Effect of Number of Retrieved Lymph Nodes on Prognosis in FIGO Stage IA1-IIA2 Cervical Cancer Patients Treated With Primary Radical Surgery

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ABSTRACT

BACKGROUND: The influence of the number of removed lymph nodes (RLNs) on patients with early-stage cervical cancer (ESCC) is still questionable. The objective of this study was to explore the prognostic value of RLNs on ESCC patients.

METHODS: A retrospective study was performed including all ESCC patients who underwent radical surgery from January 2016 to December 2018. Cox regression analysis was performed to verify the correlation between the number of RLNs and the prognosis (recurrence-free survival [RFS], disease-specific survival [DSS]) of ESCC. According to the guidelines, all the patients were divided into high-risk and non-high-risk groups. The optimal cut-off values of RLNs were determined by receiver operating characteristic curve analysis and Youden index and further the prognostic value of them was explored.

RESULTS: A total 1101 patients were enrolled. The number of RLNs was an independent prognostic influence factor of the prognosis of ESCC ($P < .001$ for RFS, $P < .001$ for DSS). The optimal cut-off values of RLNs (40 in the high-risk group and 23 in the non-high-risk group) were significantly associated with the prognosis of ESCC, in the high-risk group ($P < .001$ for RFS, $P = .002$ for DSS) and non-high-risk group ($P < .001$ for RFS, $P < .001$ for DSS), respectively.

CONCLUSIONS: More extensive lymph node dissection (RLNs ⩾ 40) could benefit the high-risk ESCC patients. However, in the non-high-risk group, moderate lymph node dissection (RLNs ≈23) could also benefit them and may reduce the incidence of related complications. Those findings may help to determine the scope of lymph node dissection in ESCC patients before operation.

KEYWORDS: Cervical cancer, number of retrieved lymph nodes, cut-off value, prognosis

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Introduction

Cervical cancer is the fourth largest female malignant tumor in the world, and the fourth leading cause of cancer deaths in women worldwide.[1] The incidence of cervical cancer in young women has increased in recent years.[2,3] Radical hysterectomy combined with pelvic lymph node (LN) dissection is the standard surgical treatment of early-stage cervical cancer (ESCC).[4] The goal of systematic LN dissection is to identify and remove the cancer cells that might have metastasized to the lymphatic tissue draining the uterine cervix and upper vagina. Besides, the number of removed lymph nodes (RLNs) is considered to be one of the objective indicators of the thoroughness of the operation.[5-8] The International Union against Cancer recommended that at least 10 LNs should be investigated to determine pN0,[6] while some researchers regarded 20 LNs as the gold standard.[7,8] However, the scope of LN dissection of ESCC has always been a controversial issue. There are limited data on the possible benefits of more extensive LN dissection of treatment in ESCC.[9-11] In addition, Ditto et al[12] concluded that the number of RLNs had no effect on survival. Chen et al[13] and Mao et al[14] observed no relationship between the number of RLNs and survival. Furthermore, most patients with early cervical cancer do not have LN metastasis, while thorough LN dissection may cause complications such as lymphedema.[15,16] Obviously, the influence of the number of RLNs on the survival of patients with ESCC is still questionable. It is not clear whether the number of RLNs is related to the prognosis of ESCC.

Therefore, this study focused on the correlation between the number of RLNs and the prognosis of ESCC and all the patients were stratified according to whether there are high-risk factors in the postoperative pathological results based on the guidelines,[17-19] aiming to determine whether the number of RLNs was related to the prognosis of ESCC and to further explore the prognostic value of the optimal cut-off thresholds of RLNs, so as to provide a basis for determining the scope of LN dissection in ESCC patients before operation.

Materials and Methods

Study population

This was a large single-center retrospective cohort study conducted in China. We retrospectively collected the data of all patients with cervical cancer from January 2016 to December

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2018 in The First Affiliated Hospital of Chongqing Medical University. All included cervical cancer patients should meet the following inclusion criteria. (1) According to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, the patients were diagnosed with stage IA1-IIA2 cervical cancer.[20] (2) In addition to routine examinations, all selected patients received enhanced magnetic resonance imaging (MRI) of whole abdomen and pelvis to comprehensively assess the patient's condition before the operation (especially whether there were swollen LN metastasis). (3) All selected patients underwent radical hysterectomy and pelvic LN dissection.[17,21] (4) All patients have complete case data, including age, detailed surgical records, and postoperative pathological results (including histology, tumor differentiation, LN metastasis, para-uterine [PU] involvement, vaginal resection margin, lymphatic vascular space invasion [LVSI], cervical stromal invasion [CSI], tumor size and the number of RLN). Exclusion criteria were as follows. (1) Those who have not received radical hysterectomy and pelvic LN dissection (PLND) treatment. (2) Those who have received initial radiotherapy, chemotherapy, or neo-adjuvant chemotherapy. (3) Those with other malignant tumors and potential diseases that may affect survival. (4) Those without regular follow-up after surgery or medical records were excluded.[17] (5) Those who have performed para-aortic LN dissection (PALND); these included patients with preoperative palpable enlargement or severe suspicion of pelvic or abdominal para-aortic LN metastasis during preoperative radiological evaluation, because most of them have experienced PALND. According to the guidelines,[17-19] patients with postoperative pathological outcomes with high-risk factors (LN metastasis, PU involvement, vaginal resection margin [positive]) were defined as high-risk group, whereas patients without above high-risk factors were defined as non-high-risk group.

Treatment and follow-up

All patients underwent radical hysterectomy and unified PLND. Furthermore, the multidisciplinary discussions and international guidelines[17-19] determined whether to perform postoperative adjuvant therapy (radiotherapy and/or chemotherapy). Patients with the following pathological risk factors: resection margin involvement, LN metastasis, parametrial invasion, lymphovascular space invasion, deep CSI, non-squamous histology, and a large tumor size, received external-beam radiotherapy (EBRT) within 4 to 6 weeks after surgery. In principle, concurrent platinum-containing chemotherapy was given during radiotherapy, unless the patient refused or could not tolerate chemotherapy.

Postoperative follow-up included once every 3 months in the first 2 years, once every 6 months in the third to fifth years, and annually after 5 years. The follow-up includes at least pelvic-rectal examination and patient medical history, and if necessary, serum tumor markers and vaginal stump cytology should be added. Computed tomography or MRI scans for high-risk groups or people with clinical indications.[17] The deadline for follow-up is December 2020.

If the lesion was confirmed by physical examination, pathological examination or images (including computer tomography, MRI, ultrasound, bone imaging, positron emission tomography or specific X-rays), it was considered for recurrence.[17] Recurrence was divided into local recurrence, including vaginal or pelvic recurrence, and distant recurrence, such as metastasis to the para-aortic LNs, abdomen, or other organs.[17] Recurrence-free survival (RFS) was defined as the time between the date of surgery and the date of recurrence (confirmed by histology or imaging).[22] Disease-specific survival (DSS) was defined as the time between the date of surgery and the date of death of the patient.[22]

Pelvic LN dissection and pathological examination

Pelvic LN dissection included dissection of common iliac, external iliac, internal iliac and obturator LNs on both sides.[22,23] Pelvic LNs were included in the LN counts.

All postoperative specimens of all patients were fixed with formalin tissue fluid within the specified time, and then sent to the histology Laboratory Center of Chongqing Medical University for further processing. Each LN compartment was carefully inspected in a fresh state, and all LNs, including some possible LNs, were placed in a dark box for tissue processing. Postoperative medical examination results (histology, tumor differentiation, LN metastasis, PU involvement, vaginal resection margin, LVSI, CSI, tumor size, and the number of RLN) were initially judged by the primary pathologist in the histology laboratory, and then reviewed by the superior physician.

Statistical processing

The data were processed by using SPSS 26.0 statistical software. Both univariate and multivariate analysis of prognostic factors were analyzed by Cox regression model and Log-Rank test, with the test level $\alpha = .05$, and then factors with $P < .05$ in the univariate Cox regression analysis, were further included in the multivariate Cox regression analysis.[24] To define the number of RLNs with the good discriminatory power in evaluating the prognosis of ESCC, the optimal threshold (cut-off value) was determined by using the receiver operating characteristic (ROC) curve and the Youden index (Youden index = sensitivity + specificity − 1). Discrimination (ie, whether the relative ranking of individual predictions was in the correct order) was qualified with the area under the curve (AUC) of the ROC curve. An AUC ranges from 0 to 1 and a model was considered to have a poor, fair, or good performance if the AUC lies between 0.5 and 0.6, 0.6, and 0.7 or is greater than 0.8, respectively.[25] RFS and DSS were analyzed by Kaplan-Meier (KM) curve and log-rank test, with the test level $\alpha = .05$.[26,27] Continuous variables were expressed using the mean ± SD or

Figure 1. Research design flow chart. CC indicates cervical cancer; DSS, disease-specific survival; ESCC, early-stage cervical cancer; KM, Kaplan-Meier; LN, lymph node; PALND, para-aortic lymph node dissection; PU, para-uterine; RFS, recurrence-free survival; RLN, retrieved lymph node; ROC, receiver operating characteristic.

using the median and range. Categorical values were expressed using an absolute number and percentage (Figure 1; Research design flow chart).

Ethics approval and consent

The study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (ethics approval number: 2021-174) and conducted in accordance with the Declaration of Helsinki. All patients provided their informed consent before starting the treatment. As it was a retrospective clinical study, all patients were contacted by telephone to obtain verbal informed consent and the methods were approved by the ethics committee. All data about the patients were anonymous or confidential.

Results

Clinic-pathological characteristics (N = 1101)

A total of 1179 patients with stages IA1-IIA2 cervical cancer received primary surgery at The First Affiliated Hospital of Chongqing Medical University from January 2016 to December 2018, among which 1101 ESCC patients meeting the criteria were enrolled, while 78 were excluded including those without radical hysterectomy + pelvic LN resection (n = 15, 19.2%), preoperative neoadjuvant therapy (n = 4, 5.1%), other malignancies (n = 8, 10.3%), missing data (n = 9, 11.5%), lost follow-up (n = 14, 17.9%), PALND was performed (n = 28, 35.9%). Summarizing the clinical and pathological characteristics of the 1101 patients in this study, whose median follow-up period was 38 months (range 6-60 months). A total of 114 patients (10.4%) relapsed, vaginal stump (n = 17, 14.9%), central pelvic region (n = 51, 44.7%), LNs (upper para-aortic; n = 12, 10.5%), peritoneal metastases (n = 12, 10.5%), metastasis to other organs (n = 22, 19.3%), of which 66 patients died due to recurrence of cervical cancer, whereas 9 patients died due to other causes (Table 1). Median follow-up time and relapse-free survival of relapse patients were 28 months (range 9-55 months) and 19 months (range 6-39 months), respectively.

Univariate and multivariate Cox regression analysis on the prognosis in FIGO stage IA1-IIA2 cervical cancer patients treated with radical surgery

The univariate Cox regression analysis was used to analyze the clinic-pathological factors that might affect the RFS and DSS of ESCC, and the factors with $P > .05$ were excluded from the multivariate analysis, including age. The factors with $P < .05$, including histology, tumor differentiation, LN metastasis, PU involvement, vaginal resection margin, LVSI, CSI, tumor size, and the number of RLNs were further included in the multivariate Cox regression analysis (Table 2).

Finally, in the multivariate Cox regression analysis, the number of RLNs was identified as independent prognostic influence factor of RFS and DSS in cervical cancer ($P < .001$ for RFS, $P < .001$ for DSS). In addition, tumor size, tumor differentiation, LVSI, PU involvement, LN metastasis, and vaginal resection margin were also independent prognostic influence factors of RFS and DSS in ESCC. However, histology was only independently associated with RFS. Cervical stromal invasion was not independently associated with either RFS or DSS (Table 2).

The optimal cut-off values of RLNs in the high-risk and non-high-risk groups

The univariate and multivariate Cox regression analysis all showed that the number of RLNs was an independent prognostic factor of RFS and DSS in ESCC ($P < .001$ for RFS, $P < .001$ for DSS).

The median follow-up times were 38 months (range 9-60 months) in the high-risk group (n = 401) and 39 months (range 6-59 months) in the non-high-risk group (n = 700), respectively. Furthermore, KM survival curve analysis was used between the 2 groups. The results showed that the 5-year RFS in the high-risk and non-high-risk groups were 80.4% (95% confidence interval [CI]: 76.284%-84.516%) and 93.5% (95% CI: 91.540%-95.460%), respectively ($P < .001$, Supplementary Figure 1A). The 5-year DSS in the high-risk and non-high-risk groups were 85.0% (95% CI: 80.492%-89.508%) and 95.3% (95% CI: 93.536%-97.064%), respectively ($P < .001$, Supplementary Figure 1B). The results indicated that both RFS and DSS rates in the high-risk group were much lower than in the non-high-risk group ($P < .001$ for RFS, $P < .001$ for DSS). Thus, it was necessary to stratify the patients according to whether there are high-risk factors in the postoperative pathological results based on the guidelines.

The ROC curve and Youden index revealed that in the high-risk and non-high-risk factor groups, the optimal cut-off values of RLN of RFS and DSS all were similar. In the non-high-risk group (n = 700), the optimal RLN cut-off of RFS was 23.5 (area under the curve = 61.1%, sensitivity = 48.8%, specificity = 75.3%, Figure 2A). The optimal cut-off value of RLN of DSS was 22.5 (area under the curve = 63.3%, sensitivity = 55.6%, specificity = 76.8%, Figure 2B). In the high-risk group (n = 401), the optimal cut-off value of RLN was 39.5 (area under the curve = 64.4%, sensitivity = 73.2%, specificity = 53.6%, Figure 2C). The optimal cut-off value of RLN of DSS was 43.5 (area under the curve = 65.1%, sensitive = 85.4%, and specificity = 41.1%, Figure 2D). Thus, in the high-risk and non-high-risk groups, the optimal cut-off values of RLN of the prognosis (RFS and DSS) were determined as 40 and 23, respectively.

To explore the relationship between the optimal RLN cut-off values with prognosis (RFS and DSS) in the high-risk and non-high-risk groups

In the high-risk group's multivariate Cox regression analysis, the number of RLNs (⩾40 vs <40) was identified as independent prognostic influence factor of RFS and DSS in ESCC ($P < .001$ for RFS, $P = .002$ for DSS). In addition, tumor differentiation and vaginal resection margin were also independent influence factors of RFS and DSS in ESCC. However, LVSI was only independently associated with RFS. Tumor size, histology, LN metastasis, PU involvement, and CSI were not independently associated with either RFS or DSS (Supplementary Table 1).

In the non-high-risk group's multivariate Cox regression analysis, the number of RLNs (⩾23 vs <23) was identified as independent prognostic influence factor of RFS and DSS in ESCC ($P < .001$ for RFS, $P < .001$ for DSS). In addition, tumor size, tumor differentiation, and LVSI were also independent influence factors of RFS and DSS in ESCC. However, histology was only independently associated with RFS. Cervical stromal invasion was not independently associated with either RFS or DSS (Supplementary Table 2).

Survival analysis between high and low RLN groups in the high-risk and non-high-risk groups

The high-risk group was divided into 2 groups according to the optimal cut-off value of RLNs: the patients with number of RLNs greater than or equal to 40 were the high RLN group, and those with number of RLNs less than 40 were the low

Table 1. Clinic-pathological characteristics.

CHARACTERISTICS		PATIENTS N = 1129 (%)
Age (years)	Median	47
	Mean ± SD	48.04 (9.206)
	Range	21-79
Tumor size	<4 cm	705 (64.0)
	⩾4 cm	396 (36.0)
Histology	Squamous cell carcinoma	915 (83.1)
	Non-squamous cell carcinoma	186 (16.9)
Tumor differentiation	Low	120 (10.9)
	Moderate	609 (55.3)
	High	372 (33.8)
CSI	<Half	647 (58.8)
	⩾Half	454 (41.2)
LVSI	Negative	957 (86.9)
	Positive	144 (13.1)
PU involvement	Negative	867 (78.7)
	Positive	234 (21.3)
Vaginal resection margin	Negative	1059 (96.2)
	Positive	42 (3.8)
LN metastasis	Negative	913 (82.9)
	Positive	188 (17.1)
Number of RLNs	Median	34
	Mean ± SD	35.56 (14.284)
	Range	10-98
Recurrence	No	987 (89.6)
	Yes	114 (10.4)
Death	No	1026 (93.2)
	Death of recurrence	66 (6.0)
	Death of other disease	9 (0.8)
Follow-up (months)	Median	38
	Mean ± SD	38.71 (10.843)
	Range	6-60

Abbreviations: CSI, cervical stromal invasion; LN, lymph node; LVSI, lymphatic vascular space invasion; PU, para-uterine; RLN, retrieved lymph node.

RLN group. Similarly, the non-high-risk group was divided into 2 groups according to their optimal cut-off value of 23. In the high-risk group, the median follow-up time was 36 months (range 6-59) in the high RLN group and 36 months (range 6-70) in the low RLN group, respectively. In the non-high-risk group, the median follow-up time was 47 months (range 19-67) in the high RLN group and 42 months (range 9-55 months) in the low RLN group, respectively.

Table 2. Univariate and multivariate Cox regression analysis on the prognosis in FIGO stage IA1-IIA2 cervical cancer patients (N = 1101).

		UNIVARIATE						MULTIVARIATE					
		RFS			DSS			RFS			DSS		
RISK FACTORS		HR	95% CI	*P*-VALUE	HR	95% CI	*P*-VALUE	HR	95% CI	*P*-VALUE	HR	95% CI	*P*-VALUE
Age(years)		0.992	0.967-1.017	.516	1.001	0.981-1.021	.946	—	—	—	—	—	—
Tumor size	(⩾4 vs <4 cm)	2.370	1.503-3.735	<.001	1.860	1.288-2.686	.001	1.539	1.051-2.254	.027	1.836	1.143-2.948	.012
Histology	(Non-squamous cell carcinoma vs Squamous cell carcinoma)	1.748	1.039-2.942	.035	1.850	1.219-2.806	.004	1.791	1.167-2.750	.008	1.472	0.858-2.528	.161
Tumor differentiation	Low			<.001			<.001			<.001			<.001
	Moderate	0.392	0.233-0.660	<.001	0.371	0.241-0.570	<.001	0.417	0.269-0.647	<.001	0.452	0.265-0.771	.004
	High	0.141	0.066-0.300	<.001	0.184	0.105-0.324	<.001	0.248	0.140-0.439	<.001	0.205	0.095-0.440	<.001
CSI	(⩾Half vs <Half)	2.881	1.791-4.637	<.001	2.287	1.573-3.325	<.001	1.369	0.913-2.054	.129	1.586	0.945-2.663	.081
LVSI	(Positive vs Negative)	3.149	1.915-5.180	<.001	3.419	2.295-5.092	<.001	2.545	1.658-3.905	<.001	2.034	1.199-3.451	.008
PU involvement	(Positive vs Negative)	1.774	1.092-2.882	.021	2.116	1.443-3.101	<.001	2.025	1.368-2.997	<.001	1.709	1.042-2.803	.034
Vaginal resection margin	(Positive vs Negative)	4.068	2.090-7.918	<.001	3.694	2.073-6.583	<.001	3.797	2.111-6.829	<.001	3.959	2.008-7.807	<.001
LN metastasis	(Positive vs Negative)	2.745	1.706-4.417	<.001	2.212	1.481-3.305	<.001	1.667	1.086-2.560	.019	2.108	1.267-3.507	.004
No. of RLNs		0.978	0.960-0.995	.013	0.982	0.968-0.996	.011	0.968	0.954-0.982	<.001	0.964	0.946-0.982	<.001

Abbreviations: CI, confidence interval; CSI, cervical stromal invasion; DSS, disease-specific survival; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; LVSI, lymphatic vascular space invasion; PU, para-uterine; RFS, recurrence-free survival; RLN, retrieved lymph node.

In the non-high-risk group, the 5-year RFS in the high and low RLN groups were 95.5% (95% CI: 93.736%-97.264%) and 87.6% (95% CI: 82.504%-92.696%), respectively ($P < .001$, Figure 3A). The 5-year DSS in the high and low RLN groups were 97.1% (95%CI: 95.336%-98.864%) and 92.6% (95% CI: 87.504%-97.696%), respectively ($P = .002$, Figure 3B). The results showed that in the high-risk group, both RFS and DSS in the low RLN group were much lower than in the non-high RLN group ($P < .001$ for RFS, $P < .001$ for DSS).

In the high-risk group, the 5-year RFS in the high and low RLN groups were 88.4% (95% CI: 83.304%-93.496%) and 72.8% (95% CI: 66.332%-79.268%), respectively ($P < .001$, Figure 3C). The 5-year DSS in the high and low RLN groups were 88.8% (95% CI: 80.764%-97.424%) and 80.6% (95% CI: 74.524%-86.676%), respectively ($P = .002$, Figure 3D). The results showed that in the high-risk group, both RFS and DSS in the low RLN group were much lower than in the high RLN group ($P < .001$ for RFS, $P = .003$ for DSS).

The optimal cut-off values of RLN, KM survival curve analysis between the high and low RLN groups in the LN metastatic patients of the high-risk group (n = 188)

Furthermore, we further grouped whether they had LN metastases in the high-risk group. The median follow-up times were 37 months (range 9-60 months) in the LN metastatic patients of the high-risk group (n = 188).

The ROC curve and Youden index revealed that in the LN metastatic patients of the high-risk group, the optimal cut-off values of RLN of RFS and DSS all were similar. In the LN metastatic patients of the high-risk group, the optimal RLN cut-off of RFS was 37.5 (area under the curve = 66.5%, sensitivity = 70.6%, specificity = 61.0%, Supplementary Figure 2A). The optimal cut-off value of RLN of DSS was 43.5 (area under the curve = 66.2%, sensitive = 92.3%, and specificity = 43.2%, Supplementary Figure 2B). Thus, in the LN metastatic patients of the high-risk group, the optimal cut-off values of RLN of the prognosis (RFS and DSS) were determined as 40.

The LN metastatic patients of the high-risk group was divided into 2 groups according to the optimal cut-off value of RLN: the patients with number of RLNs greater than or equal to 40 were the high RLN group, and those with number of RLNs less than 40 were the low RLN group. In the LN metastatic patients of the high-risk group, the median follow-up time was 36 months (range 6-59) in the high RLN group and 35 months (range 6-70) in the low RLN group, respectively.

In the LN metastatic patients of the high-risk group, the 5-year RFS in the high and low RLN groups were 90.9% (95% CI: 84.824%-96.976%) and 69.8% (95% CI 59.608%-79.992%), respectively ($P = .002$, Supplementary Figure 3A). The 5-year DSS in the high and low RLN groups were 92.4% (95% CI: 86.912%-97.888%) and 76.2% (95% CI: 65.812%-86.588%), respectively ($P = .023$, Supplementary Figure 3B). The results showed that in the LN metastatic patients of the high-risk group, both RFS and DSS in the low RLN group were much lower than in the high RLN group ($P = .002$ for RFS, $P = .023$ for DSS).

Discussion

The scope of LN dissection has always been a controversial issue. So far, there are limited data on the possible benefits of a more extensive LN dissection of treatment of ESCC.[9-11] Furthermore, thorough LN dissection may cause complications such as lymphedema.[15,16] Therefore, this study tried to determine whether the number of RLNs was related to the prognosis of ESCC. In this study, medical records of 1101 patients with FIGO stage IA1-IIA2 cervical cancer undergoing initial radical treatment. The recurrence rate of FIGO stage IA1-IIA2 cervical cancer was 3.2% to 24.5%.[28,29] However, the choice of stages in published research varied. Pieterse et al[9] included patients with stage IA1-IIA cervical cancer; Shah et al[11] included patients with stage IA2-IIA cervical cancer; and Ditto et al[12] included patients with stage IA2-IVA cervical cancer. In this study, univariate and multivariate Cox regression analysis on all the patients treated with primary radical surgery in FIGO stage IA1-IIA2 cervical cancer (N = 1101) all showed that the number of RLN was an independent prognostic factor influence of RFS and DSS in ESCC patients. This was consistent with previous clinical findings and many literature reports. This suggested that we need to not only focus on factors such as tumor size, LVSI, and so on, which have been confirmed as independent prognostic factors of ESCC in many literature reports.[22,29,30] At the same time, we should also pay attention to the significant prognostic value of RLN number in early cervical cancer.

In this study, according to the guidelines,[17-19] all patients were divided into high-risk and non-high-risk groups based on postoperative pathological results whether there were high-risk factors (LN metastasis, PU involvement, vaginal resection margin [positive]). Furthermore, KM survival curve analysis indicated that both RFS and DSS in the high-risk group were much lower than in the non-high-risk group. Meanwhile, in this study, the optimal cut-off values of RLN were 23 in the high-risk group and 40 in the non-high-risk group, respectively. In addition, there are limited data to determine whether the impact of the number of RLNs on survival in cervical cancer patients is related to the high-risk factors.[31] This suggested that we should not treat all ESCC patients equally. Thus, we considered that it was necessary to stratify the patients according to whether there are high-risk factors in the postoperative pathological results based on the guidelines.

However, there is no consensus on the minimal number of RLNs in the treatment of cervical cancer.[23] Therefore, in this study, we attempted to explore the prognostic value of the optimal cut-off thresholds of RLN and to further determine whether the minimum number of LNs should be considered in LN dissection. In this study, ROC curve analysis and Youden index revealed that the optimal cut-off values of RLN were 23

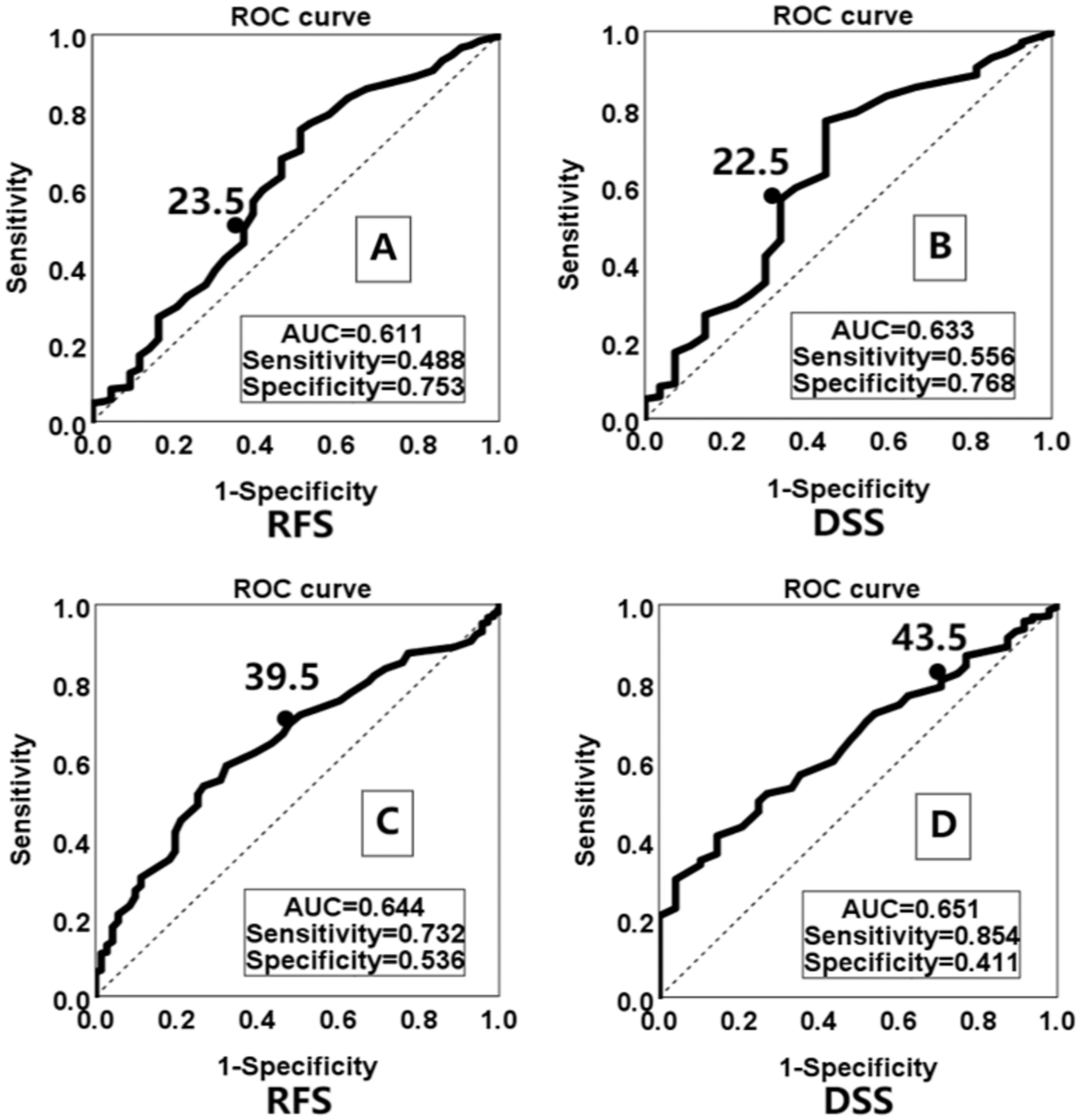

Figure 2. The optimal cut-off values of RLN in the high-risk (N = 401) or non-high-risk (N = 700) groups. Black dot: the area under the curve at this point is the largest. (A) The optimal cut-off of RLN of RFS was 23.5 in the non-high-risk group (area under the curve = 61.1%, sensitivity = 48.8%, specificity = 75.3%). (B) The optimal cut-off of RLN was 22.5 in the non-high-risk group (area under the curve = 63.3%, sensitivity = 55.6%, specificity = 76.8%). (C) The optimal cut-off of RLN value of RFS was 39.5 in the high-risk group (area under the curve = 64.4%, sensitivity = 73.2%, specificity = 53.6%). (D) The optimal cut-off value of RLN of DSS was 43.5 in the high-risk group (area under the curve = 65.1%, sensitivity = 85.4%, and specificity = 41.1%). Dotted line, reference line; solid line, RLN curve. AUC indicates area under the curve; DSS, disease-specific survival; RFS, recurrence-free survival; RLN, removed lymph node; ROC, receiver operating characteristic.

in the high-risk group and 40 in the non-high-risk group, respectively. Furthermore, both multivariate Cox regression analysis and KM survival curve analysis all showed that the optimal cut-off values of RLN were significantly associated with the prognosis of ESCC in the high-risk and non-high-risk groups, respectively. This suggested that in the high-risk group, to a certain extent, more extensive LN dissection (RLN ⩾ 40) could not only reduce recurrence but also increase the survival. However, in the non-high-risk group, moderate LN dissection (RLN ≈ 23) could also increase its survival and may reduce the incidence of related complications such as lower limb lymphedema. Most patients with early cervical cancer do not have LN metastasis, while thorough LN dissection may cause some serious complications, such as lymphedema.[15,16,32-35] The incidence of lower-limb lymphedema after LN dissection ranges from 3.6% to 32.5%.[32-34] However, the effect of number of RLN on lower-extremity lymphedema remains questionable. The number of RLN was reported as a risk factor for lower limb lymphedema in several studies.[15,16,32-35] Of course, that is not all.[22,33,36] This inconsistency may be due to differences in

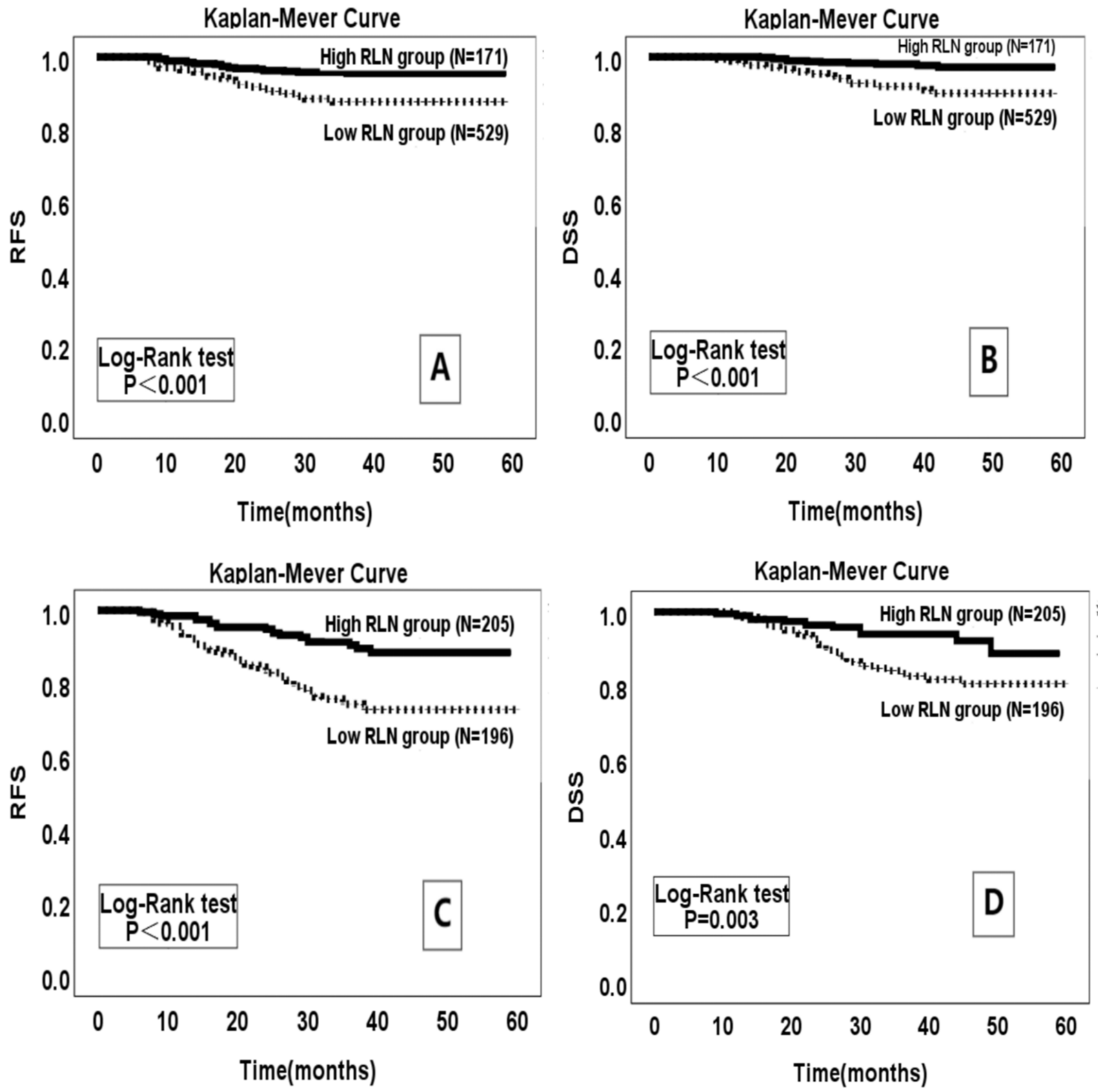

Figure 3. KM survival curve analysis between the high and low RLN groups in the high-risk or non-high-risk groups. (A) The RFS between the high and low RLN groups in the non-high-risk group ($P < .001$). (B) The DSS between the high and low RLN groups in the non-high-risk group ($P < .001$). (A and B) Dashed line: high RLN group (n = 171); solid line: low RLN group (n = 529). (C) The RFS between the high and low RLN group in the high-risk groups ($P < .001$). (D) The DSS between the high and low RLN groups in the high-risk group ($P = .003$). (C and D) Dashed line: high RLN group (n = 205); solid line: low RLN group (n = 196). DSS indicates disease-specific survival; KM, Kaplan-Meier; RFS, recurrence-free survival; RLN, removed lymph node.

the number of RLN between institutions and the diagnostic criteria for lower-limb lymphedema.

It is worth mentioning that a study that would separately group the bulk cervical cancer and non-bulk cervical cancer patients according to the optimal cut-off value (40) of RLN showed that broader LN dissection could increase the survival of bulk cervical cancer patients. While, that study also indicated that the optimal cut-off value (40) of RLN was not an independent prognostic factor in patients with non-bulk cervical cancer.[22] That study is similar to our results. In addition, this suggested that we should not be stratified only by tumor size mentioned above. At the same time, we should also attach importance to the significance of stratifying all the patients with ESCC according to the high-risk factors (LN metastasis, PU involvement, vaginal resection margin [positive]). In this study, we not only grouped all patients by whether they have high-risk factors, but also further grouped the high-risk group by whether they have LN metastasis. In the LN metastatic patients of the high-risk group, the best cut-off value of ROC curve is about 40, which is consistent with the results of our high-risk group. It is worth mentioning that the LN metastatic patients of the high-risk group were further grouped according to the optimal cut-off value of 40. KM survival curve showed that the optimal threshold of RLN was significantly correlated with the prognosis of the LN metastatic patients of the high-risk group. In addition, patients with metastatic pelvic LNs are likely to experience a higher rate of distant or mixed relapse(s) and dismal clinical outcomes.[37] Besides, recent lines of evidence have shown that the number of metastatic pelvic LNs could better predict prognostic outcomes within stage IIIC1 cervical cancer and have potential implications for therapeutic decision-making in the treatment of patients with stage IIIC1 CC.[37] While, it has also been shown that in patients of high-risk cervical cancer treated with radical surgery and adjuvant treatment, with log odds of positive LNs $\geqslant -1.05$, intensified chemotherapy might be required, considering the high rate of distant failure.[38] In this context, in fact, this is not difficult to understand, because in the LN metastatic patients of the high-risk group, the more extensive the LN dissection, the more metastasis-positive nodes may be identified and cleared, the less the residual positive LNs may be, thus improving their prognosis to a certain extent. Of course, a recent study showed that in patients with positive LNs, radical surgery did not improve their prognosis, and it was suggested that they should directly undergo whole course radiotherapy and chemotherapy.[39] However, in fact, the study did not contradict the conclusions of this study, because the study did not explore the impact of the number of RLNs on their prognosis. Besides, in the radical surgery of patients with positive LNs in that study, the number of RLNs may not reach a certain number (eg, RLN $\geqslant$ 40 in this study). On the contrary, that study is a supplement to the research conclusion to some extent.

What needs to be explained is that, in this study, univariate Cox regression analysis showed significant association with tumor size in all cervical cancer patients, which was also showed in the multivariate Cox regression analysis, in the non-high-risk group. However, no significant association of tumor size was shown with the high-risk group in the multivariate Cox regression analysis. This may be because this is a single central study. And other independent prognostic factors including the number of RLNs and other factors were more strongly associated with cervical cancer prognosis. However, this did not deny the importance of tumor size in predicting cervical cancer prognosis. Indeed, many articles have reported that tumor size was an important predictor of cervical cancer prognosis.[22,30]

This study had the following limitations. First, this was a single-center retrospective study, and our conclusion should be further demonstrated by a multicenter prospective study. Second, the monitoring cycle is not long. Third, we used postoperative pathological specimens for analysis. While, according to the clinical stage (PU involvement and vaginal margins status) and the imaging examination stage (LN metastasis), we may determine the scope of LN dissection before surgery,[20,40] although imaging studies (computed tomography, MRI, and positron emission tomography) may not accurately diagnose LN transfer.[41,42] In this study, the area under the curve of the ROC curve ranged between 0.6 and 0.7. This suggested the predictive value of the optimal threshold was considered to have a fair performance,[25] as it may be disturbed by some human factors.

Conclusions

In conclusion, this study indicated that the number of RLNs was significantly associated with the prognosis of ESCC patients. In the high-risk ESCC patients, to a certain extent, more extensive LN dissection (RLN $\geqslant$ 40) could reduce recurrence and increase the survival. However, in the non-high-risk ESCC patients, moderate LN dissection (RLN $\approx$ 23) could increase its survival and may reduce the incidence of related complications such as lower limb lymphedema. Those findings may help to determine the scope of LN dissection in patients with cervical cancer before operation.

Author Contributions

SJ contributed to the data collation, writing, review and editing, and approval of the article. PJ contributed to the data collection, formal analysis, writing original draft, and approval. TJ was involved in the data collection, visualization, and investigation. YT was involved in the data collection and software. JZ was involved in the visualization and investigation. NL contributed to the data collection and conceptualization. WK was involved in the data collection and validation. YH contributed to the data collection. RY contributed to the conceptualization, supervision, review and editing, and approval of the article.

Data Sharing Statement

Datasets used and/or analyzed in this study can be obtained from corresponding authors upon reasonable request.

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Supplemental Material

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