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Original Research

Number of lymph node in early-stage cervical cancer after radical surgery, does it matter?

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Objective: To determine the number of lymph nodes obtained from radical hysterectomy with pelvic lymphadenectomy (RHPL) and survival rates of the early-stage cervical cancer patients with various numbers of removed lymph nodes (RLNs) and metastatic lymph nodes (MLNs). *Materials and methods*: 407 patients with early-stage cervical cancers who underwent RHPL were included in this study. We reviewed all medical records from January 2005–June 2020 and excluded the patients who had incomplete medical record, loss of follow-up visits and received neo-adjuvant chemotherapy. *Results*: Three-hundred-and-fifty-four patients were analyzed. The median time of follow-up was 44.3 months, the average number of RLNs was 23 (range 7–29) and 91.7% of our cases had >12 RLNs. MLNs were found in 36 cases (10.2%). The patients with RLNs <12 had a significantly lower 5-year cancer-specific survival (CSS) compared to those with RLNs >12 (73.6 % and 97.0%, respectively, *p*-value < 0.001) but 5-year progression-free survival (PFS) was not different between both groups. Based on lymph node status, the 5-year PFS and CSS of node-negative vs. node-positive patients were 99.3% vs. 76.2% and 97.5% vs. 74.0%, respectively. *Conclusion*: An extensive lymphadenectomy had a survival benefit in early-stage cervical cancer patients. The patients with RLNs >12 had better 5-year CSS. MLNs and RLNs <12 are significant prognostic factors for PFS and CSS.

Keywords

Early-stage cervical cancer; Lymphadenectomy; Number of lymph node; Survival outcome

1. Introduction

Cervical cancer is the fourth most common cancer worldwide. In 2018, there were 569,847 new cases and 311,365 deaths [1]. The majority of new cases and deaths occur in developing countries. In Thailand, cervical cancer is the second most common cancer with 14.2% of incidences [2]. There were approximately 9158 new cases and 4705 deaths in 2020.

The standard treatment of early-stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy (RHPL) [3]. The adjuvant treatments are considered for the patient with some post-operative factors including lymph node status, surgical margin, lymph vascular space invasion (LVSI), stromal invasion and tumor size [3–6]. Many studies reported that lymph node metastasis is an important prognostic factor affecting survival outcomes [5, 7].

The therapeutic role of more extensive lymphadenectomy in cervical cancer is controversial. The analysis of the Surveillance, Epidemiology, and End Results (SEER) database reported that a more extensive lymphadenectomy is associated with improved survival in the early-stage cervical cancer patients with negative lymph node [8]. On the other hand, Mao *et al.* [9] showed that the number of removed lymph nodes (RLNs) is not an independent prognostic factor for patients with node-negative early cervical cancer.

Although the European Organization for Research and Treatment of Cancer—Gynecological Cancer Group (EORTC-GCG) purposed that pelvic lymphadenectomy specimens containing more than 11 examined lymph nodes is one of the quality indicators for RHPL [10], there is no consensus in a minimum number of RLNs related to the prognosis. This study was conducted to determine the number of lymph nodes obtained from RHPL and survival rates of the early-stage cervical cancer patients with various number of RLNs and metastatic lymph nodes (MLNs).

2. Materials and methods

This retrospective descriptive study was approved by the ethical committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University. We included all women with stage IA2, IB1 and IIA1 based on the 2018 FIGO staging system and underwent RHPL at Vajira Hospital from January 2005 to June 2020. We excluded the patients who received neo-adjuvant chemotherapy or had an incomplete medical record. Patients who loss of follow-up visit were also excluded.

Before 2018, the cancer stage was documented clinically by old FIGO staging criteria. A computerized tomography (CT) scan or magnetic resonance imaging (MRI) were unavailable for all patients. Type II or type III Piver hysterectomy with pelvic lymphadenectomy was performed by the experienced gynecologic oncologists. A para-aortic lymphadenectomy was considered when the pre-operative

imaging or intra-operative finding showed para-aortic lymphadenopathy.

The clinicopathological characteristics of all patients were age, surgical approach, cell type, cell differentiation, tumor size, stromal invasion, LVSI, surgical margin, number of RLN and MLN, FIGO 2008 and 2018 staging, adjuvant treatment and follow-up period.

The adjuvant treatments after surgery were prescribed for high-risk and intermediate-risk patients [11, 12]. The high-risk patients received concurrent chemoradiation (CCRT) based on the study of Peters WA *et al.* [11] and the intermediate-risk patients received radiation (RT) based on GOG-92 study [12]. The surveillance after treatment completion was every 3 months for the first 2 years, 6 months for 3–5 years, then annually.

All data were analyzed using STATA statistical software, version 15.1 (StataCorp, College Station, TX, USA). The descriptive statistics were used to analyze demographic data and were summarized as numbers with percentage, mean with standard deviation (SD) and median with range. Comparisons were made by a Chi-square or Fisher's exact test for categorical variables and *t*-test for continuous variables. The independent sample *t*-test and Mann-Whitney U test were used to compare differences between two independent groups. Progression-free survival (PFS) and cancer-specific survival (CSS) of the patients were analyzed by the Kaplan-Meier method. The log-rank test was used to examine the statistical difference. Multivariate analysis of survival was performed by the Cox's proportional hazard model. The statistical significance was considered when a *p*-value was less than 0.05.

3. Results

A total of 407 patients have met the inclusion criteria. Fifty-three patients were excluded because 33 had incomplete medical records, 13 were loss of follow-up and 7 received neo-adjuvant chemotherapy. Three-hundred-and-fifty-four patients were analyzed. The clinical and pathologic features display in Tables 1,2. The median age at diagnosis of patients was 44 years (range: 22–88). Two most common histopathology were squamous cell carcinoma (63.3%) and adenocarcinoma (34.5%). The rare histopathology was neuroendocrine 6 cases (1.7%), undifferentiated 2 cases (0.6%). Ninety-one patients (25.7%) had received an adjuvant treatment after their operation because of the high-risk histopathological results including vaginal margin involvement in 7 cases (0.2%), parametrial involvement in 20 cases (6.5%), MLN in 36 cases (10.2%), deep stromal invasion in 47 cases (19.3%) and tumor size ≥2 cm in 211 cases (59.6%).

The median number of removed lymph node (RLN) was 23 (range: 17–29). The number of cases who had RLN 10 nodes or less, 11–20, 21–30, and 31 or more were 24 (6.8%), 114 (32.2%) 137 (38.7%) and 79 cases (22.3%), respectively. According to the recommendation of EORTC-GCG on pelvic lymphadenectomy specimens, 91.7% of our cases had ≥12 RLNs. The MLNs were found in 36 cases (10.2%). Increase of the number of RLNs does not significantly increase the detection of MLNs (*p*-value = 0.101).

Of 354 patients, the 5-year cancer-specific survival (CSS) was 95.48% and 5-year progression-free survival (PFS) was 97.89%. The 5-year CSS of the patients with RLNs <12 was significantly lower than the patients with RLNs ≥12 (73.6% and 97.0%, respectively) with *p*-value < 0.001 (Table 3 and Fig. 1). In subgroup analysis of node-negative patients, the 5-year CSS of the patients with RLNs <12 and ≥12 were 73.8% and 98.6%, respectively (*p*-value = 0.002). In term of 5-year PFS, there was no significant difference between the patients with RLNs <12 and ≥12 in entire cohort or subgroup analysis of node-negative patients. Based on lymph node status, the 5-year PFS and CSS of node-negative vs. node-positive patients were 99.3% vs. 76.2% and 97.5% vs. 74.0%, respectively (Table 3). There was a significant difference in survival between node-negative and node-positive groups.

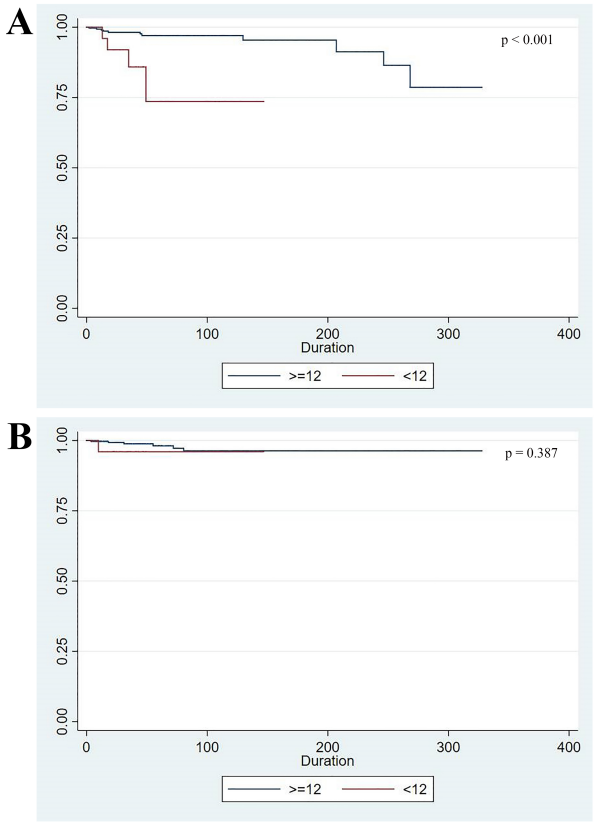

Fig. 1. Survival stratified by the groups of lymph nodes in early-stage cervical cancer. (A) Cancer-specific survival. (B) Progression-free survival.

Of 7 recurrent cases (1.98%), 4 cases (57.2%) had local recurrence and 3 cases (42.8%) had distant recurrence. Five of 7 recurrent cases (71.4%) had MLNs after RHPL. The mortality rate was 4.2% (15 cases). Six of 15 death cases (40%) had positive lymph node and 9 of 15 had negative lymph node.

Table 1. Demographic and clinical data stratified by the number of pelvic nodes removed.

Clinical characteristics	Total	Number of RLNs		*p*-value
		<12	>12	
Number of patients	354 (100.0)	35 (8.3)	319 (91.7)	
Mean age (years) ± SD	44.6 ± 10.0	45.5 ± 10.5	44.5 ± 9.9	0.618
Mean BMI (kg/m^2) ± SD	24.37 ± 3.67	23.7 ± 3.6	24.2 ± 4.3	0.538
Surgical approach				
Laparotomy	342 (96.6)	27 (93.1)	309 (96.9)	0.288
Laparoscopy	12 (3.4)	2 (6.9)	10 (3.1)	
Cell type				
Squamous cell carcinoma	224 (63.3)	13 (44.8)	211 (64.9)	0.159
Adenocarcinoma	122 (34.5)	15 (51.7)	107 (32.9)	
Undifferentiated	2 (0.6)	0 (0)	2 (0.6)	
Neuroendocrine	6 (1.7)	1 (3.4)	5 (1.5)	
Adjuvant treatment				
No	263 (74.3)	19 (65.5)	244 (75.1)	0.259
Yes	91 (25.7)	10 (34.5)	81 (24.9)	
- CCRT	61 (17.2)	7 (24.1)	54 (16.6)	
- RT	22 (6.21)	2 (6.9)	20 (6.2)	
- CMT	8 (2.3)	1 (3.4)	7 (2.2)	

SD, standard deviation; BMI, body mass index; RLNs, removed lymph nodes; CCRT, concurrent chemoradiation; RT, radiation; CMT, chemotherapy.

A significant prognostic factor for PFS was MLN which a hazard ratio (HR) was 11.05 on univariate analysis (95% CI: 2.43–50.20, *p*-value = 0.002) and 8.60 on multivariate analysis (95% CI: 1.81–40.79, *p*-value = 0.007) (Table 4 and Fig. 2). The other factors including age, surgical approach, cell type, histologic grade, tumor size, stromal invasion, LVSI, vaginal margin, parametrial involvement, total number of RLNs, FIGO stage and adjuvant treatment, were not significant prognostic factors for PFS. In term of CSS, adenocarcinoma, moderate and high grade, RLNs <12, positive lymph node and adjuvant treatment were significant prognostic factors on univariate analysis. The multivariate analysis showed RLNs <12, positive lymph node and adjuvant treatment to be independent prognostic factors for CSS with HR 5.21 (95% CI: 1.49–18.16, *p*-value = 0.009), 3.86 (95% CI: 1.01–14.84, *p*-value = 0.049) and 7.42 (95% CI: 1.66–33.15, *p*-value = 0.009), respectively.

4. Discussion

The EORTC-GCG purposed the quality assurance for RHPL for cervical cancer in 2008 in order to audit and assure the quality of surgical care [10]. The recommended minimum number of removed pelvic lymph node is 12. In our study, the median number of RLNs was 23 and 91.7% of all cases had ≥12 RLNs. Suprasert P *et al.* [13] studied 843 cervical cancer patients in Chiangmai, Thailand and exclude 17 patients with RLN less than 11. They reported that the mean number of RLNs was 26. Other literatures revealed the median number of RLN, ranging from 17–34 lymph nodes [9, 14–16].

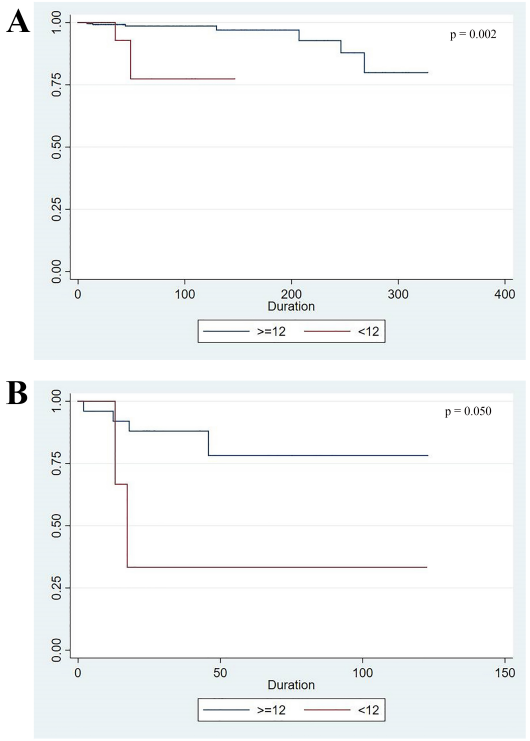

Fig. 2. CSS stratified by the groups of negative lymph nodes (A) and positive lymph nodes (B).

The benefit of more extensive lymphadenectomy in early-stage cervical cancer had been proved in our study. RLNs ≥12 is associated with 5-yr CSS of early-stage cervical cancer patient with negative LN but it is not associated with 5-

Table 2. Pathological characteristics stratified by the number of pelvic nodes removed.

Pathological characteristics	Total	Number of RLNs		*p*-value
		<12	>12	
Histologic grade				
Low	140 (45.3)	9 (31.0)	131 (40.3)	0.671
Moderate	142 (46.0)	14 (48.3)	128 (39.4)	
High	27 (8.7)	3 (4.0)	24 (7.4)	
Tumor size (cm)				
<2	143 (40.4)	14 (48.3)	129 (39.7)	0.367
≥2	211 (59.6)	15 (52.2)	196 (603)	
Stromal invasion				
Superficial	131 (53.7)	11 (47.8)	120 (54.3)	0.680
Middle	66 (27.0)	8 (34.8)	58 (26.2)	
Deep	47 (19.3)	4 (17.4)	43 (19.5)	
LVSI				
Not present	250 (80.9)	23 (96.4)	274 (97.9)	0.818
Present	59 (19.1)	1 (3.6)	6 (2.1)	
Vaginal margin involvement				
Not present	301 (97.7)	27 (88.4)	179 (82.9)	0.629
Present	7 (2.3)	2 (1.4)	5 (2.3)	
Parametrial involvement				
Not present	289 (93.5)	27 (93.1)	262 (93.6)	0.922
Present	20 (6.5)	2 (6.9)	18 (6.4)	
Lymph node metastasis				
Negative	318 (89.8)	24 (82.8)	294 (90.5)	0.189
Positive	36 (10.2)	5 (17.2)	31 (9.5)	
Lymph node metastasis				
Negative	318 (89.8)	24 (82.8)	294 (90.5)	0.237
Positive ≤5	32 (9.0)	5 (17.2)	27 (8.3)	
Positive >5	4 (1.1)	0 (0.0)	4 (1.2)	

RLNs, removed lymph nodes; LVSI, lymphovascular space invasion.

yr PFS. Wang R *et al.* [15] found the therapeutic benefit of lymphadenectomy in stage IB1 cervical cancer patients. The PFS and CSS of the patients with ≤10 RLNs were significantly lower than those with >10 RLNs (*p*-value = 0.026 and 0.012, respectively). A large retrospective study using SEER database, enrolled 5522 women with cervical cancer stage IA2–IIA from 1988–2005 [8]. In the entire cohort and node-negative patients, the hazard ratio (HR) of the patients with >30 RLNs, comparing with the patients with ≤10 RLNs, was 0.71 and 0.64, respectively. On the contrary, some previous report did not find the relation between RLN number and DFS or CSS in the patient with negative LN [9, 13, 14, 16]. In subgroup analysis of node-positive patient, there is no correlation between the number of RLN and DFS or CSS [8, 13, 15]. One study demonstrated the benefit of lymphadenectomy in 136 patients with MLN [14]. The number of RLN in this group was associated with DFS with *p*-value of 0.014 but there was no correlation with CSS. The rate of MLN in our cohort was 10.2% (36 cases) which was lower than previous reports, ranging from 14.1–19.4% [8, 13, 15–17] so the authors cannot perform subgroup-analysis on survival.

Table 3. Five-years for progression-free survival (PFS) and cancer-specific survival (CSS).

Variables	5-year PFS (%)	*p*-value*	5-year CSS (%)	*p*-value
Age (years)				
<60	97.46	0.851	93.44	0.114
≥60	98.35		98.02	
Surgical approach				
Laparotomy	97.76	0.814	95.71	0.504
Laparoscopy	100.00		85.71	
Cell type				
Squamous cell carcinoma	99.01	0.965	97.06	0.089
Adenocarcinoma	97.23		92.34	
Undifferentiated	100.00		100.00	
Neuroendocrine	100.00		100.00	
Histologic grade				
Low	100.00	0.088	98.94	0.038
Moderate	94.56		91.92	
High	100.00		90.63	
Tumor size (cm)				
<2	97.37	0.928	96.60	0.709
≥2	98.29		94.70	
Stromal invasion				
Superficial	99.21	0.129	97.44	0.110
Middle	95.35		87.29	
Deep	93.66		94.66	
LVSI				
Not present	97.87	0.321	95.54	0.154
Present	94.74		88.80	
Vaginal margin				
Not present	97.27	0.302	94.25	0.537
Present	100.00		100.00	
Parametrial involvement				
Not present	98.17	0.211	94.05	0.434
Present	87.50		100.00	
Total number of RLNs				
<12	96.00	0.387	73.60	<0.001
≥12	98.10		97.00	
Lymph node metastasis				
Negative	99.32	<0.001	97.54	<0.001
Positive	76.23		74.02	
Lymph node metastasis				
Negative	99.32	<0.001	97.54	<0.001
Positive ≤5	79.55		79.2	
Positive >5	NR		NR	

RLNs, removed lymph nodes; LVSI, lymphovascular space invasion; PFS, progression-free survival; CSS, cancer-specific survival.

Lymph node status is one of the important prognostic factors in early-stage cervical cancer patients underwent RHPL [4, 7]. The DFS and OS were significantly different between the patients with and without MLN [18, 19]. The number of MLN is associated with survival. The patients with >2 MLNs had a significantly lower rate of DFS and OS, compared to those with 1–2 MLNs [4, 6]. Our result showed a similar trend. The 5-yr PFS and CSS of node-positive patients were significantly lower than node-negative patients.

Table 4. Univariate and multivariate analysis for progression-free survival and cancer-specific survival.

Factors	Progression-free survival						Cancer-specific survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR_{adj}	95% CI	*p*-value	HR	95% CI	*p*-value	HR_{adj}	95% CI	*p*-value
Age (yr)												
<60	1.00	Reference					1.00	Reference				
≥60	0.87	(0.19–3.88)	0.851				0.41	(0.13–1.27)	0.123			
Surgical approach												
Laparotomy	1.00	Reference					1.00	Reference				
Laparoscopy	-	-	NA				2.81	(0.36–21.97)	0.325			
Cell type												
Squamous cell carcinoma	1.00	Reference					1.00	Reference		1.00	Reference	
Adenocarcinoma	0.77	(0.15–3.99)	0.758				3.02	(1.03–8.82)	0.043	1.70	(0.47–6.13)	0.415
Histologic grade												
Low	1.00	Reference					1.00	Reference		1.00	Reference	
Moderate	6.31	(0.76–52.46)	0.088				4.02	(1.01–16.03)	0.049	2.42	(0.50–11.76)	0.274
High	-	-	NA				6.39	(1.26–32.55)	0.026	2.91	(0.36–23.25)	0.313
Tumor size (cm)												
<2	1.00	Reference					1.00	Reference				
≥2	0.93	(0.20–4.17)	0.928				1.23	(0.42–3.63)	0.709			
Stromal invasion												
Superficial	1.00	Reference		1.00	Reference		1.00	Reference				
Middle	3.96	(0.36–43.78)	0.262	2.48	(0.22–28.61)	0.466	5.10	(0.99–26.28)	0.052			
Deep	6.87	(0.71–66.66)	0.096	5.26	(0.54–51.44)	0.153	2.36	(0.33–16.81)	0.392			
LVSI												
Not present	1.00	Reference					1.00	Reference				
Present	0.72	(0.09–5.98)	0.760				2.48	(0.72–8.50)	0.148			
Vaginal margin												
Not present	1.00	Reference					1.00	Reference				
Present	-	-	NA				0.00	(NR)	1.000			
Parametrial involvement												
Not present	1.00	Reference					1.00	Reference				
Present	2.45	(0.29–20.41)	0.407				0.00	(NR)	1.000			

Table 4. Continued.

Factors	Progression-free survival						Cancer-specific survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR_{adj}	95% CI	*p*-value	HR	95% CI	*p*-value	HR_{adj}	95% CI	*p*-value
Total number of RLNs												
<12	2.43	(0.29–20.88)	0.403	2.85	(0.31–25.76)	0.930	6.90	(2.03–23.37)	0.002	5.21	(1.49–18.16)	0.009
≥ 12	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Lymph node metastasis												
Negative	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Positive	11.05	(2.43–50.20)	0.002	8.60	(1.81–40.79)	0.007	15.09	(4.56–49.91)	<0.001	3.86	(1.01–14.84)	0.049
Lymph node metastasis												
Negative	1.00	Reference					1.00	Reference				
Positive ≤ 5	7.97	(1.44–44.08)	0.017				10.94	(2.91–41.06)	<0.001			
Positive >5	117.52	(9.62–1436.04)	<0.001				100.42	(17.18–587.07)	<0.001			
FIGO stage												
IA2–IB3	1.00	Reference					1.00	Reference				
IIA1–IIB	1.62	(0.19–13.50)	0.655				2.01	(0.44–9.26)	0.371			
Adjuvant treatment												
No	1.00	Reference					1.00	Reference		1.00	Reference	
Yes	2.39	(0.53–10.69)	0.256				11.10	(3.45–35.72)	<0.001	7.42	(1.66–33.15)	0.009

RLNs, removed lymph nodes; LVSI, lymphovascular space invasion.

Additionally, the authors found that the recurrence rate in node-positive patients was greater than that of the node-negative patients.

The surgical complications associated with lymphadenectomy are lymphedema, lymphocyst formation, blood vessel or nerve injury etc. Lower lymphadenoma is one of the most common complication effecting the quality of life of many patients. A systematic review including 23 articles, revealed the factors associated with lymphedema after treatment of cervical cancer [20]. The extension of lymphadenectomy and number of RLN increase the risk of lymphedema [20]. Sentinel lymph node (SNL) mapping might be a promising option to minimize the risk of lower limb lymphedema. A systematic review and meta-analysis showed that the pooled detection rate and sensitivity of SLN mapping was 89.2% and 90%, respectively [21]. A retrospective study at MD Anderson Cancer Center, US included 188 patients underwent SLN mapping [22]. A false negative rate in this study was 3.6%. Lennox *et al.* [23] compared a survival outcome between 1078 cervical cancer patients in pelvic lymphadenectomy group and 110 patients in SLN mapping group. There was no difference in 2-year and 5-year recurrence-free survival. SLN mapping with ultra-staging protocol might be helpful to detect an MLN including micro-metastasis and isolated tumor cells. These patients would be received a proper adjuvant treatment by the accurate stage.

Lymphadenectomy in our institute is up to the standard of EORTC-GCC. The authors reported the benefit of lymphadenectomy on survival of early-stage cervical cancer patients. Although some histopathologic results including lymph node status are incomplete because of the retrospective data and counting method of lymph node may be different among pathologists, these were reviewed by a pathologist to obtain the complete results. This study was conducted in one center so the number of patients is inadequate to perform subgroup analysis, especially node-positive group. In addition, the pre-operative imaging study was unavailable for all patients. The further study should be prospectively and collaborated with multicenter.

5. Conclusions

In conclusion, an extensive lymphadenectomy had a survival benefit in early-stage cervical cancer patients. The patients with RLNs $\geq$12 had better 5-year CSS. MLNs and RLNs $<$12 are significant prognostic factors for PFS and CSS. Precise detection of positive lymph node is important to prescribe the appropriate adjuvant treatment and determine the exact prognosis.

Author contributions

PI collected the data, managed the database, performed the statistical analysis and wrote the manuscript. WC designed the study, managed the database, performed the statistical analysis and edited the manuscript. NB performed the pathological review and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Participant of patients in this study was obtained through an opt-out methodology. The institutional review board of Faculty of Medicine Vajira Hospital, Navamindradhiraj University approved the study, code 042/63.

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Conflict of interest

The authors declare no conflict of interest.

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