxicities were observed in 1 patient out of 11 patients who received boost irradiation. There was no acute GU toxicity in this group. The patient who had acute GI toxicities was 64 years old with a FIGO stage IIB disease. She received a boost of 5.4 Gy on the 1.8 cm sized left internal iliac node. During RT, she complained of abdominal pain and diarrhea and was diagnosed with radiation enteritis. She needed a break in RT and received conservative management for the enteritis. Then, she fully recovered from it and completed the planned course of RT. Late GI and GU toxicities occurred in 1 patient in boost group. The patient who experienced late GI toxicity was 59 years old. She had parametrial invasion and 3 involved pelvic nodes (with a maximum size of 1.4 cm) in the right internal iliac and bilateral external iliac chain. She received an additional boost of 5.4 Gy on the positive pelvic nodes. Eight months after completion of EBRT, she complained of abdominal pain and was diagnosed with radiation colitis in abdominopelvic CT. She recovered after conservative management without sequelae.

4. Discussion

The aim of this retrospective study was to evaluate clinical outcome according to pelvic LN involvement and determine whether boost irradiation to the involved PLN could improve locoregional control without complication. Several studies have investigated the effect of dose escalation to positive pelvic node on OS and disease control. For example, Grigsby et al[14] have demonstrated that dose escalation does not improve PC. In Radiation Therapy Oncology Group (RTOG) 0116, boost did not improve nodal control either.[15] On the contrary, Yoon et al[16] and Ariga et al[17] have reported that nodal control can be improved by nodal boost irradiation without increasing complications. Although dose escalation to pelvic node remains debatable, American College of Radiology recommended pelvic nodal boost to involved LN within 56 to 65 Gy in 2011.[18]

In this study, there was no death or disease progression in the boost irradiation group. In survival analysis, boost irradiation to the enlarged pelvic node demonstrated insignificant difference in OS ($P = .065$) but significant difference in PFS compared with no-boost ($P = .023$). The 2-year and 5-year PRFS did not show significant difference but a tendency of increased risk of pelvic recurrence in the no-boost group. This might be due to the small number of patients used in this study and a relatively short follow-up duration in the boost group. Therefore, clear results might be obtained if larger data set is used with a longer follow-up period. Although we need to follow-up longer, our preliminary results demonstrated the importance of boost irradiation for PLN.

We performed survival analysis according to pelvic node status. Our results showed that the 5-year OS rates in

Table 4

Univariate and multivariate analysis for OS and PFS in LN-positive patients.

Variable	No. of patients	UVA for OS		MVA for OS	UVA for PFS	MVA for PFS
		P	*P*	HR (95% CI)	*P*	*P*
ECOG*						
0–1	38	.238			.052	
2	8					
FIGO†						
IB	0	.033	.511	1	.034	
IIA	2			1.155		
IIB	33			(0.752–1.772)		
IIIA	2					
IIIB	5					
IVA	4					
Parametrial invasion*						
Present	2	.258			.598	
Absent	44					
Pretreatment Hb, g/dL‡						
≤ 10	9	.612			.711	
> 10	35					
Pretreatment SCC Ag, ng/mL†						
≤ 2	5	.856			.983	
> 2	38					
Primary mass size, cm *						
≤ 4	18	.767			.503	
> 4	28					
Pelvic LN size, cm†						
≤ 1.5	22	.276			.677	
> 1.5	21					
Pelvic LN number†						
Single	24	.459			.4	
Multiple	19					
Initial response of primary mass*						
CR	34	.215			.3	
PR	11					
Initial response of pelvic LN*						
CR	37	.05	.091	1	.474	
PR	7			2.173		
SD	1			(0.884–5.340)		

CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, Hb = hemoglobin, HR = hazard ratio, LN = lymph node, MVA = multivariate analysis, OS = overall survival, PFS = progression free survival, PR = partial response, SCC Ag = squamous cell carcinoma antigen, UVA = univariate analysis.

* Exclude 1 patient for whom no information was available.

† Exclude 2 patients for whom no information was available.

‡ Exclude 3 patients for whom no information was available.

the PLN-positive and PLN-negative groups were 63.6% and 81.0%, respectively, with a significant difference ($P = .010$). The 5-year PFS rates in the PLN-positive and PLN-negative groups were 61.0% and 71.4%, respectively ($P = .042$). These results demonstrated that PLN was an important prognostic factor related to survival, consistent with results of previous studies.[14,19,20] Furthermore, in our study, distant failure was predominant in the nodal area such as supraclavicular, axillary, retroperitoneal, and para-aortic nodes in PLN-positive patients. Ariga et al[17] have also reported that distant metastases, especially in para-aortic nodes, are predominant failure in PLN-positive patients. In multivariate analysis for 626 patients in the Gynecologic Oncology Group, positive para-aortic LN has been suggested to be the most significant prognostic indicator for recurrence and survival.[21] In a randomized controlled trial of RTOG, prophylactic extended field radiotherapy (EFRT) of para-aortic LN has significantly improved the 10-year OS rate (44% vs 55%, $P = .02$).[9] On the contrary, Han et al[7] have compared EFRT with standard pelvic RT in patients involved in common iliac nodes with radical hysterectomy and PLN dissection and revealed that there is no significant difference in 4-year OS rate (90% vs 67.2%, $P = .291$) or 4-year PFS rate (70% vs 59%, $P = .568$). However, considering the small data set and short follow-up time used in that study, they have discussed that

Table 5

Acute and late complication (≥ grade 3) including pelvic node status.

Acute complication				
	Pelvic node positive		**Pelvic node negative**	**Total**
	Boost	No boost		
Gastrointestinal	1	0	4	5
Genitourinary	0	0	0	0
Late complication				
	Pelvic node positive		**Pelvic node negative**	**Total**
	Boost	No boost		
Gastrointestinal	1	3	2	6
Genitourinary	1	1	5	7

additional studies using more data and longer follow-up period would be needed.

Node-related factors for pelvic nodal control in PLN-positive patients were evaluated in this study according to the size of involved nodes. Ariga et al[17] have demonstrated that the maximum size and the number of positive nodes are not significantly associated with nodal control ($P=.082$). On the contrary, our results revealed that 13 (62%), 7 (33%), and 1 (5%) patients in the large node group (≥1.5 cm, n=21) had CR, PR, and stable disease, respectively. In the small node group (<1.5 cm, n=21), all nodes showed CR with a significant difference ($P=.007$). Hata et al[22] have also suggested that LNs larger than 24 mm might require higher doses up to about 55.8 Gy to improve nodal control. They compared nodal response rate of 111 metastatic PLNs in 62 patients and found that only 1 patient had LN progression. She received whole pelvic RT of 50.4 Gy. In further evaluation about the size of metastatic nodes of the patient, among 3 enlarged pelvic LNs, 1 LN with 16 mm was controlled. However, the other 2 LNs measured at 24 and 28 mm progressed.

In addition, Song et al[23] have performed survival analysis for 155 patients with pelvic LNs and divided them into 2 groups (≥15 mm LN and <15 mm LN). Five-year OS of the 2 groups (≥15 mm LN and <15 mm LN) were 58% and 82%, respectively. Their 5-year disease-free survival rates were 50% and 67% with statistically significant differences ($P<.001$). These findings supported that local control of enlarged pelvic LN could affect OS. In our study, the 5-year OS rates in ≥1.5 cm and <1.5 cm pelvic LN groups were 68.9% and 53.0%, respectively. Their 5-year PFS rates were 66.3% and 54.3%, respectively. However, these differences were not statistically significant ($P=.307$ and $P=.314$, respectively).

Furthermore, we evaluated prognostic factors affecting OS and PFS in this study. Multivariate analysis revealed that pelvic LN involvement and primary mass response after radiotherapy were significant factors affecting OS and PFS. In a recent study, Kobayashi et al[24] have analyzed the details of recurrences after definitive radiation without boost irradiation. They found that half of non-CR patients (8 of 16 patients) showed local persistence and recurrence. However, among patients with CR, 30% of them developed recurrence. The sites of recurrence were intra-RT field in 44% of patients, suggesting that dose escalation to primary tumor is required to improve the long-term outcome of poor responders after radiotherapy.

There are concerns about dose escalation to pelvic nodes because it might increase late complications. Severe complications in GI and GU tracts in high-dose irradiation to the pelvis have been reported in other studies.[25,26] On the contrary, Wakatsuki et al[27] have reported that there are no grade 3 or greater toxicities after nodal boost irradiation for a total dose of >58 Gy. In a systematic review, acute complication of more than grade 3 has occurred in 15% to 23% patients.[28] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration has reported that that 1% to 3% patients have experienced late toxicities of more than grade 3 in 16 trials (range of EBRT dose: 40 to 50 Gy).[29] Our results showed that one of late toxicity more than grade 3 occurred. The percentage of patients with toxicities in the nodal boost group was lower than that of previous reports.

There are a few limitations in this study. First, the size of the boost irradiation group was small and the follow-up period was short. Low recurrence rate in boost irradiation group may reflect a bias in recruitment selection. Therefore, further follow-up and reassessment of disease course and morbidities are needed. Second, the dose distribution to the boost irradiated pelvic LN from HDR-ICR could not be accounted for in this study because image guided brachytherapy was not done in our institution. Lee et al[30] have reported that fractional HDR dose delivered to the pelvic nodes in obturator, external, and internal iliac chain ranged from 1.0 to 1.5 Gy per fraction when performing tandem-based HDR applications of 5 to 5.5 Gy for 5 fractions.

In conclusion, there was no recurrence or failure in the boost irradiation group with a significant difference ($P=.023$) in PFS. The percentage of toxicities in the nodal boost group in this study was lower than that of previous reports. Therefore, boost irradiation to PLN could improve locoregional control especially in large pelvic LN (≥1.5 cm). However, further follow-up and assessment are needed. PLN involvement is a significant prognostic factor related to poor OS and PFS of patients with uterine cervical cancer, suggesting that selective treatment strategy such as dose escalation in large pelvic LN using advanced technology is needed to improve treatment outcome of high-risk patients.

Author contributions

Conceptualization: Kyu Hye Choi, Ji Yoon Kim, Yeon Sil Kim.
Data curation: Kyu Hye Choi, Ji Yoon Kim, Dong Soo Lee, SooYoon Sung, Soo Young Hur, Jong-Sup Park, Yeon Sil Kim.
Formal analysis: Kyu Hye Choi, SooYoon Sung, Hee Hyun Park, Yeon Sil Kim.
Funding acquisition: Kyu Hye Choi.
Investigation: Ji Yoon Kim, Yun Hee Lee, Sei-Chul Yoon, Yeon Sil Kim.
Methodology: Ji Yoon Kim, Dong Soo Lee, Yun Hee Lee, Sea-Won Lee, Sei-Chul Yoon, Yeon Sil Kim.
Project administration: Dong Soo Lee, Yeon Sil Kim.
Supervision: Dong Soo Lee, Yun Hee Lee, Sea-Won Lee, SooYoon Sung, Hee Hyun Park, Sei-Chul Yoon, Soo Young Hur, Jong-Sup Park, Yeon Sil Kim.
Writing – original draft: Kyu Hye Choi.
Writing – review & editing: Kyu Hye Choi, Ji Yoon Kim, Yeon Sil Kim.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[2] Oh CM, Won YJ, Jung KW, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2013. Cancer Res Treat 2016;48:436–50.
[3] Kamura T, Tsukamoto N, Tsuruchi N, et al. Multivariate analysis of the histopathologic prognostic factors of cervical cancer in patients undergoing radical hysterectomy. Cancer 1992;69:181–6.
[4] Monk BJ, Cha DS, Walker JL, et al. Extent of disease as an indication for pelvic radiation following radical hysterectomy and bilateral pelvic lymph node dissection in the treatment of stage IB and IIA cervical carcinoma. Gynecol Oncol 1994;54:4–9.
[5] Girardi F, Lichtenegger W, Tamussino K, et al. The importance of parametrial lymph nodes in the treatment of cervical cancer. Gynecol Oncol 1989;34:206–11.
[6] Kim JH, Kim HJ, Hong S, et al. Post-hysterectomy radiotherapy in FIGO stage IB-IIB uterine cervical carcinoma. Gynecol Oncol 2005;96:407–14.
[7] Han TJ, Wu HG, Kim HJ, et al. Effects of concurrent chemotherapy and postoperative prophylactic Paraaortic irradiation for cervical cancer with common iliac node involvement. J Korean Soc Ther Radiol Oncol 2010;28:125–32.
[8] Haie C, Pejovic MH, Gerbaulet A, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. Radiother Oncol 1988;11:101–12.

[9] Rotman M, Pajak TF, Choi K, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. JAMA 1995;274:387–93.
[10] Perez CA, Grigsby PW, Chao KS, et al. Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. Int J Radiat Oncol Biol Phys 1998;41:307–17.
[11] Grigsby PW, Heydon K, Mutch DG, et al. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys 2001;51:982–7.
[12] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[13] National Cancer Institute NIoH, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2011. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed March 17, 2017.
[14] Grigsby PW, Singh AK, Siegel BA, et al. Lymph node control in cervical cancer. Int J Radiat Oncol Biol Phys 2004;59:706–12.
[15] Small WJr, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. Int J Radiat Oncol Biol Phys 2007;68:1081–7.
[16] Yoon MS, Ahn SJ, Nah BS, et al. Metabolic response of lymph nodes immediately after RT is related with survival outcome of patients with pelvic node-positive cervical cancer using consecutive [^{18}F]fluorodeoxyglucose-positron emission tomography/computed tomography. Int J Radiat Oncol Biol Phys 2012;84:e491–497.
[17] Ariga T, Toita T, Kasuya G, et al. External beam boost irradiation for clinically positive pelvic nodes in patients with uterine cervical cancer. J Radiat Res 2013;54:690–6.
[18] Gaffney DK, Erickson-Wittmann BA, Jhingran A, et al. ACR appropriateness Criteria(R) on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. Int J Radiat Oncol Biol Phys 2011;81:609–14.
[19] Atahan IL, Onal C, Ozyar E, et al. Long-term outcome and prognostic factors in patients with cervical carcinoma: a retrospective study. Int J Gynecol Cancer 2007;17:833–42.
[20] Kim YJ, Lee KJ, Park KR, et al. Prognostic analysis of uterine cervical cancer treated with postoperative radiotherapy: importance of positive or close parametrial resection margin. Radiat Oncol J 2015;33:109–16.
[21] Stehman FB, Bundy BN, DiSaia PJ, et al. Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. Cancer 1991;67:2776–85.
[22] Hata M, Koike I, Miyagi E, et al. Radiation therapy for pelvic lymph node metastasis from uterine cervical cancer. Gynecol Oncol 2013;131:99–102.
[23] Song S, Kim JY, Kim YJ, et al. The size of the metastatic lymph node is an independent prognostic factor for the patients with cervical cancer treated by definitive radiotherapy. Radiother Oncol 2013;108:168–73.
[24] Kobayashi R, Yamashita H, Okuma K, et al. Details of recurrence sites after definitive radiation therapy for cervical cancer. J Gynecol Oncol 2016;27:e16.
[25] Burman C, Kutcher GJ, Emami B, et al. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123–35.
[26] Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109–22.
[27] Wakatsuki M, Ohno T, Kato S, et al. Impact of boost irradiation on pelvic lymph node control in patients with cervical cancer. J Radiat Res 2014;55:139–45.
[28] Green J, Kirwan J, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev 2005;CD002225.
[29] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802–12.
[30] Lee LJ, Sadow CA, Russell A, et al. Correlation of point B and lymph node dose in 3D-planned high-dose-rate cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys 2009;75:803–9.