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ORIGINAL ARTICLE

Radical hysterectomy with or without para-aortic lymphadenectomy for patients with stage IB2, IIA2, and IIB cervical cancer: outcomes for a series of 308 patients

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Abstract
Background Although many studies have already shown that lymph node metastasis is one of the major prognostic factors for cervical cancer, the therapeutic significance of para-aortic lymphadenectomy for the surgical treatment of cervical cancer remains controversial.
Methods A total of 308 patients diagnosed with stage IB2, IIA2, or IIB cervical cancer and treated with radical hysterectomy were retrospectively investigated to assess the incidence of para-aortic lymph node metastasis and the clinicopathological factors linked to cervical cancer prognosis.
Results Para-aortic lymph node metastases were pathologically confirmed in 13 of the 136 patients (9.6 %) who underwent para-aortic lymphadenectomy. The incidence of para-aortic lymph node metastasis was significantly higher in the patients who had common iliac lymph node metastases (odds ratio 31.5, $p < 0.001$) according to logistic regression analysis. Common iliac lymph node metastasis was related to risk of recurrence (hazard ratio 2.43, $p = 0.003$) and death (hazard ratio 2.62, $p = 0.007$) in Cox regression analysis. Kaplan–Meier analysis and Cox regression analysis showed that para-aortic lymphadenectomy did not have a positive impact on survival in 308 patients or 140 pN1 patients, but para-aortic lymphadenectomy was related to better overall survival with a marginal trend toward significance ($p = 0.053$) in 30 patients with common iliac lymph node metastasis.
Conclusions Indication for para-aortic lymphadenectomy in the surgical treatment of stage IB2, IIA2, or IIB cervical cancer needs to be individualized. Patients with common iliac lymph node metastasis are possible candidates, and a prospective study is needed to clarify this issue.

Keywords Cervical cancer · Common iliac lymph node metastasis · Para-aortic lymphadenectomy · Radical hysterectomy

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Introduction

Cervical cancer is a common cancer in women worldwide, and many patients are diagnosed at an advanced stage, even though cancer screening programs have reduced the incidence of invasive cervical cancer. The five-year overall survival (OAS) rate of women with locally advanced FIGO (International Federation of Gynecology and Obstetrics) stage IB2, IIA2, or IIB cervical cancer is about 60 % according to a FIGO annual report [1]. Considering the associated 5-year OS of 60 %, the treatment of FIGO stage IB2–IIB cervical cancer is not well defined, and there is plenty of scope for discussion regarding the initial treatment of patients with stage IB2–IIB cervical cancer.

Many studies have already shown that lymph node metastasis is one of the major prognostic factors for cervical cancer, along with FIGO stage, tumor size, and tumor histology [2, 3]. In the surgical treatment of cervical cancer, pelvic lymph nodes (PLNs) are systematically removed and a radical hysterectomy is performed. Since the PLNs are the regional lymph nodes for cervical cancer and initial sites of metastasis, the significance of pelvic lymphadenectomy (PLA) is well accepted. On the other hand, para-aortic lymphadenectomy (PALA) is not included in the standard procedure as the para-aortic lymph nodes (PALNs) are not regional but distant lymph nodes for cervical cancer. Nevertheless, metastasis to PALNs is not rare in locally advanced cervical cancer. It is reported that metastasis to PALNs is present in 11 % of stage IB2 patients, 13 % of stage IIA patients, and 16 % of stage IIB patients by surgical staging [4]. It is also well accepted that patients with PALN metastasis show lower OAS and progression-free survival (PFS) when compared with patients with cervical cancer at the same FIGO stages who do not have PALN metastasis [5].

Several studies have reported the diagnostic value of PALA in cervical cancer. Although a variety of imaging techniques are available in this field, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), the accuracy of diagnoses made utilizing those modalities is too low. The negative predictive values (NPVs) of CT, MRI, PET, and PET-CT are 53–92, 75–91, 87–94, and 83–92 %, respectively [4]. Systematic PALA or PALN biopsy besides RH+PLA has a diagnostic role to play in the detection of pathological PALN metastases, and can point to the appropriate adjuvant therapies to apply.

However, the therapeutic significance of systematic PALA remains controversial. A lack of large-scale studies of systematic PALA for cervical cancer has meant that it has not been possible to verify the utility of systematic PALA as a treatment option for improving the prognosis of patients with locally advanced (stages IB2–IIB) cervical cancer. In the study reported in the present paper, we retrospectively evaluated a series of 308 patients with locally advanced cervical cancer (FIGO stages IB2, IIA2, or IIB) who received RH with or without PALA in multiple cancer centers to determine the significance of PALA as an initial surgical procedure for locally advanced cervical cancer.

Patients and methods

From 2005 to 2010, 308 patients diagnosed with FIGO stage IB2, IIA2, or IIB cervical cancer underwent primary surgical treatment at three regional cancer centers (Saitama Cancer Center, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, The University of Tokyo Hospital). One hundred seventy-two patients underwent radical hysterectomy + pelvic lymphadenectomy (RH+PLA), and 136 patients underwent radical hysterectomy + pelvic lymphadenectomy + para-aortic lymphadenectomy (RH+PLA+PALA). RH+PLA was conducted routinely in Saitama Cancer Center and RH+PLA+PALA was conducted routinely in the University of Tokyo Hospital and in the Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital with some exceptions, considering the risk of para-aortic lymph node metastasis. RH was performed by Piver's type 3 hysterectomy. PALA was conducted by removing para-aortic nodes (PANs) up to the level of the inferior mesenteric artery (IMA) and, if infra-IMA node metastasis was identified by intraoperative pathological examination, PANs were also removed up to the level of the left renal vein. Patients who received neoadjuvant therapy prior to surgical treatment were excluded from this study. Patients with a high risk of recurrence (pT2b, pN1, and/or deep myometrial invasion) were offered one of the following adjuvant therapies. Radiotherapy was administered with whole-pelvic external beam irradiation (50 Gy in 25 fractions or 50.8 Gy in 28 fractions, five times per week) and, if PAN metastasis was confirmed, the radiation field was extended up to the para-aortal area (upper margin of the eleventh thoracic vertebral body). Also, 75 mg/m^2 (triweekly) or 40 mg/m^2 (weekly) of cisplatin was administered systemically during the period of radiation therapy mentioned above as concurrent chemoradiation therapy. If the radiation field was extended to the para-aortal area, the dose of cisplatin was reduced to 50 mg/m^2 (triweekly) or 30 mg/m^2 (weekly). Chemotherapy consisted of a platinum-based regimen for six cycles at three-week intervals. The regimens were TP (paclitaxel 135 mg/m^2 and cisplatin 50 mg/m^2), TC (paclitaxel 175 mg/m^2 and carboplatin AUC = 6) or MEP (mitomycin C 7 mg/m^2 on day 1, etoposide 100 mg/m^2 on days 1, 3, and 5, and cisplatin 75 or 50 mg/m^2 on day 1). Sequential chemoradiation therapy was performed by administering two cycles of the above-mentioned platinum-based chemotherapy systemically at three-week intervals, after which radiation therapy was implemented.

This multi-institutional retrospective study was approved by the Institutional Review Board of each institution.

Analysis of clinicopathologic features

The following data were collected from charts: age at operation, clinical stage (FIGO 2008), operative procedure (RH+PLA or RH+PLA+PALA), tumor cell histology, size of the cervical tumor, pathological parametrial invasion, pathological pelvic lymph node metastasis, depth of myometrial invasion, lymphovascular space invasion, pathological para-aortic node metastasis, type of adjuvant therapy (if performed), progression-free survival (PFS) and overall survival (OAS), site of recurrence, and late adverse complications related to surgical procedures.

Statistical analysis

The clinicopathologic factors were compared by Student's *t*-test (for continuous variables), Pearson's chi-square test, or Fisher's exact test (for categorical variables). To identify independent predictors of PAN metastasis, multivariate analysis was performed using a logistic regression model. PFS and OAS curves were estimated using the Kaplan–Meier method, while PFS or OAS curves of the two or three groups were compared by log-rank test. To determine the effect of each clinicopathologic variable on PFS or OAS, the relative risks with 95 % confidence intervals (95 % CI) were estimated using the Cox proportional hazards regression model. A p value of <0.05 was regarded as statistically significant. All statistical analyses were performed using JMP v.12.1.0 (SAS Institute Inc.).

Results

Prognostic factors in the surgical treatment of cervical cancer

Clinicopathologic characteristics of the 308 patients enrolled in this study are presented in Fig. 1 and in Table S1 of the Electronic supplementary material (ESM). Mean age at operation, tumor cell histology, number of positive nodes, and incidence of common iliac lymph node metastasis were similar in the two groups who underwent different operative procedures, but clinical stage, tumor size, lymphovascular space invasion, parametrial involvement, depth of cervical invasion, and type of adjuvant therapy were not. Kaplan–Meier analysis revealed that the 5-year overall survival rate was 83.4 % in clinical stage IB2, 81.3 % in clinical stage IIA2, and 77.3 % in clinical stage IIB cervical cancer patients; 77.9 % in patients with a bulky tumor, 72.2 % in pN1 patients, and 70.5 % in patients with parametrial invasion (Fig. S1 in the ESM). The log-rank test revealed that bulky tumor ($p = 0.011$), lymph node metastasis ($p = 0.001$), and parametrial invasion ($p = 0.008$) were poor prognostic factors for cervical cancer. Kaplan–Meier analysis indicated that there was no significant difference in PFS and OAS between the patients in the two groups who underwent different operative procedures.

Among 308 patients, 140 patients (45.5 %) were pathologically confirmed as lymph-node positive (pN1). Common iliac nodes were involved in 30 of those 140 patients (9.74 %). Kaplan–Meier analysis and a log-rank test revealed that patients with common iliac node metastasis showed poor prognosis compared to pN1 patients without common iliac node metastasis in terms of PFS ($p = 0.013$) and OAS ($p = 0.020$). The five-year overall survival rate of patients with common iliac node metastasis was 58.3 % (Fig. 2). Cox regression analysis was conducted with three variables: size of tumor, pN1, and common iliac node metastasis. Common iliac node metastasis was revealed to be related to risk of recurrence (hazard ratio 2.43, $p = 0.003$) and risk of death (hazard ratio 2.62, $p = 0.007$) (Table 1).

PAN metastasis was pathologically confirmed in 13 of the 136 patients (9.6 %) who underwent PALA. Twelve of those PAN metastases were accompanied by pelvic lymph node (PLN) metastases (92.3 %), and 9 of those PAN metastases were accompanied by common iliac lymph node metastases (69.2 %). The incidence of PAN metastasis was significantly higher in patients who had common iliac lymph node metastases (odds ratio 31.5, $p < 0.001$) according to logistic regression analysis

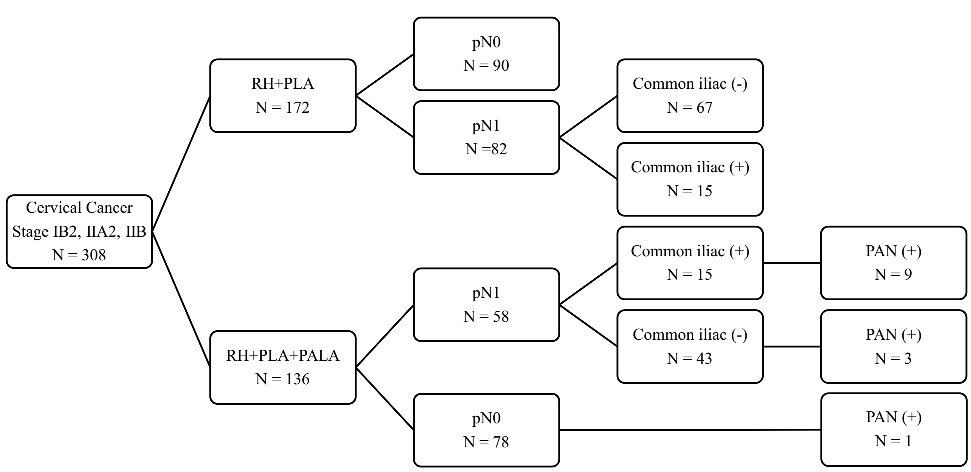

Fig. 1 Study profile. *RH* radical hystectomy, *PLA* pelvic lymphadenectomy, *PALA* para-aortic lymphadenectomy, *common iliac* (+)/(−) pathologically positive/negative common iliac lymph node metastasis, *PAN* (+)/(−) pathologically positive/negative para-aortic lymph node metastasis

(Table 2). Neither clinical stage, tumor size, parametrial involvement, nor tumor cell histology were correlated to PAN metastasis.

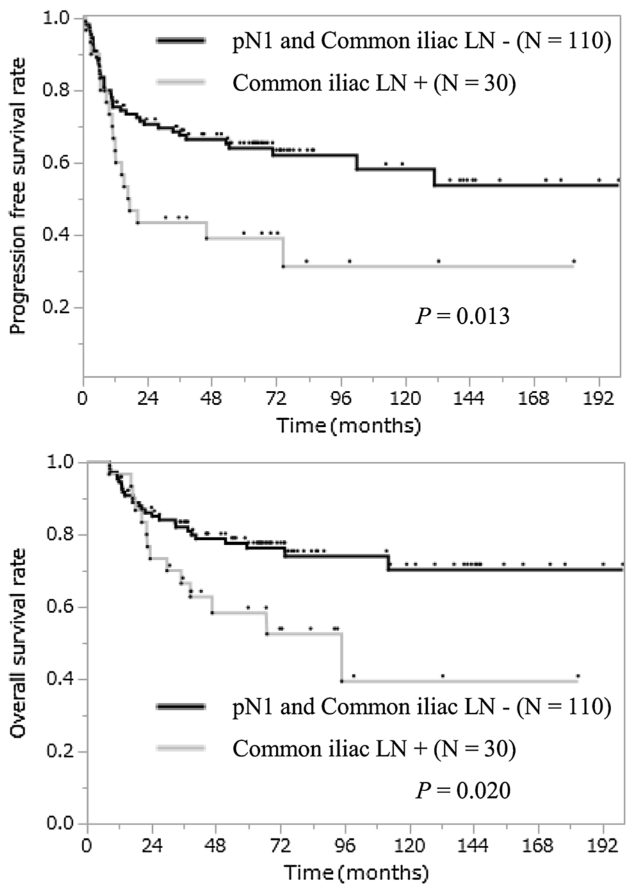

Fig. 2 Progression-free survival and overall survival curves in 140 patients with lymph node metastasis according to common iliac lymph node status

Outcome of patients with lymph node metastasis

To assess the prognostic impact of PALA, 140 patients with lymph node metastases were further analyzed. Table 3 shows clinicopathologic features of those patients. Clinical stage, tumor size, and tumor cell histology were similar in the two groups who underwent different operative procedures, but lymphovascular space invasion, parametrial invasion, depth of cervical invasion, and adjuvant therapy were not. Kaplan–Meier analysis and a log-rank test revealed that the prognosis of patients treated with RH+PLA+PALA was better than that of patients treated with RH+PLA in terms of PFS ($p = 0.044$) but not OAS ($p = 0.120$). The five-year PFS rate and OAS rate in the RH+PLA+PALA group were 67.2 and 79.3 %, respectively (Fig. 3). To eliminate bias from other factors such as tumor size, parametrial invasion, and type of adjuvant therapy, multivariate analysis was conducted using a Cox proportional hazards model. Cox regression analysis showed that RH+PLA+PALA was not related to risk of recurrence (hazard ratio 0.68, $p = 0.159$) or risk of death (hazard ratio 0.66, $p = 0.226$) in pN1 patients (Table S2 in the ESM).

Next, to assess the prognostic impact of PALA in the patients with a high risk of PAN metastasis, 30 patients with common iliac lymph node metastasis were analyzed. Table S3 in the ESM shows clinicopathologic features of those patients. The clinicopathologic features did not differ statistically between the two groups who underwent different operative procedures, except for type of adjuvant therapy. Kaplan–Meier analysis and a log-rank test revealed that the prognosis of the patients treated with RH+PLA+PALA was better than that of the patients treated with RH+PLA in terms of PFS ($p = 0.021$) and OAS ($p = 0.013$). The five-year PFS rate and OAS rate in the RH+PLA+PALA group were 60.0 and 79.4 %, while

Table 1 Cox regression analysis of progression-free survival and overall survival in 308 patients

	PFS			OAS		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Tumor size			<0.001			0.003
<4 cm		Ref			Ref	
>4 cm	3.51	(1.72–8.44)		3.30	(1.43–9.55)	
Parametrial involvement			0.036			0.109
Negative		Ref			Ref	
Positive	1.58	(1.03–2.44)		1.54	(0.91–2.62)	
Lymph node metastasis			0.029			0.213
Negative		Ref			Ref	
Positive	1.71	(1.06–2.79)		1.46	(0.80–2.68)	
Common iliac node metastasis			0.003			0.007
Negative		Ref			Ref	
Positive	2.43	(1.37-4.18)		2.62	(1.32-5.01)	

Table 2 Risk factors for PAN metastasis (RH+PLA+PALA, 136 cases)

Characteristic	Univariate analysis			Multivariate analysis	
	PAN negative	PAN positive	*p* value	Odds ratio	*p* value
sClinical stage			0.725		
IB2	39 (28.7 %)	3 (2.2 %)			
IIA2	13 (9.6 %)	1 (0.7)			
IIB	71 (52.2 %)	9 (6.6 %)			
Tumor size			1.000		
<4 cm	31 (22.8 %)	3 (2.21 %)			
>4 cm	92 (67.6 %)	10 (7.4 %)			
Lymphovascular space invasion			0.009		0.020
No	43 (31.6 %)	0 (0.0 %)		Reference	
Yes	80 (58.8 %)	13 (9.6 %)		7053489	
Parametrial involvement			1.000		
No	86 (63.2 %)	9 (6.6 %)			
Yes	37 (27.2 %)	4 (2.9 %)			
Depth of cervical invasion			0.3443		
<2/3	38 (27.9 %)	2 (1.5 %)			
>2/3	85 (62.5 %)	11 (8.1 %)			
Tumor cell type			0.544		
Squamous	81 (59.56 %)	10 (7.4 %)			
Nonsquamous	42 (30.9 %)	3 (2.2 %)			
Common iliac node metastasis			<0.001		<0.001
Negative	112 (85.5 %)	4 (3.05 %)		Reference	
Positive	6 (4.6 %)	9 (6.9 %)		31.5	

those in the RH+PLA group were 20.0 and 38.9 %, respectively (Fig. S2 in the ESM). To eliminate bias from other prognostic factors such as tumor size, parametrial invasion, and type of adjuvant therapy, multivariate analysis was conducted using a Cox proportional hazards model. Cox regression analysis revealed that PALA had a statistically marginally positive effect on OAS (hazard ratio 0.30, $p = 0.053$) in patients with common iliac lymph node metastasis, but not on PFS (hazard ratio 0.56, $p = 0.292$). The presence of a bulky tumor had negative effects on PFS and OAS ($p = 0.018$, $p = 0.075$, respectively) (Table S4 in the ESM).

Site of recurrence

Site of recurrence was assessed in the two treatment groups. In the RH+PLA group, 20 patients (11.6 %) had local recurrences, 30 patients (17.4 %) had distant recurrences, 3 patients (1.7 %) had both at the time of the first recurrence, and the site of recurrence was not documented for 1 patient. In the RH+PLA+PALA group, 11 patients (8.1 %) had local recurrences, 22 patients (16.2 %) had distant recurrences, and 6 (4.4 %) had both. There was no significant difference in the sites of recurrence between the two treatment groups.

Complications after surgery

Long-term complications relating to operative procedures were investigated. The incidences of lymphocele, lymphedema, and small bowel/colonic obstruction (grade $\geq$2), which negatively affect quality of life in postoperative patients, were compared in two groups. The long-term complications in 53 patients treated with RH+PLA and 1 patient treated with RH+PLA+PALA were not documented. Among the 119 patients treated with RH+PLA, 2 (1.7 %) experienced lymphocele, 8 patients (6.7 %) experienced lymphedema, and 19 patients (16.0 %) experienced small bowel/colonic obstruction. Among 135 patients treated with RH+PLA+PALA, 6 patients (4.4 %) experienced lymphocele, 19 patients (14.1 %) experienced lymphedema, and 19 patients (15.0 %) experienced colonic/small intestinal obstruction. None of the patients had a grade $\geq$4 complication. No significant difference was observed between the two treatment groups in the incidences of these long-term complications.

Discussion

There were two main findings of this study. First, common iliac lymph node metastasis is a poor prognostic factor in

Table 3 Clinicopathologic characteristics of patients with lymph node metastasis treated with RH+PLA or RH+PLA+PALA

Characteristic	RH+PLA ($N = 82$)		RH+PLA+PALA ($N = 58$)		p value
Mean age in years (range)	45.1	(25.3–68.0)	48	(32.0–71.0)	0.052
Clinical stage					0.267
IB2	33	40.2 %	20	34.5 %	
IIA2	11	13.4 %	4	6.9 %	
IIB	38	46.3 %	34	58.6 %	
Tumor size					0.137
<4 cm	8	9.8 %	11	19 %	
>4 cm	74	90.2 %	47	81 %	
Lymphovascular space invasion					0.011
No	0	0 %	5	8.6 %	
Yes	82	100 %	53	91.4 %	
Parametrial involvement					0.008
No	28	34.2 %	33	56.9 %	
Yes	54	65.9 %	25	43.1 %	
Depth of cervical invasion					0.004
<2/3	4	4.9 %	12	20.7 %	
>2/3	78	95.1 %	46	79.3 %	
Tumor cell type					0.619
Squamous	25	30.5 %	20	34.5 %	
Nonsquamous	57	69.5 %	38	65.5 %	
Number of positive nodes					0.97
1	29	35.4 %	19	32.8 %	
2	14	17.1 %	9	15.5 %	
3	10	12.2 %	8	13.8 %	
>4	29	35.4 %	22	37.9 %	
Common iliac node metastasis					0.282
Negative	67	93.9 %	43	74.1 %	
Positive	15	6.1 %	15	25.9 %	
Adjuvant therapy					0.011
None	3	3.7 %	0	0 %	
Radiation	61	74.4 %	32	55.2 %	
Sequential chemoradiation	6	7.3 %	14	24.1 %	
Systemic chemotherapy	7	8.5 %	4	6.9 %	
CCRT	5	6.1 %	8	13.8 %	

patients with stage IB2, IIA2, or IIB cervical cancer and a strong predictor of PAN metastasis. Second, the indication for PALA needs to be individualized in the surgical management of patients with stage IB2, IIA2, or IIB cervical cancer. Patients with common iliac lymph node metastasis are possible candidates.

The incidence of PAN metastasis in stage IB2, IIA2, or IIB cervical cancer was 9 %, but this jumped up to 60 % if a common iliac lymph node was positive. The incidence of PAN metastasis in stage IB–IIB cervical cancer is reported to be 10–40 %, and most PAN metastases are accompanied by pelvic lymph node metastases [6–9]. The lymphatic route from the cervix has been studied and reviewed in detail [10, 11]. Cancer cells from a cervical tumor spread first to the nodes of the obturator and external iliac, which are sentinel lymph nodes of the cervix, and then proceed to the common iliac and PAN. This route for lymphatic spread supports our finding that common iliac lymph node metastasis is an independent predictor of PAN metastasis, and that PAN metastasis is not rare if a common iliac lymph node is positive.

PALA was not observed to have a clinical benefit in patients with stage IB2, IIA2, or IIB cervical cancer in this study. Since PAN metastasis is not common in patients without common iliac lymph node metastasis, PALA may be a redundant procedure in most of those patients. Indeed,

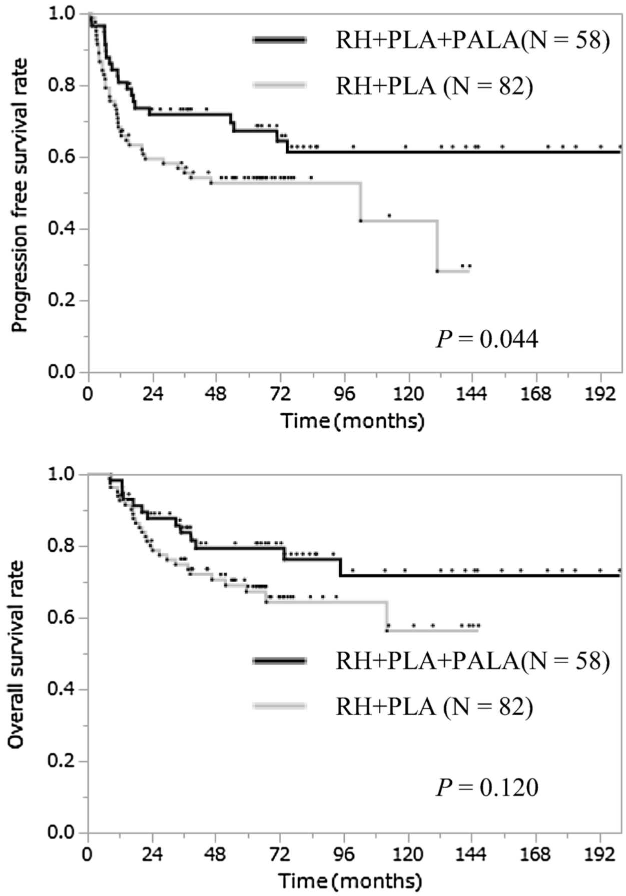

Fig. 3 Progression-free survival and overall survival curves in 140 patients with lymph node metastasis according to operative procedure implemented

the incidence of adverse events due to PALA was not high, indicating that PALA needs to be individualized in the surgical management of patients with stage IB2, IIA2, and IIB cervical cancer.

There is a possibility that PALA enhances therapeutic outcomes in patients with common iliac lymph node metastasis. Common iliac node metastasis is already considered to be a poor prognostic factor [12, 13], and this was confirmed by the results of this study. PALA enables metastatic lymph nodes in PAN to be detected and the appropriate adjuvant radiation field to be applied. A randomized control trial (RCT) that compared surgical staging with clinical staging such as computed tomography and magnetic resonance imaging prior to the chemoradiation therapy for stage IIB–IV cervical cancer was conducted [14]. In that study, there was no demonstrable benefit of pretreatment surgical staging, and clinical staging appeared to significantly prolong OAS and PFS compared to surgical staging. On the other hand, this study observed a positive impact of PALA for the surgical treatment of cervical cancer with common iliac lymph node metastasis. One of the reasons for this discrepancy may be the difference in the clinical stages of the cancer cases included in the two studies. Since the cancers of the patients enrolled in this study were less advanced than those of the patients in that RCT, the PAN metastases seen in this study may have been less aggressive. Another prospective multicenter study showed that applying PALA led to the same survival rate for patients with a small PAN metastases (smaller than 5 mm) and for those without PAN metastases, but not for the patients with larger PAN metastases (larger than 5 mm) [15]. PALA may have a survival impact when the PAN metastasis is only moderately aggressive.

PAN metastasis is known to be a prognostic factor for cervical cancer patients treated with surgery [9, 16]. This study revealed that PALA can be used to address this issue. Intraoperative frozen section analysis may be a useful method to identify common iliac lymph node metastases during surgery. The accuracy of intraoperative frozen section analysis of common iliac lymph nodes was evaluated in 209 patients, and the positive and negative predictive values were 100.0 % and 99.5 %, respectively [12]. Since the diagnostic reliability of frozen sections is well documented and established, it may not be difficult to access common iliac lymph node metastases intraoperatively in order to decide whether PALA should be performed. Sentinel lymph node mapping is a useful method to identify lymph node metastasis during surgery. Although most of the sentinel lymph nodes in cervical cancer patients are detected in the obturator and the external and internal iliac areas, it is reported that a sentinel lymph node is present in the para-aortic area in 2 % of cervical cancer patients [17]. Sentinel lymph node mapping permits the detection of solitary PAN metastases, even though they are rare. However, sentinel lymph node mapping of larger tumors (≥2 cm) and more advanced tumors (≥IB2) is reported to be associated with a low detection rate and sensitivity [18], so its efficacy in patients with stage IB2, IIA2, or IIB cervical cancer may be limited at present.

This study has several limitations. First, the clinicopathologic backgrounds of the patients were not equally distributed because this was a historical study. We tried to eliminate statistical bias from confounding factors using multivariate analyses. However, a prospective large-scale study will be needed to reach a clear conclusion. Second, adjuvant therapy was not applied consistently in this study. Since the effectiveness of concurrent chemoradiation therapy (CCRT) has been demonstrated in the adjuvant setting, more and more patients with lymph node metastases are being treated with postoperative CCRT. Although CCRT did not have a statistically significantly positive impact on prognosis in this study, standardizing the adjuvant therapy applied may be important when evaluating PALA in a future prospective study. Third, there is room for argument regarding the range of PALA. Most PAN metastases occur under inframesenteric nodes, and most infrarenal node metastases are associated with metastases to inframesenteric nodes [6]. However, it is reported that 25–30 % of PAN metastases were isolated infrarenal aortic lymph node metastases with negative inframesenteric nodes [19]. Since there are only a few reports of studies of PAN metastases in cervical cancer, it is important to accumulate such cases in order to determine whether it is necessary to dissect an infrarenal node when the inframesenteric nodes are negative.

In conclusion, the indication for para-aortic lymphadenectomy in the surgical treatment of stage IB2, IIA2, or IIB cervical cancer needs to be individualized. Patients with common iliac lymph node metastasis are possible candidates, and a prospective study is needed to clarify this issue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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