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Prognostic factors associated with radiotherapy for cervical cancer with computed tomography-detected para-aortic lymph node metastasis

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Patients with cervical cancer diagnosed with a para-aortic lymph node (PALN) metastasis by computed tomography (CT) scan were analyzed to identify associated prognostic factors. A total of 55 patients were reviewed, and 27 of these patients underwent extended-field radiotherapy (EFRT). The median PALN dose in patients receiving EFRT was 45 Gy (range, 27–57.6 Gy). Of the 55 patients, 28 underwent pelvic radiotherapy (RT); concurrent chemoradiotherapy (CCRT) was administered to 41 patients. The Kaplan–Meier method was used to calculate the actuarial rate. Multivariate analysis was performed using the Cox proportional hazards model. Five-year overall survival (OS) rates were 41% and 17.9% in patients undergoing EFRT and pelvic RT ($P = 0.030$), respectively. Age < 53 years ($P = 0.023$), FIGO Stage I–II ($P = 0.002$), and treatment with EFRT ($P = 0.003$) were independent predictors of better OS. The use of CCRT ($P = 0.014$), Stage I–II ($P = 0.002$), and treatment using EFRT ($P = 0.036$) were independent predictors of distant metastasis. In patients undergoing EFRT plus CCRT, the 5-year OS was 50%. Three-year PALN disease-free rates were 8.8%, 57.9% and 100% ($P < 0.001$) in CCRT patients who received PALN doses of 0 Gy, ≤45 Gy and ≥50.4 Gy, respectively. Although PALN metastasis is thought to be distant metastasis in cervical cancer, EFRT plus CCRT shows a good outcome, particularly in younger patients in an early FIGO stage. Cervical cancer with a PALN metastasis should not be considered incurable. Doses ≥50.4 Gy for treating PALN may result in better disease control.

Keywords: para-aortic lymph node; cervical cancer; extended-field; prognostic factors; concurrent chemoradiotherapy

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INTRODUCTION

Cervical cancer outcomes following definitive radiotherapy can be improved by concurrent chemotherapy [1, 2]. However, clinical trials of concurrent therapies have been limited to patients with pelvic diseases. For cervical cancer patients, once a paraaortic lymph node (PALN) metastasis occurs, prognosis is poor [3]. PALN metastasis occurs midway between locoregional and systemic disease in cervical cancer. The distant metastasis (DM) rate beyond the PALNs ranges from 18.2–54.9% [4–8] following extended-field radiotherapy (EFRT). The 5-year survival rate is from 24–57.1% [4–6, 8–12].

Nearly all patients examined in previous studies had histologically proven PALN metastasis. However, surgical staging was not performed due to the risk of complications and the negative impact of staging on treatment outcomes [13]. Therefore, many patients may not have histologically proven PALN metastasis. In these cases, PALN metastasis is detected by computed tomography (CT), magnetic resonance imaging (MRI), or ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET). CT is widely used as a non-invasive staging tool for patients with cervical cancer. However, no studies have evaluated treatment outcomes for patients with CT-detected PALN metastasis. Additionally, no comprehensive study has reported prognostic factors for PALN metastasis. Thus, we conducted a retrospective study to identify prognostic factors in patients with cervical cancer.

MATERIALS AND METHODS

Patient characteristics

Using data collected from November 1993 to January 2010, we retrospectively analyzed 55 patients with cervical cancer who had been diagnosed with PALN metastasis by CT. Lymph nodes >1 cm in diameter were considered to be abnormal according to the radiographic criteria used for declaring PA lymph node positivity by CT [14]. The institutional review board of Chang Gung Memorial Hospital approved this study (97-1743B). Table 1 lists patient characteristics. All patients underwent physical examination, abdominal CT scan, chest X-ray, cervical biopsy, and laboratory tests, including a complete blood count, blood urea nitrogen (BUN), creatinine, squamous cell carcinoma antigen (SCC-Ag), and carcinoembryonic antigen (CEA), before radiotherapy. No patients underwent PET before radiotherapy. Only two patients had surgically confirmed PALN metastasis independent of a CT-detected positive status. Patients with other distant metastases but no inguinal lymph node metastasis, and those with incomplete radiotherapy, were excluded from this study.

Radiotherapy and chemotherapy

EFRT was performed for 27 patients who initially underwent 1.8–2 Gy external beam radiation therapy (EBRT) to the whole pelvis and PALN region once daily with five fractions per week. EBRT was performed using intensity-modulated radiotherapy (IMRT) in three patients, anteroposterior (AP)-posteroanterior (PA) opposing portals in three patients, and the 4-field technique in the remaining 21 patients. The superior margin of the PALN field was located at the upper border of L1–L2 in 21 patients and L3–L4 in six patients. The PALN dose was 27–57.6 Gy (median, 45 Gy). For the 28 patients who underwent pelvic RT, AP/PA opposing portals, the four-field technique, and IMRT were used in 4, 22 and one patient(s), respectively. Typically, the whole pelvic dose was between 39.6 and 45 Gy and administered in 22–25 fractions. A parametrial boost (to 46.8–59.4 Gy) with central shielding was delivered to IIB and IIIB patients. Eight patients with a poor response to initial EFRT received low pelvis RT (50.4–59.4 Gy) without central shielding. Four patients underwent a 3D conformal boost to 61–70.2 Gy without brachytherapy after whole pelvic RT.

Treatment was administered using 10 or 15 MV X-rays from a linear accelerator (2100C, 2100EX, Varian Medical Systems, Palo Alto, CA, USA). Of the 55 patients, 51 received intracavitary brachytherapy twice per week using an ^{192}Ir high-dose-rate unit (MicroSelectron, Nucletron Co., Veenandaal, The Netherlands) after EBRT. These procedures have been described previously [15]. Prescribed doses were 22.5–27 Gy and were administered in 4–6 fractions for point A. Concurrent chemoradiotherapy (CCRT) was administered to 41 patients. Concurrent chemotherapy consisted of a cisplatin-based regimen in most patients. The regimens used included monthly 5-fluorouracil plus cisplatin ($n = 24$), weekly cisplatin ($n = 8$), monthly cisplatin ($n = 3$), monthly 5-fluorouracil plus cisplatin and mitomycin ($n = 3$), bleomycin plus cisplatin ($n = 1$), 5-fluorouracil plus mitomycin ($n = 1$), and 5-fluorouracil plus bleomycin ($n = 1$).

Follow-up and statistics

Physical examination, laboratory tests, abdominal CT scans, and chest X-rays were used for follow-up analysis. An independent *t*-test and the chi-square test or Fisher's exact test were used to compare continuous and categorical data between groups, respectively.

The definition of response rate was based on World Health Organization (WHO) guidelines [16]. Complete response (CR) was defined as tumor disappearance, partial response was defined as a > 50% tumor reduction in the cross product, and progressive disease was defined as a > 25% increase in the tumor cross product. A stable disease was defined as a tumor size between that for a partial response and progressive disease. Survival time was calculated from the end of treatment to the date of death or last follow-up. Pelvic failure (PF) was defined as persistent disease or any recurrence within the pelvic field, and DM was defined as recurrence beyond the PALNs. The Kaplan–Meier method was used to construct curves for overall survival (OS), cancer-specific

Table 1 Characteristics of patients without ($n = 28$) and with ($n = 27$) EFRT

Parameters	Pelvic RT	EFRT	*P*-value
Age			0.898
<53 years	13 (46.4%)	13 (48.1%)	
≥53 years	15 (53.6%)	14 (51.9%)	
Pathology			
squamous cell carcinoma	24 (85.7%)	24 (88.9%)	1.000
others (non-SCC)	4 (14.3%)	3 (11.1%)	
Stage			0.480
I–II	13 (46.4%)	10 (37 %)	
III–IV	15 (53.6%)	17 (63 %)	
Hemoglobin			0.461
<10 g/dl	9 (32.1%)	13 (48.1%)	
≥10 g/dl	14 (50.0%)	11 (40.7%)	
unknown	5 (17.9%)	3 (11.1%)	
Pelvic node metastasis on CT scan			0.001
no	16 (57.1 %)	4 (14.8%)	
yes	12 (42.9 %)	23 (85.2%)	
Highest level of PALN metastasis			0.271
L3–L4	10 (35.7%)	6 (22.2%)	
L1–L2	18 (64.3%)	21 (77.8%)	
Size of PALN metastasis			0.079
≤1.5 cm	17 (60.7%)	10 (37.0%)	
>1.5 cm	11 (39.3%)	17 (63.0%)	
Hydronephrosis			0.698
no	17 (60.7 %)	15 (55.6 %)	
yes	11 (39.3 %)	12 (44.4%)	
SCC-Ag level			0.644
<40 ng/ml	19 (67.9%)	15 (55.6%)	
≥40 ng/ml	6 (21.4%)	8 (29.6%)	
unknown	3 (10.7%)	4 (14.8%)	
CEA level			0.446
<10 ng/ml	16 (57.1 %)	12 (44.4 %)	
≥10 ng/ml	6 (21.4%)	10 (37.0 %)	
unknown	6 (21.4 %)	5 (18.5 %)	
Concurrent chemotherapy			0.246
no	9 (32.1%)	5 (18.5 %)	
yes	19 (67.9 %)	22 (81.5%)	
Intracavitary brachytherapy			0.568
no	3 (10.7%)	1 (3.7%)	
12–18.5 Gy at point A	3 (10.7%)	0 (0%)	
20–27 Gy at point A	22 (78.6%)	26 (96.3%)	

CT = computed tomography, SCC-Ag = squamous cell carcinoma antigen, CEA = carcinoembryonic antigen, EFRT = extended-field radiotherapy.

survival (CSS), DM and PF. The log-rank test was used to compare survival curves. Multivariate analysis was performed using the Cox regression model with the stepwise forward procedure. A logistic regression model was used to predict PALN control rate by dose. All variables, including age, stage, pathology, positive pelvic nodes, PALN level, PALN size, hemoglobin, EFRT, brachytherapy dose, CCRT, SCC-Ag and CEA, were treated as categorical data. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 17.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Outcomes and complete response rate of PALNs

The median follow-up time was 61.1 months (7–161 months) for living patients. The 5-year OS and PF rates were 29.8% and 32%, respectively. Patients undergoing EFRT showed a higher 5-year OS rate (41%) compared to those who underwent pelvic RT (17.9%) ($P = 0.030$) (Fig. 1). The CSS rate was also higher in EFRT patients ($P = 0.007$) (Fig. 2). However, corresponding PF rates for EFRT and pelvic RT were 29.9% and 33.4%, respectively ($P = 0.515$). In patients who underwent EFRT plus CCRT, the 5-year OS rate was 50%. CR rates of PALN metastasis were 42.1%, 66.7% and 100% ($P = 0.009$) in CCRT patients who received PALN doses of 0 Gy, ≤45 Gy and ≥50.4 Gy, respectively; the corresponding 3-year PALN disease-free rates among the different dose groups were 8.8%, 57.9% and 100%, respectively ($P < 0.001$). Logistic regression for PALN recurrence in CCRT patients revealed that the PALN dose was an independent factor ($P = 0.001$) (odds ratio 0.944; 95% CI 0.913–0.976). Plot fitting showed a dose–response relationship (Fig. 3). Details of distant metastases are shown in Table 2. The most common site was the supraclavicular lymph node (SCLN). Incidences of SCLN recurrences were 25.9% and 21.4% in patients with and without EFRT, respectively. In 13 patients with SCLN relapse, four patients received SCLN

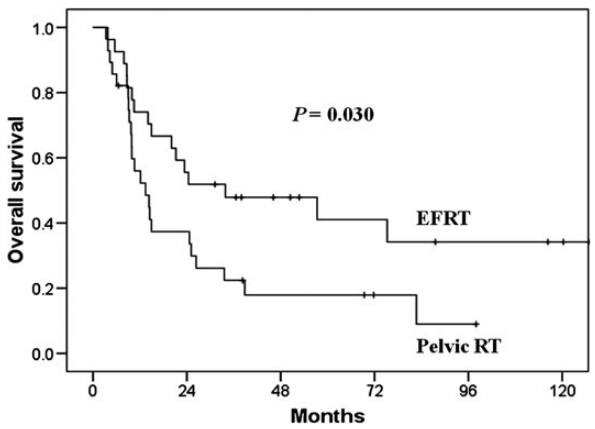

Fig. 1. The overall survival rates in patients with and without EFRT.

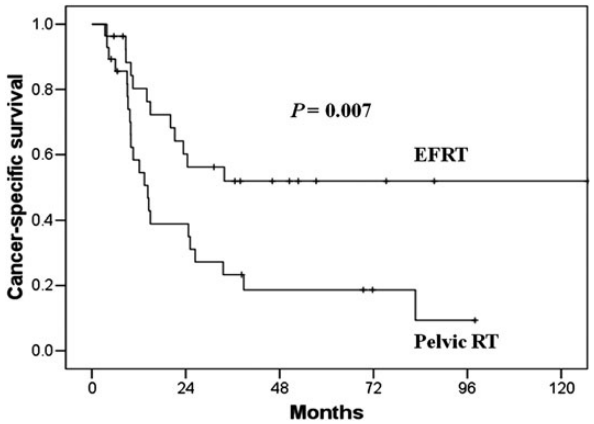

Fig. 2. The cancer-specific survival rates in patients with and without EFRT.

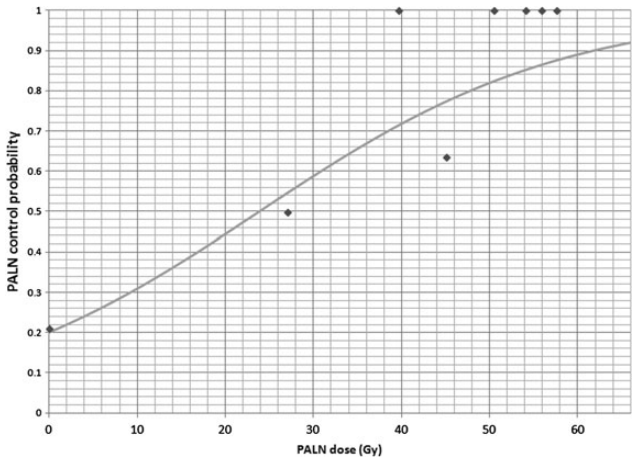

Fig. 3. The dose–response relationship using a logistic regression model for PALN recurrence in patients with CCRT. The diamond symbol indicates the observed PALN control rate. The fitted curve indicates the expected PALN control probability.

Table 2 Distant metastasis beyond PALN

Relapse patterns	Pelvic RT ($n = 28$)	EFRT ($n = 27$)
SCLN	6	7
Mediastinal LN	1	5
Lung	5	3
Liver	5	3
Bone	5	0
Skin	0	1
Peritoneum	3	2
Pancreas	1	0
Spleen	1	0
Hepatic hilar LN	0	2

SCLN = supraclavicular lymph node.

Table 3 Univariate and multivariate analyses of overall survival (OS) rates

Parameters	UVA		MVA	
	5-year OS (%)	*P*-value	HR (95% CI)	*P*-value
Age (<53 vs ≥53 years)	56.4 vs 26.0	0.011*	2.249 (1.118–4.526)	0.023*
Stage III/IV (yes vs no)	22.7 vs 41.1	0.021*	3.243 (1.514–6.948)	0.002*
Pathology (SCC vs non-SCC)	35.5 vs 14.3	0.092		0.086
High level of PALN (yes vs no)	24.7 vs 41.7	0.070		0.133
PALN size > 1.5 cm (yes vs no)	34.2 vs 24.7	0.602		0.472
HDR-ICBT Point A dose > 20 Gy	31.6 vs 17.9	0.103		0.787
Positive pelvic node (yes vs no)	30.2 vs 28.0	0.793		0.971
Hemoglobin (g/dl) (<10 vs ≥10)	31.8 vs 30.5	0.866		0.672
SCC-Ag level (ng/ml) (<40 vs ≥40)	39.2 vs 26.8	0.341		0.470
CEA (ng/ml) (<10 vs ≥10)	43.6 vs 31.3	0.426		0.389
EFRT (yes vs no)	41.0 vs 17.9	0.030*	0.346 (0.173–0.694)	0.003*
CCRT (yes vs no)	35.6 vs 15.7	0.311		0.714

CCRT = concurrent chemoradiotherapy, SCC-Ag = squamous cell carcinoma antigen, CEA = carcinoembryonic antigen, HR = hazard ratio, CI = confidence interval, UVA = univariate analysis, MVA = multivariate analysis. *Statistically significant.

Table 4 Univariate and multivariate analyses of cancer-specific survival (CSS) rates

Parameters	UVA		MVA	
	5-year OS (%)	*P*-value	HR (95% CI)	*P*-value
Age (<53 vs ≥53 years)	34.2 vs 36.9	0.447		0.080
Stage III/IV (yes vs no)	23.6 vs 51.4	0.010*	3.243 (1.443–6.007)	0.004*
Pathology (SCC vs non-SCC)	36.3 vs 21.4	0.423		0.187
High level of PALN (yes vs no)	31.5 vs 41.7	0.165		0.565
PALN size > 1.5 cm (yes vs no)	44.6 vs 25.7	0.479		0.167
HDR-ICBT Point A dose > 20 Gy	37.2 vs 17.9	0.054		0.119
Positive pelvic node (yes vs no)	36.3 vs 31.4	0.824		0.906
Hemoglobin (g/dl) (<10 vs ≥10)	31.8 vs 33.4	0.765		0.998
SCC-Ag level (ng/ml) (<40 vs ≥40)	41.8 vs 29.2	0.587		0.831
CEA (ng/ml) (<10 vs ≥10)	45.5 vs 36.1	0.619		0.686
EFRT (yes vs no)	51.9 vs 18.7	0.007*	0.307 (0.148–0.634)	0.001*
CCRT (yes vs no)	37.6 vs 25.7	0.482		0.717

CCRT = concurrent chemoradiotherapy, SCC-Ag = squamous cell carcinoma antigen, CEA = carcinoembryonic antigen, HR = hazard ratio, CI = confidence interval, UVA = univariate analysis, MVA = multivariate analysis. *Statistically significant.

salvage irradiation (60 Gy/30 fractions), and two of the four patients are alive.

Univariate and multivariate analyses for outcome

Table 3 shows the results of the univariate and multivariate analyses. A FIGO Stage III–IV ($P = 0.002$), age ≥53 years ($P = 0.023$), and pelvic RT ($P = 0.003$) were independent predictors of lower OS. A FIGO Stage III–IV ($P = 0.004$) and pelvic RT ($P = 0.001$) were also independent predictors of lower CSS (Table 4). A FIGO Stage III–IV ($P = 0.002$), no CCRT ($P = 0.014$), and pelvic RT ($P = 0.032$) were independent predictors of DM in addition to PALNs (Table 5). In analyses of patients undergoing EFRT, the only prognostic factor of CSS was Stage III–IV ($P = 0.031$) (HR

Table 5 Univariate and multivariate analyses of distant metastasis (DM) rates

Parameters	UVA		MVA	
	5-year DM (%)	*P*-value	HR (95% CI)	*P*-value
Age (<53 vs ≥53 years)	66.4 vs 62.7	0.775		0.606
Stage III/IV (yes vs no)	75.0 vs 51.2	0.025*	3.781 (1.622–8.815)	0.002*
Pathology (SCC vs non-SCC)	63.7 vs 100	0.401		0.330
High level of PALN (yes vs no)	67.3 vs 63.5	0.146		0.288
PALN size > 1.5 cm (yes vs no)	66.4 vs 64.6	0.461		0.923
HDR-ICBT Point A dose > 20 Gy	36.1 vs 28.6	0.090		0.374
Positive pelvic node (yes vs no)	70.5 vs 56.4	0.283		0.624
Hemoglobin (g/dl) (<10 vs ≥10)	71.6 vs 60.7	0.333		0.969
SCC-Ag level (ng/ml) (<40 vs ≥40)	60.0 vs 78.2	0.400		0.508
CEA (ng/ml) (<10 vs ≥10)	60.9 vs 60.1	0.753		0.727
EFRT (yes vs no)	55.1 vs 77.2	0.085	0.452 (0.515–0.948)	0.036*
CCRT (yes vs no)	60.4 vs 81.1	0.122	0.354 (0.154–0.814)	0.014*

CCRT = concurrent chemoradiotherapy, SCC-Ag = squamous cell carcinoma antigen, CEA = carcinoembryonic antigen, HR = hazard ratio, CI = confidence interval, UVA = univariate analysis, MVA = multivariate analysis. *Statistically significant.

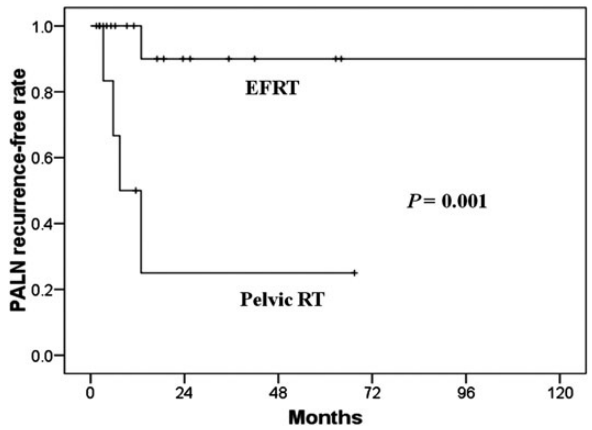

Fig. 4. The PALN recurrence-free rate in patients with a complete response of PALN metastasis following concurrent chemotherapy with or without EFRT.

6.432; 95% CI 6.103–31.645). Non-SCC showed a statistical trend ($P = 0.055$). Stage III–IV ($P = 0.062$) and non-SCC ($P = 0.053$) also achieved a statistical trend for OS. The 5-year PF and DM rates were 29.9% and 55.1%, respectively.

PALN recurrence in patients undergoing chemotherapy with concurrent pelvic RT or EFRT

If the initial CCRT achieved CR for PALN metastasis in patients undergoing chemotherapy with concurrent pelvic RT or EFRT, the corresponding 5-year PALN recurrence rates were 75% and 10%, respectively ($P = 0.001$) (Fig. 4). We noted four patients (19%) with in-field failure, one patient (4.8 %) with out-field failure, and one patient (4.8 %) with both-field failure in EFRT plus CCRT group with CT scan follow-up ($n = 21$). No patient with in-field failure received PALN salvage irradiation.

Adverse events in patients undergoing CCRT plus EFRT

A combination of extended-field RT and concurrent chemotherapy was associated with high rates of acute and long-term toxicity according to a study by the RTOG [17, 18]. We reported acute and long-term toxicity in these patients (Table 6). In general, fewer than 20% of patients had Grade 3 or greater acute hematologic or gastrointestinal (GI) toxicities. Grade 3 or greater late GI or genitourinary (GU) toxicities were found in more than 10% of patients.

DISCUSSION

Managing PALN metastasis remains a challenge for cervical cancer from a prophylactic and therapeutic standpoint in radiation oncology. Clinical stage is correlated with the incidence of PALN metastasis in patients with an initial diagnosis of cervical cancer. In the largest series to date, Berman *et al.* reported that the incidence of PALN metastasis was 5% for Stage IB, 16% for Stage II, and 25% for Stage III [19]. Although surgical staging can accurately detect PALN metastasis, other factors such as surgical complications, delayed radiotherapy, and radiation-induced bowel complications [10] can compromise its advantage. Lai *et al.* conducted the first randomized study to evaluate surgical staging for

Table 6 Adverse events in patients undergoing CCRT plus EFRT ($n = 22$)

Adverse events	Grade				
	1	2	3	4	Grade 3–4 (%)
Acute					
Hepatic	1	0	0	0	0
Infection/febrile neutropenia	3	0	1	0	4.5
Renal	3	3	0	0	0
Hematologic					
Leukopenia	9	3	3	1	18.2
Anemia	5	12	4	0	18.2
Thrombocytopenia	8	4	0	0	0
Gastrointestinal					
Nausea	3	1	0	0	0
Vomiting	3	2	0	0	0
Diarrhea	8	8	4	0	18.2
Late					
Enterocolitis	2	0	1	1	9.1
Proctitis	2	0	1	1	9.1
Cystitis	1	0	0	1	4.5

CCRT = concurrent chemoradiotherapy, EFRT = extended-field radiotherapy, CTC = common toxicity criteria.

locally advanced cervical cancer [13] and found worse OS and progression-free survival than that observed in clinical staging. Mota *et al.* did not suggest routine pretreatment with surgical staging in patients with locally advanced cervical cancer [20]. However, non-invasive detection of PALN metastasis is an alternative approach [21]. A CT scan is the most commonly used tool for detecting LN metastasis. Different criteria (>1, or > 1.5 cm) for CT-detected positive PALN metastasis have been noted in contradictory studies. A meta-analysis reported a sensitivity of 46.4% and a specificity of 93.2% using the size criterion of >1.5 cm [22]. Whitley *et al.* reported a sensitivity of 80% and a specificity of 92% using the size criterion of >1 cm [14]. Matsukuma *et al.* reported a sensitivity of 71.4% and a specificity of 96.8% using the size criterion of >1 cm [23]. If the >1.5 cm criterion was used, sensitivity and specificity were 57.1% and 98.4%, respectively. Therefore, the size criterion of >1 cm was deemed acceptable in our study. As in the present study, Kazumoto *et al.* used the >1 cm criterion in their report of treatment outcomes [24]. FDG-PET scanning showed a sensitivity of 75% and a specificity of 92% for detecting PALN metastasis [25]. Kitajima *et al.* reported sensitivities of 16.7%, 66.7% and 93.3% for detecting metastatic lesions ≤4 mm, 5–9 mm and ≥10 mm, respectively [26]. Although PET is more sensitive than CT, PET is not routinely used in Taiwan for pretreatment staging of cervical cancer due to health insurance limitations. Therefore, CTs remain an important tool for clinical staging, particularly in a hospital without Medicare coverage of PET scans for cervical cancer.

There are some differences between our study and previous studies related to PALN metastasis. The follow-up time of the present study was > 5 years. A longer follow-up time allows for more conclusive results. Because histologically proven PALN metastases have been noted in most studies (Table 7), RT fields should include PALN. As a result, studies using only pelvic RT in affected patients have not been reported. Although only two patients (7.7%) in our study showed pathologic evidence of PALN involvement, the EFRT outcome was comparable to those reported in other studies. The Kazumoto study, with similarly diagnosed criteria and treatment techniques, reported outcomes including tolerability and control rate of low-dose cisplatin with EFRT in patients with PALN metastases diagnosed by CT imaging [24]. A higher PALN dose than in our study can result in a higher 5-year OS (56.3%) with feasible tolerability. Only 6.25% (1/16) of PALN recurrence was noted in the Kazumoto study. This suggests a dose–response relationship in patients with PALN metastasis detected on CT images. Based on the results of Kazumoto *et al.* and our studies, a higher PALN dose with concurrent chemotherapy may result in longer survival and feasible tolerability. The results of this study can be applied for patients in whom fine-needle aspiration or surgical staging is not considered. Additionally, PET can detect distant metastases other than PALNs. Consequently, PET is useful for patients with a CT-detected PALN metastasis before aggressive treatment such as EFRT plus CCRT.

Few studies have reported PALN response rates. Walker *et al.* [8] and Kim *et al.* [5] reported response rates of 96% and 85% after EFRT with concurrent chemotherapy, respectively. In the present study, EFRT with concurrent chemotherapy resulted in a good response rate (94.7%). We also found that a PALN irradiation dose can yield a different PALN response in patients receiving concurrent chemotherapy. In this study, doses >50 Gy were correlated with a complete response and higher PALN disease-free rate. This is the first article to report a dose–response relationship of PALN irradiation in patients diagnosed with cervical cancer and simultaneous isolated PALN metastasis.

The role of concurrent cisplatin-based chemotherapy is well established in patients with locally advanced cervical cancer [1, 2, 27]. However, its efficacy is unclear in patients initially diagnosed with PALN metastasis. Stryker *et al.* suggested that cisplatin-based chemotherapy may be beneficial [6]. In our study, the 5-year OS rate of 20 patients undergoing EFRT plus CCRT (44.7%) agreed with that reported in other recent studies [5, 8]. Walker *et al.* [8] delivered EFRT plus paclitaxel and cisplatin to patients with PALN metastasis and

Table 7 Literature review of outcomes following EFRT for PALN metastasis

Investigators	Tissue evidence	Dose (Gy)	Chemotherapy	Outcome
Piver *et al.,* 1981 [40] (*n* = 31)	100%	44–60	0%	5-year DFS: 9.6%
Potish *et al.,* 1983 [41] (*n* = 18)	0%	43.5–50.75	0%	5-year DFS: 40%
Robin *et al.,* 1984 [11] (*n* = 14)	100%	40–50	0%	5-year OS: 57.1%
Vigliotti *et al.,*1992 [12] (*n* = 43)	97.7%	39.6–60	0%	5-year OS: 32%
Varia *et al.,* 1998 [7] (*n* = 86)	100%	45	100% (CF)	3-year OS: 39%
Varia *et al.,* 1998 [7] (*n* = 51)	100%	45	100% (CH)	3-year OS: 29%
Cosin *et al.,* 1998 [36] (*n* = 46)	100%	45.76 (mean)	>50% (c)	5-year DFS: 43% (grossly resectable)
Kim *et al.,* 1998 [10] (*n* = 43)	100%	45 (mean)	56% (C)	5-year OS: 24%
Goff *et al.,* 1999 [9] (*n* = 14)	100%	45	Not all (c)	5-year OS: 52%
Stryker *et al.,* 2000 [6] (*n* = 35)	100%	42.5–51	17%	5-year OS: ~ 30%
Grigsby *et al.,* 2001 [4] (*n* = 43)	100%	14.4–65	0%	5-year OS: 32%
Walker *et al.,* 2009 [8] (*n* = 27)	100%	50.4–54	100% (CP)	5-year OS: 45%
Kim *et al.,* 2009 [5] (*n* = 33)	30%	59.4	100% (C ± P)	5-year OS: 47%
Tsai *et al.,* 2010 [42] (*n* = 6)	unknown	45	100% (C)	5-year OS: 66.7%
Kim *et al.,* 2012 [43] (*n* = 101)	unknown	59.4	100% (C ± P)	3-year OS: 69%
Small *et al.*, 2011 [17] (*n* = 16)	unknown	54-59.	100% (C)	2-year OS: 54%
Kazumoto *et al.*, 2011 [24] (*n* = 16)	0%	54-60	100% (C)	5-year OS: 56.3%
Present study (*n* = 27)	7.4%	27–57.6 (median 45)	81.5% (C)	3-year OS: 47.9% 5-year OS: 41.0%

OS = overall survival, DFS = disease-free survival, DM = distant metastasis, NS = no significance, NA= no analysis, CCRT = concurrent chemoradiotherapy, EFRT = extended-field radiotherapy, C = cisplatin as a major regimen, F= 5-FU, P = paclitaxel, c = cisplatin as a partial regimen.

noted excellent OS of Stage IIIB (*n* = 12) and IVA (*n* = 3) patients. Half of the IIIB and all IVA patients were alive after at least 45 months. The mean survival time until death of Stage IIIB patients was 28 months. Monk *et al.* reported in a Phase III trial that paclitaxel and cisplatin may be superior to other cisplatin doublet combinations for Stage IVB, recurrent, or persistent cervical carcinoma [28]. FIGO stage is a very important prognostic factor in cervical cancer patients without PALN metastasis. Even after treatment with EFRT in 27 patients, the FIGO stage was a prognostic factor for CSS and a trend for OS. Poor pelvic control and DM may contribute to poor OS and CSS in an advanced FIGO stage. Non-SCC also showed a poor prognostic trend for OS and CSS. Its role in outcomes in this study is comparable with those found previous reports [29–32].

However, the benefit of a CR of the PALNs could not be translated into a survival benefit since advanced stages of pelvic control may compromise the effect of a CR. Based on our results, which demonstrated that a CR of the PALNs decreased DM beyond the PALNs and increased CSS in patients without PF, adding paclitaxel to cisplatin and a PALN dose >50 Gy may improve the outcome (local control and DM) in Stage III–IV patients. However, further randomized studies are required to confirm the effect of paclitaxel.

Age 53 years or older was also predictive of OS in the present study. Previous studies have shown controversial conclusions regarding the age effect in patients undergoing pelvic irradiation. For example, Kunos *et al.* reported excess hematological but not genitourinary toxicity in patients 55 years or older receiving cisplatin and undergoing pelvic irradiation [33]. These patients had a similar progression-free survival and OS compared with younger patients. In contrast, Monk *et al.* [34] noted better OS and progression-free survival in patients 51–60 years of age, and Seo *et al.* noted worse OS in patients aged 70 years or older [35]. Our population of patients (PALN metastasis) was different from those examined in previous studies. It is difficult to interpret worse OS in elderly patients. However, age in our study was not significantly associated with CSS or DM. Additionally, non-cervical cancer-related factors may be involved in OS.

A major limitation of this study was that it was a retrospective comparison due to selection bias of EFRT. Because few patients showed pathologic evidence of PALN metastasis in the present study, the choice of EFRT or pelvic RT was

dependent on physician preference. Since most PALN metastases are accompanied by concurrent pelvic lymphadenopathy [36], some physicians may identify a false-positive PALN metastasis in patients without pelvic lymphadenopathy. Other concerns, such as hematological toxicity, enterotoxicity and nephrotoxicity, can lead a physician to choose pelvic RT as a conservative treatment, particularly in pelvic node-negative, elderly, poor performance, or hydronephrotic patients. Patients undergoing pelvic RT showed more favorable prognostic factors, including small PALN size, negative pelvic nodes, a low SCC-Ag level, a low CEA level and a high hemoglobin level. However, poor outcomes (OS, CSS and DM) were noted in these patients according to univariate and multivariate analyses. Our analysis revealed no role of positive pelvic node in outcomes. This may be because the positive pelvic node, which was treated by radiotherapy, was effectively controlled such that the presence of pelvic LN metastasis did not affect outcome. Based on the present analysis, EFRT is beneficial for PALN-positive patients, and pelvic RT is a suboptimal treatment for CT-detected PALN metastasis despite CCRT. Although a combination of EFRT and concurrent chemotherapy was associated with high rates of acute and long-term toxicities [17, 18], our results showed that the observed complications were acceptable (Table 6). For patients with comorbidity or old age, IMRT may be suitable due to acceptable acute and late toxicities [37, 38]. PET-CT is suggested in CT-detected PALN metastasis for detecting metastasis beyond PALN and for treatment planning of EFRT. Therefore, we do not recommend pelvic RT for CT-detected PALN metastasis, except for palliative therapy.

We first noted a dose–response relationship for PALN recurrence in patients undergoing CCRT. An ~ 20% PALN control rate was noted in patients undergoing pelvic RT (i.e. PALN dose = 0 Gy). This implies that chemotherapy has a mild therapeutic effect on PALN metastases if the PALN is not irradiated. We also noted that the progression of a PALN metastasis presented in-field failure. Therefore, this supports an adequate PALN dose for better PALN control. An initial PALN dose of ≥50.4 Gy showed an estimated >80% PALN control rate according to our logistic regression model (Fig. 3). In fact, none of the patients whose PALN dose was ≥50.4 Gy had an in-field PALN recurrence. Kazumoto *et al.* reported that 93.8% of PALN was controlled using a PALN dose 54–60 Gy [24]. This is compatible with the results of the present study, and an adequate dose to PALN is suggested. Once in-field PALN recurrence is noted due to a previous low PALN dose, re-irradiation using brachytherapy may be considered [39].

CONCLUSION

In conclusion, cervical cancer with simultaneous PALN metastasis is not incurable. EFRT plus CCRT can be used to achieve a good outcome, particularly in patients with an early FIGO stage and young age. Doses of ≥50.4 Gy for PALN can be used to achieve better disease control.

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