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Who can benefit from a lymph node boost in definitive chemoradiotherapy for node-positive cervical cancer: an evaluation of nodal failure in patients without nodal boost

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ABSTRACT

This study was performed to identify risk factors for pelvic nodal failure (PNF) after definitive concurrent chemo-radiotherapy (CCRT) in patients with metastatic pelvic lymph nodes (mPLNs) from squamous cell carcinoma (SCC) of the cervix. We retrospectively reviewed data on 80 patients who received definitive CCRT between 2005 and 2014 at our hospital. All patients underwent brachytherapy and whole-pelvic radiotherapy (WPRT) without nodal boost. mPLNs was diagnosed by magnetic resonance imaging and positron emission tomography. The rate of PNF and factors affecting PNF were analysed. A total of 156 mPLNs were found. The median number of mPLNs was 2 per patient (range 1–6); the median short diameter was 1.7 cm (range 1.0–4.2 cm). After a median follow-up of 64 months, 10 (6.4%) mPLNs failed in 13 (16.3%) patients. The 5-year PNF-free survival (PNFFS), disease-free survival and overall survival rates were 83.4, 62.7 and 74.7%, respectively. The mPLN size was not associated with the risk of PNF. However, pre-radiotherapy SCC antigen (SCC-Ag) >6.8 ng/mL and number of mPLNs >2 were significant risk factors for PNF. Using the two risk factors, we categorized the patients into three risk groups. The 5-year PNFFS rates in patients with 0, 1 and 2 risk factors were 100.0, 78.3 and 44.4%, respectively ($P < 0.01$). SCC-Ag level and number of mPLNs were significant factors for PNF. Patients with both risk factors developed frequent PNF after WPRT without nodal boost. The two risk factors can be a guide in deciding whether to administer nodal boost radiotherapy.

Keywords: uterine cervical neoplasms; lymph nodes; radiotherapy dosage; risk factors

INTRODUCTION

Metastatic pelvic lymph nodes (mPLNs) are found in 4.8–40% of patients at diagnosis of cervical cancer [1–3]. Patients having mPLNs had poorer survival outcomes than those without PLN involvement [4–6]. To overcome the negative prognostic impact of mPLNs, more intense treatment has been recommended for patients with node-positive cervical cancer [7]. For cases in which curative radiotherapy is performed, chemotherapy is concurrently administered with radiotherapy to enhance the therapeutic effect, and escalating the radiation dose to the mPLNs with nodal boost is commonly recommended [7, 8]. Previous studies have shown that a higher nodal dose was associated with better regional control [9–12]. Large mPLNs presumably require a larger radiation dose for successful sterilization of the tumor in the lymph nodes [8]. Nonetheless, it is unclear what amount of radiation dose is necessary and which lymph nodes should be irradiated with an additional dose after whole pelvic radiotherapy (WPRT). Given that increased radiation dose beyond 45–50.4 Gy of WPRT can elevate the risk of bowel toxicity [13], it is necessary to carefully select patients who can benefit from nodal boost irradiation.

At our hospital, pelvic nodal boost had not been performed in radiotherapy for node-positive cervical cancer until 2014. mPLNs received dose from WPRT and intracavitary brachytherapy (ICBT), without nodal boost. In this study, we analysed regional control

probability after WPRT without nodal boost and stratified patients into risk groups to predict pelvic nodal failure (PNF). By evaluating regional control in our patients, we sought to identify a group of patients who need nodal boost in definitive concurrent chemoradiotherapy (CCRT) for node-positive squamous cell carcinoma (SCC) of the cervix.

MATERIALS AND METHODS

Patients and treatment

A total of 1204 patients received radiotherapy for cervical cancer at our hospital between January 2005 and December 2014. The radiotherapy included postoperative radiotherapy ($n = 638$), definitive radiotherapy ($n = 364$), palliative radiotherapy ($n = 102$) and salvage radiotherapy ($n = 100$). Definitive radiotherapy was performed as CCRT ($n = 298$), radiotherapy alone ($n = 61$) or neoadjuvant chemotherapy followed by CCRT ($n = 5$). Among the 298 patients with definitive CCRT, 240 patients had SCC, 36 had adenocarcinoma and 22 had other histological types of cancer of the cervix. The International Federation of Gynecology and Obstetrics (FIGO) stage (2009 FIGO [14]) of the 240 patients with SCC were as follows: stage I in 17 patients, stage II in 153 patients, stage III in 58 patients and stage IV in 12 patients.

The medical records of patients who received definitive CCRT for PLN-positive SCC of the cervix at our hospital between 2005 and 2014 were retrospectively reviewed. Inclusion criteria for this study were as follows: histologically confirmed SCC of the cervix, presence of mPLNs defined by magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), absence of para-aortic lymph nodes and distant organ metastasis, completion of planned WPRT and ICBT, and with a minimum of 6-months follow-up after completion of radiotherapy. Patients who had previously received pelvic lymph node dissection or hysterectomy were excluded from this analysis. Among the 240 patients with cervical SCC treated with definitive radiotherapy, 160 were excluded from our study. Details of the excluded patients are as follows: distant organ metastasis ($n = 12$), absence of mPLNs ($n = 97$), presence of para-aortic lymph node metastasis ($n = 29$), absence of pre-radiotherapy PET-CT ($n = 14$) and <6 months of follow-up duration ($n = 8$). Finally, 80 patients who met the inclusion criteria were included in our study.

For nodal staging, MRI and PET-CT scans were performed before the initiation of CCRT in all patients. A gynecological examination, measurement of SCC antigen (SCC-Ag) and abdominopelvic CT were also conducted. The definition of mPLNs was as follows: short-axis diameter ≥1 cm on MRI and significant FDG uptake on PET-CT. In PET-CT, a maximum standardized uptake value (SUVmax) of pelvic lymph node larger than 2.5 cm was considered significant.

A total of 156 mPLNs were found in 80 patients. Locations of the mPLNs were as follows: internal/external iliac chain in 66 (82.5%) patients and simultaneous common iliac and internal/external iliac chains in 14 (17.5%) patients. The median number of mPLNs was 2 per patient (range 1–6). The median short diameter of the mPLNs was 1.7 cm (range 1.0–4.2 cm). The distribution of mPLN size of all 156 nodes is depicted in Figure 1.

WPRT was administered daily, 5 consecutive days per week, with a total dose of 45 Gy in 25 fractions, using high-energy photon beams. 3D conformal radiotherapy was performed using opposed anteroposterior/posteroanterior (AP/PA) fields or a four-field technique using AP/PA and two lateral fields. The WPRT upper field border was placed at the L4–L5 interspace. After 45 Gy, a 4-cm wide central shielding was inserted into the whole pelvic field with a dose of 5.4 Gy in 3 fractions using the AP/PA field. In no patient was boost radiotherapy to the mPLNs or prophylactic para-aortic lymph node irradiation performed. High-dose-rate ICBT using a conventional 2D technique was conducted after WPRT at 45 Gy. Six fractions of ICBT were administered three times per week, with a fraction dose of 3–6 Gy. A total dose of 18–36 Gy was prescribed by the International Commission on Radiation Units and Measurements at point A. Most ($n = 78$, 97.5%) patients received a dose of 24 Gy ICBT in 6 fractions. Median overall treatment time (OTT) was 52 days (range 44–77 days).

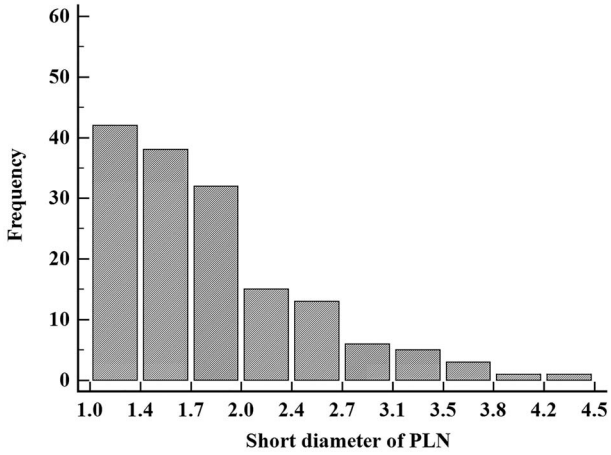

Fig. 1. Distribution of size in 156 metastatic pelvic lymph nodes among 80 patients; *x*-axis values are in cm.

All patients received CCRT. Six cycles of weekly cisplatin (40 mg/m^2) or 2 cycles every 3 weeks of cisplatin (60 mg/m^2) and 5-fluorouracil (1000 mg/m^2) was administered. After completion of CCRT, 3 cycles of adjuvant cisplatin and 5-fluorouracil was provided to 5 patients according to the physician's discretion. Details of the patients and treatments are shown in Table 1. This study was approved by the institutional review board of the xxx hospital and was classified exempt to obtain informed consent of the participants.

Follow-up and lymph node evaluation

After the completion of treatment, patients had follow-up visits with routine surveillance exams 1 month after completion of radiotherapy, every 3 months during the first 2 years, every 6 months up to 5 years and once a year thereafter. The surveillance exams consisted of gynecological examination, SCC-Ag, a Papanicolaou test and an abdominopelvic MRI. A PET-CT scan was taken at 1 month after the completion of radiotherapy and at 6-month intervals thereafter for 5 years. PNF was defined as progression of mPLNs in follow-up MRI or PET-CT. Sites of PNF were categorized as the initially involved pelvic lymph node (iPLN) and new development of pelvic nodal metastasis within the WPRT field (nPLN).

Table 1. Patients' characteristics

Characteristic		Number (%)
Age, years	≤ 50	34 (42.5)
(median 52, range, 25–75)	> 50	46 (57.5)
FIGO stage	I/II	62 (77.5)
	III/IV	18 (22.5)
Size of cervical mass, cm	≤ 5.0	39 (48.7)
(median 5.1, range 1.0–8.5)	> 5.0	41 (51.2)
Pre-radiotherapy SCC-Ag level, ng/mL	≤ 6.8	37 (46.3)
(median 7.3, range 0.4–113.5)	> 6.8	43 (53.7)
Chemotherapeutic regimen	Cisplatin	44 (55.0)
	Cisplatin and 5-fluorouracil	36 (45.0)
Completion of planned chemotherapy	Yes	61 (76.2)
	No	19 (23.7)
Dose of brachytherapy	24 Gy/6 fractions	78 (97.5)
	Other	2 (2.5)
Overall treatment time, days	≤51	40 (50.0
(median 52, range 44–77)	>51	40 (50.0)
Number of positive pelvic lymph nodes	≤2	64 (80.0)
(median 2, range 1–6)	>2	16 (20.0)
Short lymph node diameter, cm	≤2.0	52 (65.0)
(median 1.7, range 1.0–4.2)	>2.0	28 (35.0%)

Statistical analysis

Pelvic nodal failure-free survival (PNFFS), disease-free survival (DFS) and overall survival (OS) were defined as the interval from the first day of radiotherapy to the date of pelvic nodal failure, distant metastasis, cancer recurrence and death, respectively. Survival probability was estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival between groups with different variables. Variables significant at $P < 0.10$ in a univariate analysis were retained in a multivariate analysis. The multivariate analysis was performed using the Cox proportional hazards regression model. A receiver operating characteristics (ROC) analysis was used to determine optimal cut-offs for continuous variables that would predict PNF. Probit regression was used to evaluate the association of mPLN size and PNF. Statistical analyses were performed with MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium) and *P*-values < 0.05 were considered significant.

RESULTS

Patterns of failure and pelvic node response

The median follow-up time was 64 months (range 7–77 months). Some 30 (37.5%) patients developed cancer recurrence. Sites of the first recurrence were as follows: cervix in 3 (3.7%) patients, regional area in 4 (5.0%), cervix and regional failures in 2 (2.5%), distant organs in 11 (13.7%) and simultaneous locoregional and distant organs in 10 (12.5%). Local cervical failure and PNF were found in 10 (12.5%) and 13 (16.3%) patients, respectively. The PNF sites among the 13 patients were as follows: iPLN in 6 (7.5%) patients, nPLN in 3 (3.7%), and simultaneous iPLN and nPLN in 4 (5.0%). Therefore, PNF at the iPLN (iPLN alone and simultaneous iPLN and nPLN) was noted in 10 (12.5%) patients. nPLN failure (nPLN alone and simultaneous nPLN and iPLN) was found in 7 (8.7%) patients. PNF locations were as follows: internal/external iliac chains in 9 (11.3%) patients and both common iliac and internal/external chains in 4 (5.0%) patients.

A total of 10 mPLNs progressed, accounting for 6.4% of all mPLNs. For 156 mPLNs, PNF frequencies according to the size of each mPLN are presented in Table 2. In mPLNs ≤3 cm, the proportion of nodal failure increased with the diameter of mPLN. The trend was also observed in mPLN between 4.1 and 6.0 cm. However, there was no nodal failure among mPLN between 3.1 and 4.0 cm. Overall, there was no significant association between the size of mPLN and the risk of PNF in the regression analysis ($P = 0.15$, Supplementary Figure 1, see online supplementary material).

Survival rates and prognostic factors

The 5-year rates of PNFFS, DFS and OS of all patients were 83.4, 62.7 and 74.7%, respectively. Risk factors related to PNFFS are demonstrated in Table 3. Pre-radiotherapy SCC-Ag >6.8 ng/mL, multiple mPLNs >2, and development of cervical failure were significant risk factors for PNF. Among the three variables, pre-radiotherapy SCC-Ag and number of mPLNs were factors related to pretreatment status. Using these two risk factors, we categorized patients into three risk groups, depending on the number of risk factors. Patients having no risk factor, 1 risk factor and 2 risk factors were classified as Group 1 ($n = 31$), Group 2 ($n = 39$) and Group 3 ($n = 10$), respectively. The PNFFS curves were significantly separated according to risk group. The 5-year PNFFS rates in Group 1, Group 2 and Group 3 patients were 100.0, 78.3 and 44.4%, respectively ($P < 0.01$) (Figure 2). In predicting nPLN failure, pre-CCRT SCC-Ag level was a significant factor (Supplementary Table 1, see online supplementary material).

Table 2. Frequency of nodal failure depending on the size of each pelvic lymph node

Short diameter of PLN (cm)	No. of PLNs	No. of progressed PLNs	Proportion of progressed PLNs (%)
1.0–2.0	112	6	5.4
2.1–3.0	34	3	8.8
3.1–4.0	9	0	0.0
4.1–6.0	1	1	100.0
Total	156	10	6.4

Table 3. Prognostic factors for pelvic lymph node failure-free survival

Characteristics		5-year PNFFS (%)	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)
Age, years	≤ 50 (*n* = 34)	81.1	0.65	-	-
	> 50 (*n* = 46)	85.2			
2009 FIGO stage	I/II (*n* = 62)	85.7	0.33	-	-
	III/IV (*n* = 18)	75.0			
Size of cervical mass, cm	≤5.0 (*n* = 39)	83.1	0.70	-	-
	>5.0 (*n* = 41)	83.7			
Pre-RT SCC-Ag, ng/mL	≤6.8 (*n* = 37)	97.1	<0.01	0.01	12.4 (1.6–95.4)
	>6.8 (*n* = 43)	71.2			
Chemotherapeutic regimen	Cisplatin (*n* = 44)	82.7	0.54	-	-
	FP (*n* = 36)	84.4			
Completion of planned chemotherapy	Yes (*n* = 61)	83.9	0.98	-	-
	No (*n* = 19)	80.8			
Overall treatment time, days	≤51 (*n* = 40)	80.7	0.48	-	-
	>51 (*n* = 40)	86.6			
Number of positive pelvic lymph nodes	≤2 (*n* = 64)	88.7	0.04	0.06	3.2 (0.9–11.1)
	>2 (*n* = 16)	58.2			
Longest short-diameter of pelvic lymph node[a], cm*	≤2.0 (*n* = 52)	85.7	0.59	-	-
	> 2.0 (*n* = 28)	77.3			
Cervical failure	Yes (*n* = 10)	53.3%	0.04	0.36	1.85 (0.5–6.9)
	No (*n* = 70)	86.4%			

HR = Hazard ratio, CI = confidence interval, pre-RT = pre-radiotherapy, FP, 5-fluorouracil and cisplatin.
[a]The short diameter of the largest lymph node in each patient was recorded.

The 5-year DFS rates for patients in Groups 1–3 were 80.4 55.0 and 36.0%, respectively ($P < 0.01$); and the 5-year OS rates were 86.9, 69.4 and 56.2%, respectively ($P = 0.14$). Of the 13 patients who developed PNF, 7 patients had died of cancer by the time of data analysis. After PNF, all patients received palliative chemotherapy. Of the 13 patients with chemotherapy, palliative radiotherapy was administered to 5 patients and lymph node dissection was performed on 1 patient. The median survival time between nodal failure and death was 12 months (range 5–41 months). In multivariate analysis, OTT >51 days and development of PNF were statistically significant factors for inferior DFS and OS (Table 4).

DISCUSSION

In this study, we observed that 83% of patients with node-positive SCC of the cervix achieved regional control after WPRT and ICBT without nodal boost irradiation. Nodal failures occurred not only in iPLN but also in nPLN. Approximately one-third of nodal failures were found in nPLN. The size of each pelvic lymph node was not significantly associated with the risk of PNF. However, a high level of pre-radiotherapy SCC-Ag and the involvement of multiple PLNs were significant risk factors for PNF. Patients with no risk factors achieved excellent regional control even without a nodal boost, whereas patients having all the risk factors developed frequent nodal failures following WPRT.

Approximately 2–28% of patients with cervical cancer develop regional recurrence after definitive radiotherapy or CCRT [2, 9–11, 15–19]. With an improvement in local control by use of advanced radiotherapeutic techniques, such as an image-guided ICBT [1, 16], regional recurrence and distant metastasis became major failures in cervical cancer treatment [15]. Regional recurrence itself results in a detrimental outcome [20] and potentially decreases the patient's quality of life. Therefore, the achievement of regional control is important in the management of cervical cancer.

To improve regional control, nodal doses of 54 to 60 Gy have been recommended for mPLN treatment [8]. In line with these

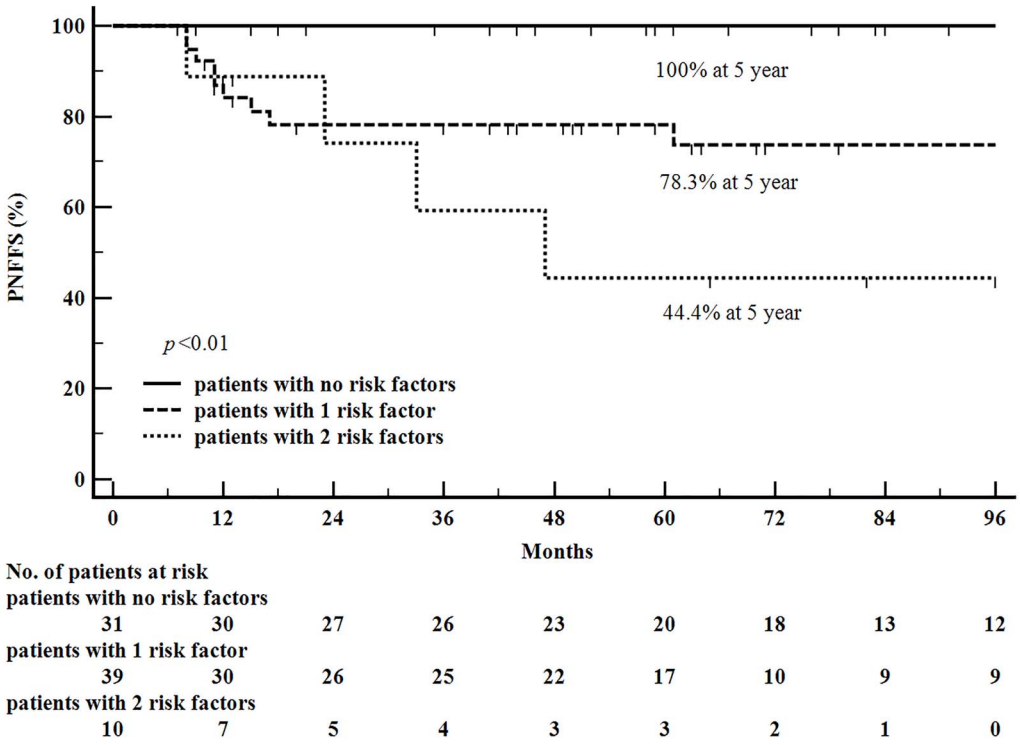

Fig. 2. Pelvic nodal failure-free survival according to risk groups. Patients were categorized into three groups, depending on the numbers of risk factors. Risk factors were defined as follows: (i) pre-radiotherapy SCC-Ag level >6.8 ng/mL, and (ii) number of positive lymph nodes >2.

Table 4. Multivariate analysis of risk factors for disease-free survival and overall survival

	DFS		OS	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years (≤50 vs >50)	1.34 (0.63–2.84)	0.44	1.09 (0.43–2.75)	0.85
2009 FIGO stage (I/II vs III/IV)	1.14 (0.40–3.25)	0.79	1.20 (0.33–4.40)	0.77
Size of cervical mass, cm (≤5.0 vs >5.0)	1.71 (0.67–4.37)	0.25	1.34 (0.43–4.18)	0.61
Pre-RT SCC-Ag, ng/mL (≤6.8 vs >6.8)	1.70 (0.59–4.88)	0.32	1.18 (0.39–3.55)	0.76
Chemotherapeutic regimen (cisplatin vs FP)	0.85 (0.31–2.35)	0.76	0.44 (0.16–1.18)	0.10
Completion of planned CTx (Yes vs no)	1.72 (0.62–4.77)	0.29	1.90 (0.52–6.97)	0.32
OTT, days (≤51 vs >51)	0.32 (0.12–0.81)	0.01	0.28 (0.09–0.90)	0.03
No. of positive pelvic lymph nodes (≤2 vs >2)	1.42 (0.58–3.49)	0.43	1.73 (0.61–4.96)	0.30
Short diameter of PLN[a], cm (≤2.0 vs >2.0)	1.45 (0.60–3.52)	0.40	2.34 (0.85–6.38)	0.09
Pelvic lymph node failure (No vs yes)	5.77 (2.20–15.2)	<0.01	5.07 (1.54–16.62)	<0.01

HR = Hazard ratio, CI = confidence interval, pre-RT, pre-radiotherapy, FP = 5-fluorouracil and cisplatin, CTx = chemotherapy.
[a]The short diameter of the largest lymph node in each patient was recorded.

recommendations, there have been several studies applying nodal boost irradiation in definitive radiotherapy for node-positive cervical cancer. Hata *et al*. demonstrated a nodal recurrence rate of 1.6% among 62 patients with MRI-defined mPLN after radiotherapy or CCRT [9]. Only two lymph nodes in one patient progressed after 50.4 Gy in 28 fractions of WPRT. The authors also found that all nodes >3.0 cm were controlled with a median nodal dose of 55.8 Gy. In a study by Vargo *et al*., 4.9% of their 61 patients with PET-positive mPLNs had nodal recurrence after CCRT, using a median nodal dose of 55 Gy in 25 fractions [21].

More recently, Bacorro *et al*. reported that 18.5% of 108 patients experienced nodal failure after a mean nodal equivalent dose (EQD2) (2-Gy equivalent dose using α/β = 10 Gy) of 55.8 Gy [22]. The authors found a benefit in nodal control by using an escalated nodal

dose among patients with high-volume nodes. Nodal boost was administered to 69% of their patients and CCRT was performed to 96% of the patients. Given that 16.2% of our 80 patients had nodal failure, the nodal control rate in the study by Bacorro *et al*. is similar to that in our study. However, unlike our study, Bacorro *et al*. found that large nodal volume (threshold: 3 cm^3) was a statistically significant factor for inferior nodal control. The mean nodal volume in their study ranged between 2.4 and 9.2 cm^3. When the volume is converted to a diameter, the nodal diameter in their study is assumed to be between 1.6 and 2.6 cm. Considering that the mPLN diameter was between 1.0 and 4.2 cm in our study, our nodal size distribution is different from that in the study by Bacorro *et al*. In our study, a statistically insignificant trend was observed attesting to a higher nodal failure rate caused by an increased mPLN diameter. The nodal failure rate in the mPLN range between $\geq$1.0 and $\leq$2.0 cm was nearly twice the rate in the mPLNs $\geq$2.1 and $\leq$ 3.0 cm. However, there was no nodal failure in the mPLNs $\geq$3.1 and $\leq$ 4.0 cm. Therefore, the absence of statistically significant association between the size of mPLNs and nodal control rate in our study is probably due to the pattern of mPLN size distribution.

As shown in the aforementioned studies, various radiotherapeutic regimens were used for nodal boost. In these studies, nodal control probabilities varied across the studies. Even if there is a radiobiological principal that radiation doses of at least 60 Gy are necessary to control 90% of a tumor $\geq$2 cm [23], it appears that this principle is not consistently applicable to pelvic nodal control in cervical cancer. The previous studies on PNF have reported that 81.5–98.4% of PLNs were controlled after definitive radiotherapy using a median nodal dose of 55–55.8 Gy [9, 21, 22]. Therefore, it is possible that not all mPLNs require high radiation doses to achieve pelvic nodal control. To select patients who require dose escalation for regional control, risk factors for nodal failure should be addressed. Most previous studies have focused on mPLN size as a risk factor for nodal failure. However, large nodal size alone is not sufficient for predicting PNF after definitive radiotherapy.

In our study, high levels of pre-CCRT SCC-Ag and multiple lymph node involvement were significant factors for PNF after CCRT. Serum SCC-Ag is produced by squamous epithelium formation of cervical cells and increases during neoplastic transformation of the squamous epithelium in the cervix [24]. High serum SCC-Ag has been suggested as a predictive biomarker for advanced disease, poor response to treatment, early relapse after treatment and poor DFS in patients with cervical cancer. SCC-Ag cut-off values varied across studies, depending on patient characteristics and treatment methods [25–27]. In this study we found that more than one-quarter of the patients with serum SCC-Ag >6.8 ng/mL developed nodal failure after WPRT at 50.4 Gy. Also, >2 mPLNs at diagnosis of cervical cancer was significantly related to frequent nodal failure in our study. The negative impact of multiple mPLNs on patient outcomes has been reported in other studies. Two previous studies have shown that patients with $\geq$3 mPLNs had significantly lower DFS and OS than those with <3 mPLNs after definitive CCRT for cervical cancer [28, 29]. In the present analysis, a combination of the two prognostic factors, pre-CCRT SCC-Ag >6.8 ng/mL and number of mPLNs >2, can be a guide in defining a high-risk group for nodal failure. High serum SCC-Ag and multiple mPLNs appear to represent extensive cancer involvement within the pelvic cavity, thereby causing frequent nodal relapses after moderate dose radiotherapy. More than 40% of the patients with the two risk factors developed nodal failure after 50.4 Gy of WPRT. Given the poor nodal control after WPRT without nodal boost, intensifying the treatment might be necessary for patients with the risk factors. Radiation dose escalation or administering more effective chemotherapy might be an option to achieve a better outcome in patients with the risk factors. However, because we analysed nodal failure risk in a relatively small number of patients, further studies are needed to optimize radiotherapy for patients at high risk of nodal failure. In addition, we found that patients without the risk factors did not develop nodal recurrence after WPRT even without nodal boost irradiation. For these patients at low risk of nodal failure, WPRT without nodal boost is thought to be sufficient when CCRT is administered. This finding suggests that it would be feasible to individualize nodal dose intensification on the basis of the risk groups.

Even though the risk groups can define patients at risk of PNF, we could not find an association between the risk groups and OS. In multivariate analyses, the prognostic factors for PNFFS, such as SCC-Ag level and mPLN number, were not associated with DFS or OS. Rather, OTT and PNF were significant factors affecting DFS and OS. Given that prognostic factors had different influences on PNFFS, DFS and OS, it is necessary to consider specific risk factors for PNFFS when pelvic nodal boost radiotherapy is planned. Since PNF itself was predictive for inferior OS in our study, an intensification of nodal treatment is expected to help improve OS. Besides, in line with another study that reported unfavorable prognosis after definitive CCRT with long OTT [30], we also found that longer OTT was a predictive factor for inferior DFS and OS. Therefore, efforts should be made to reduce OTT to <51 days to achieve a favorable outcome.

When nodal failures occurred in our patients, one-third of the failures were found in lymph node regions other than that of the initially involved lymph node in our study. Considering that nodal boost irradiation can be administered to iPLN regions only, nPLN recurrence itself might be a challenging issue in clinical practice. Similar to our findings, previous studies have shown that PNF developed at both iPLN and nPLN after definitive radiotherapy [15, 18]. The proportions of nPLN failures of all the PNF were different depending on the dose of nodal boost. Nomden *et al*. have shown that the sites of PNF were within the elective pelvic target volume (n = 29 patients), within the nodal boost volume (n = 24 patients) and in both the elective and nodal boost volumes (n = 22 patients) among 75 patients with in-field PNF [15]. Also, in a study by Ramlov *et al*., PNFs were found in the elective pelvic volume (n = 2), nodal boost volume (n = 3) and both the elective and nodal boost volumes (n = 3) after a median nodal dose of 62 Gy EQD2 [18]. Given the possibilities of nPLN failure, dose escalation to whole PLN chains might be an option for patients at high-risk of nPLN failure. In our study, a high level of pre-radiotherapy SCC-Ag was associated with the risk of nPLN failure. Further studies are necessary to determine the optimal treatment for preventing nPLN failure.

Recently, intensity-modulated radiotherapy (IMRT) has been widely adopted in the management of cervical cancer. IMRT can provide a high radiation dose to the target while minimally affecting surrounding organs [31]. Boost radiotherapy to the mPLN can be implemented by using IMRT. Even though IMRT was not performed in

our patients, the risk factors for PNF in our study can help better stratify patients who require boost radiotherapy for mPLN. In addition, more effective systemic treatments such as maintenance chemotherapy after CCRT or the addition of an immune check-point inhibitor to CCRT are expected to give benefit for patients with locally advanced cervical cancer. Ongoing clinical trials like OUTBACK [32] or CALLA [33] can be of assistance in validating the efficacy of systemic treatments in the future.

We note the limitations of our study. Firstly, we included a small number of patients who were treated at a single center during a relatively long time period of 10 years. Due to the small sample size and the retrospective study design, there might be a bias in analysing risk factors for survival. Besides, there is the possibility of over- or under-estimation of actual radiation dose to pelvic nodal regions. In definitive radiotherapy for cervical cancer, ICBT is administered after or during WPRT. In our study, the dose of ICBT was prescribed to point A using a 2D brachytherapy technique, and central shielding was applied after WPRT of 45 Gy in this study. The point A is located 2 cm superior to the external cervical os and 2 cm lateral to the cervical canal [34], and the midline shielding is a field blocking the midline of the pelvis using 4 cm-wide shields to administer radiation to the parametrium with shielding of the rectum and bladder. Therefore, nodal doses might vary depending on the location of the lymph nodes. Moreover, we cannot measure the ICBT radiation dose that extends to the pelvic nodal regions. Given that the radiation dose from ICBT significantly contributes to the dose in the pelvic nodal area [35, 36], our patients presumably received >45–50.4 Gy to their pelvic nodes. Therefore, such uncertainties of pelvic nodal doses should be considered when applying our results to other patients. Despite this drawback, we think that our study has important implications for the determination of risk groups for PNF in definitive CCRT for node-positive cervical cancer.

CONCLUSIONS

In the absence of pelvic nodal boost, ~80% of patients achieved nodal control after definitive CCRT for node-positive SCC of the cervix. Levels of pre-radiotherapy SCC-Ag and the number of mPLNs were significant factors for predicting PNF. Patients with both risk factors developed frequent nodal failures. Therefore, nodal boost radiotherapy can be optimized by using the risk factors in definitive radiotherapy for patients with node-positive cervical cancer.

SUPPLEMENTARY DATA

Supplementary data are available at the *Journal of Radiation Research* online.

ACKNOWLEDGMENT

The institutional review board of the Samsung Medical Center approved this study (SMC 2019-03-163-001).

CONFLICT OF INTEREST

None declared.

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