

## Research Article

# Para-Aortic Lymph Node Dissection for Patients with Node-Negative Cervical Squamous Cell Carcinoma: A Retrospective Cohort Study

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**Objective.** The current guidelines for cervical cancer are uncertain regarding whether the para-aortic lymph nodes (PALNs) need to be removed. For patients with negative PALNs, whether the addition of PALN dissection (PALND) can be translated into survival benefits is unknown. **Methods.** The medical records of 3,995 patients with FIGO stage IB-IIA cervical squamous cell carcinoma (CSCC) who underwent abdominal radical surgery between 2006 and 2014 at our center were retrospectively reviewed. Two groups were identified: PALN-negative patients who underwent PALND (+PALND) and those who did not (−PALND). The groups were matched by propensity score matching (PSM). Survival was analyzed using the Kaplan–Meier method and the Cox proportional hazards model. Subgroups were stratified by the variables known at the time of diagnosis. **Results.** After PSM, 313 patients were matched to the −PALND (cohort 1) and +PALND (cohort 2) groups. Cohort 2 patients had a poorer prognosis than cohort 1 patients in terms of overall survival (OS,  $P = 0.014$ ), and PALND was an independent prognostic factor for OS ( $P = 0.021$ ). There were no differences in recurrence patterns between the groups. Subgroup analysis showed that cohort 2 patients had worse OS than cohort 1 patients when they were aged  $\leq 47$  years ( $P = 0.033$ ), were premenopausal ( $P = 0.032$ ), were in stage IB ( $P = 0.009$ ), or had preoperative SCC-Ag  $< 6.5$  ( $P = 0.009$ ). **Conclusions.** PALND negatively impacts OS in early-stage PALN-negative CSCC patients. For CSCC patients who are clinically PALN-negative, especially those who are young, are premenopausal, have tumors confined to the cervix, and have relatively low SCC-Ag values, PALND may “rub salt on the wound.”

## 1. Background

Cervical cancer is a malignant tumor in the female reproductive system with the highest incidence worldwide [1]. The widespread application of cervical cytology screening in recent decades has enabled the early detection and treatment of cervical cancer, and the mortality of cervical cancer has decreased significantly [2]. For patients with early-stage cervical cancer, radical surgery is still the primary treatment [3].

In the current National Comprehensive Cancer Network (NCCN) guidelines, the recommendation for early-stage operable cervical cancer patients is to perform radical

hysterectomy (RH) and pelvic lymph node dissection (PLND) with or without para-aortic lymph node dissection (PALND) [4]. Whether the para-aortic lymph nodes (PALNs) need to be removed has not been confirmed. In this situation, how can we decide whether to perform PALND?

It is well accepted that patients with PALN metastasis show poorer overall survival (OS) and progression-free survival (PFS) following surgical resection than patients with the same International Federation of Gynecology and Obstetrics (FIGO) stages (2009 version) who do not have PALN metastasis [5], and PALN involvement has become an essential part of cervical cancer staging in the new FIGO staging system (2018 version) [6]. Additionally, extended-

field radiation is indicated in cases of PALN dissemination [7]. Therefore, for patients with suspected PALN metastasis, surgeons should remove the nodes without hesitation. However, PALN metastases are found in less than 10% of patients with early-stage cervical cancer [8], and the anatomy surrounding PALNs is complex. The routine addition of PALND might add considerable operation time and increase surgical complications, such as vascular, ureteral, and nerve injury, as well as the risk of infection, lymphocyst formation, lymphedema, and thrombophlebitis, even by an expert surgeon [9, 10]. For patients with clinically negative PALN, should we perform PALND routinely? To answer this question, we must know whether additional PALND translates to a survival benefit in patients with negative PALNs. To the author's knowledge, there is currently no large-scale study on patients with negative PALN only.

In contrast to other gynecological tumors, the lymph node metastasis pattern of cervical cancer is relatively clear and has been studied and reviewed in detail, from regional lymph nodes to distant lymph nodes [11]. In general, cancer cells from the cervical tumor first spread to the nodes of the obturator and external iliac, which are the sentinel lymph nodes of the cervix, and then proceed to the common iliac and PALN, similar to a "ladder," where the common iliac lymph node is a key site in the middle of the ladder [12]. It is very rare that PALNs are positive and pelvic lymph nodes are negative, occurring in less than 1.5% of patients with early-stage cervical cancer [13]. Theoretically, the probability of positive PALNs and negative common iliac lymph nodes should be even lower. Therefore, for patients who have undergone common iliac lymph node resection and are confirmed as negative by pathology, there is a small likelihood of overlooking PALN metastasis.

Cervical squamous cell carcinoma (CSCC) accounts for more than 80% of cervical cancers, and the lymph node metastasis rate is lower than that of other pathological types of cervical cancer [14]. Therefore, we planned this large retrospective cohort study on PALND for patients with early-stage CSCC who were PALN-negative. Patient data from our center were collected and analyzed. Propensity score matching (PSM) [15] was used for protocol analysis.

## 2. Patients and Methods

**2.1. Patients.** After Institutional Review Board approval, the medical records of all CSCC patients with FIGO stage IB1-IIa2 (2009 version) who underwent abdominal RH ± bilateral salpingo-oophorectomy and PLND ± PALND between 2006 and 2014 at Fudan University Shanghai Cancer Center (FUSCC) were reviewed using our institutional cancer registry. The study was approved by the ethics committee at our center and the work has been reported in line with the STROCSS criteria [16].

**2.2. Treatment.** All the enrolled patients had undergone standard surgery by experienced gynecological oncologists in our center. PALND is usually conducted along the flow of the abdominal lymphatics up to the level of the inferior

mesenteric artery (IMA). When infra-IMA node metastasis was suspected by preoperative evaluation or intraoperative exploration, PALNs were also removed up to the level of the left renal vein. Adjuvant treatment was provided to patients with risk factors according to the NCCN guidelines. Individuals who had two or more intermediate-risk factors (tumor diameter  $\geq 4$  cm,  $\geq 1/2$  depth of stromal invasion, or lymphovascular space invasion (LVSI) positive) and those who had a minimum of one high-risk factor (parametrium positive, lymph node metastasis, or surgical margins involved) received adjuvant radiotherapy or concurrent chemoradiotherapy.

**2.3. Follow-Up.** After the treatment was completed, the patients were followed up regularly: every 3 months for the first two years, every 6 months from the second year to the fifth year, and once a year thereafter. The follow-up items included symptom consultation, pelvic physical examination, squamous cell carcinoma antigen (SCC-Ag), ultrasonography, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, and vaginal cytology test. The site of recurrence was documented as locoregional or distant, and it was recorded as a distant recurrence when both were present. Distant recurrences were identified as metastases beyond the pelvis. PFS was defined as the time (months) from diagnosis to disease recurrence. OS was defined as the time (in months) from initial diagnosis to death from any cause. Data on patients with no evidence of disease recurrence or death were censored at the date of the last follow-up.

**2.4. Study Design.** The flow chart of the study is shown in Figure 1. A total of 3,995 patients with stage IB1-IIA2 CSCC underwent radical surgery in our center. After excluding patients with incomplete information, 3,085 patients remained. Then, we excluded patients with positive PALNs, less than 3 months of follow-up, positive or unknown common iliac lymph nodes, and uncertain recurrence sites. Finally, 2,427 patients were included in this study. According to the aforementioned theory of lymph node metastasis patterns in cervical cancer, for patients who had undergone common iliac lymph node resection and had negative postoperative pathology, the PALN was also defaulted to negative. In this set of data, only 2 patients (0.47%) had negative common iliac lymph nodes, but postoperative pathology showed positive PALNs, indicating that common iliac lymph nodes can indeed be used as an indicator of the status of PALNs. The number of remaining patients with "RH + PLND" and negative common iliac lymph nodes was 2,095, while 332 patients who underwent "RH + PLND + PALND" and PALN removal were negative. Then, we used PSM to keep the baselines of the two groups ("−PALND" and "+PALND") of patients consistent (ratio = 1, caliper = 0.01), thereby reducing possible confounding factors in the subsequent prognostic analysis. PSM was performed through a multiple logistic regression model in which PALND was the dependent variable and the covariates were potential confounding factors, including

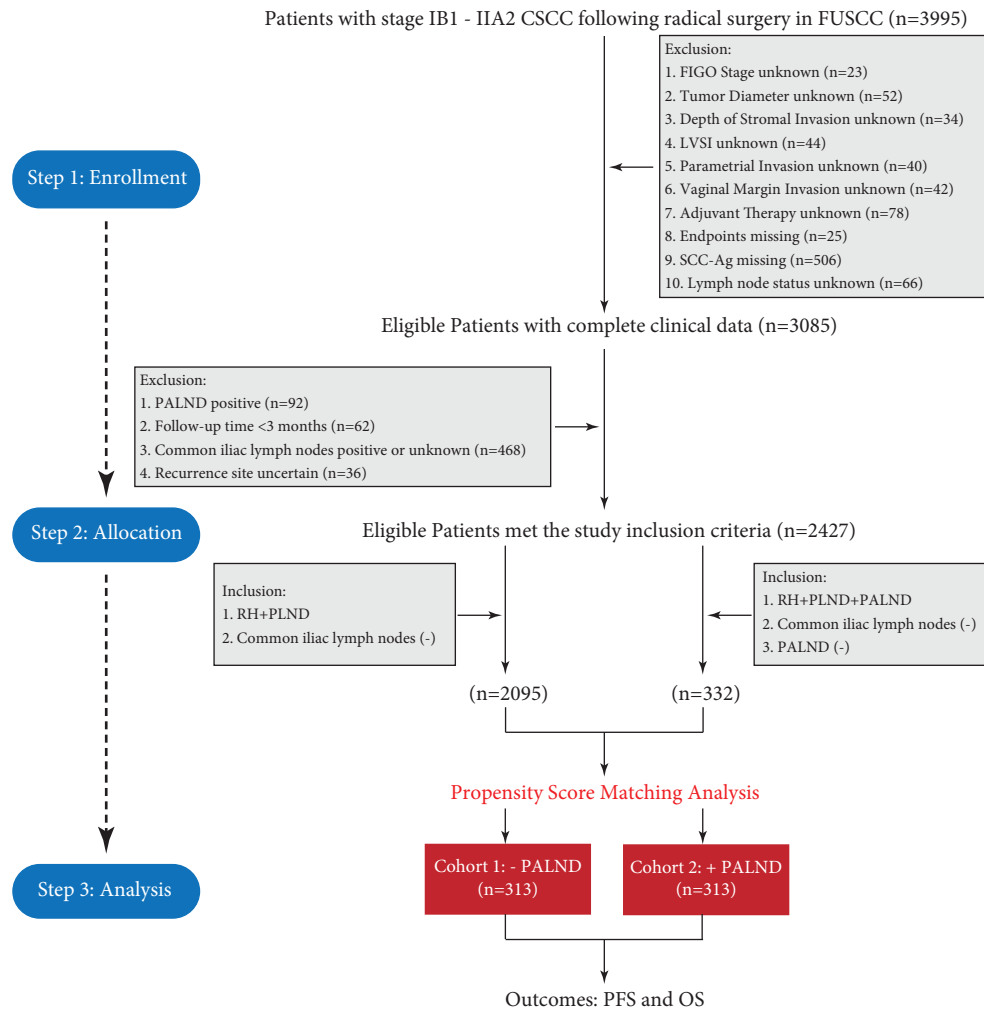


FIGURE 1: Flow chart of the study. CSCC: cervical squamous cell carcinoma; FUSCC: Fudan University Shanghai Cancer Center; FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; SCC-Ag: serum squamous cell carcinoma antigen; PALN: para-aortic lymph node; RH: radical hysterectomy; PLND: pelvic lymph node dissection; PALND: para-aortic lymph node dissection; PFS: progression-free survival; OS: overall survival.

patient age, menopausal status, FIGO stage, tumor diameter, depth of stromal invasion, parametrial invasion, LVSI, vaginal margin invasion, pelvic lymph node metastasis, adjuvant therapy, and preoperative serum SCC-Ag. Patients who were found to be outside the caliper were excluded. Unmatched patients were also excluded.

**2.5. Statistical Analysis.** Continuous variables, including patient age, number of PALNs resected, and preoperative SCC-Ag, were divided into two groups by their respective medians. Pearson's chi-square test and Fisher's exact test were used to compare clinicopathological factors between groups. Survival curves between different groups of patients were estimated by Kaplan–Meier survival curves and the log-rank test, with stratification according to the factors. Calculations of hazard ratios (HRs) with 95% confidence intervals (CIs) were made through multivariate analyses using Cox proportional hazards models to evaluate the prognostic factors related to survival. All statistical analyses were

performed on all matched/paired patients.  $P < 0.05$  was considered to indicate a statistically significant difference. The statistical analyses of the observed data were performed by SPSS (Version 22.0, Chicago, USA) and R (Version 3.5.1, Vienna, Austria).

### 3. Results

**3.1. Patient Characteristics.** As shown in Figures 1 and S1, the patients were matched by PSM: 313 were allocated to the -PALND group (cohort 1), and 313 were allocated to the +PALND group (cohort 2). The median patient age at the time of surgery was 47 years (range, 22–73 years), the median preoperative SCC-Ag value was 6.5 ng/ml (range, 0.1–70 ng/ml), and the median follow-up time was 83.2 months (range, 4–161 months). Table 1 summarizes the patient demographics and tumor characteristics before and after matching. Before matching, statistically significant differences were noted between the two groups with respect

TABLE 1: Relationship between PALND and clinicopathological features before and after propensity score matching.

Variable	Before matching		P value	After matching		P value
	-PALND (N=2095)	+PALND (N=332)		-PALND (N=313)	+PALND (N=313)	
Age, years						
≤47	1096 (52.3%)	206 (62.0%)	0.001	198 (63.3%)	199 (63.6%)	0.934
>47	999 (47.7%)	126 (38.0%)		115 (36.7%)	114 (36.4%)	
Menopausal status						
Premenopausal	1377 (65.7%)	248 (74.7%)	0.001	234 (74.8%)	235 (75.1%)	0.927
Postmenopausal	718 (34.3%)	84 (25.3%)		79 (25.2%)	78 (24.9%)	
FIGO stage						
IB	1063 (50.7%)	154 (46.4%)	0.14	142 (45.4%)	141 (45.0%)	0.936
IIA	1032 (49.3%)	178 (53.6%)		171 (54.6%)	172 (55.0%)	
Tumor diameter (cm)						
≤4	1536 (73.3%)	198 (59.6%)	<0.001	187 (59.7%)	187 (59.7%)	1
>4	559 (26.7%)	134 (40.4%)		126 (40.3%)	126 (40.3%)	
Depth of stromal invasion						
<½	668 (31.9%)	57 (17.2%)	<0.001	53 (16.9%)	53 (16.9%)	1
≥½	1427 (68.1%)	275 (82.8%)		260 (83.1%)	260 (83.1%)	
LVSI						
Negative	1362 (65.0%)	204 (61.4%)	0.207	198 (63.3%)	197 (62.9%)	0.934
Positive	733 (35.0%)	128 (38.6%)		115 (36.7%)	116 (37.1%)	
Parametrial invasion						
Negative	2008 (95.8%)	319 (96.1%)	0.84	306 (97.8%)	306 (97.8%)	1
Positive	87 (4.2%)	13 (3.9%)		7 (2.2%)	7 (2.2%)	
Vaginal margin invasion						
Negative	2023 (96.6%)	325 (97.9%)	0.205	310 (99.0%)	309 (98.7%)	1
Positive	72 (3.4%)	7 (2.1%)		3 (1.0%)	4 (1.3%)	
Pelvic lymph node metastasis						
Negative	1688 (80.6%)	239 (72.0%)	<0.001	227 (72.5%)	227 (72.5%)	1
Positive	407 (19.4%)	93 (28.0%)		86 (27.5%)	86 (27.5%)	
Adjuvant therapy						
No	643 (30.7%)	59 (17.8%)	<0.001	55 (17.6%)	55 (17.6%)	1
Yes	1452 (69.3%)	273 (82.2%)		258 (82.4%)	258 (82.4%)	
Preoperative SCC-Ag						
<6.5 ng/mL	1588 (75.8%)	226 (68.1%)	0.003	218 (69.6%)	218 (69.6%)	1
≥6.5 ng/mL	507 (24.2%)	106 (31.9%)		95 (30.4%)	95 (30.4%)	

PALND: para-aortic lymph node dissection; FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; SCC-Ag: serum squamous cell carcinoma antigen.

to patient age ( $P = 0.001$ ), menopausal status ( $P = 0.001$ ), tumor diameter ( $P < 0.001$ ), depth of stromal invasion ( $P < 0.001$ ), pelvic lymph node metastasis ( $P < 0.001$ ), adjuvant therapy ( $P < 0.001$ ), and preoperative SCC-Ag ( $P = 0.003$ ). After matching, the baseline characteristics between the two groups were well balanced without significant differences.

**3.2. OS and PFS of the Matched Cohorts: -PALND vs. +PALND.** At the last follow-up, 26 patients died, and 66 patients experienced recurrence. When we compared the prognosis of the two cohorts, we found a remarkable result: Kaplan–Meier analysis and the log-rank test revealed that patients in cohort 2 with PALND showed poorer prognosis than patients in cohort 1 without PALND in terms of OS ( $P = 0.014$ , Figure 2(a)); however, there was no significant difference in PFS between the two groups ( $P = 0.521$ , Figure 2(b)). To eliminate bias from other prognostic factors, such as FIGO stage, tumor diameter, depth of stromal invasion, LVSI, parametrial invasion, vaginal margin invasion, pelvic lymph node metastasis, adjuvant

therapy, and SCC-Ag, we examined the impact of these prognostic factors on survival by multivariate analysis. The results showed that PALND was an independent prognostic factor for OS ( $P = 0.021$ , Figure 3).

**3.3. OS of the Matched PALND Cohort According to the Number of PALNs Removed.** Next, we analyzed whether patient OS was related to the number of PALNs removed. According to the median value, we divided the +PALND group into the PALND < 5 and PALND ≥ 5 groups, and Kaplan–Meier analysis showed that there was no significant difference in OS between the two groups ( $P = 0.709$ , Figure 4).

**3.4. Recurrence Patterns between Groups.** In total, 28 patients in the -PALND group and 38 patients in the +PALND group experienced relapse. In terms of the site of recurrence, there were no differences in recurrence patterns between the two groups, but there was a higher but not significant distant recurrence rate in patients with PALND (69.4% vs. 65.2%,  $P = 0.774$ , Table S1).

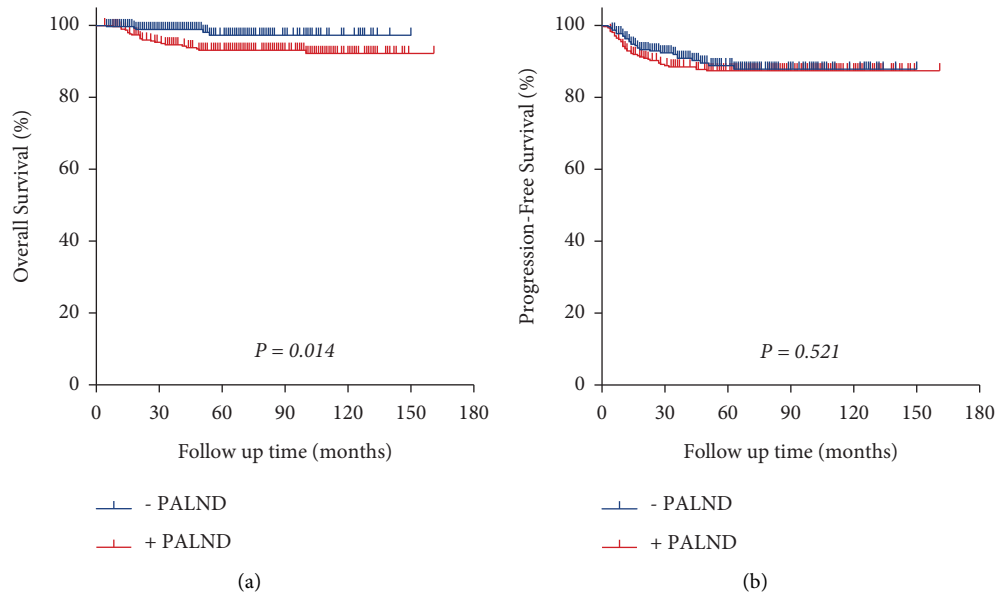


FIGURE 2: Kaplan–Meier estimates of OS (a) and PFS (b). OS: overall survival; PFS: progression-free survival; PALND: para-aortic lymph node dissection.

Variable	P value
FIGO Stage	0.458
Tumor Diameter (cm)	0.870
Depth of Stromal Invasion	0.733
LVSI	0.244
Parametrial Invasion	0.113
Vaginal Margin Invasion	0.033
Pelvic Lymph Node Metastasis	0.159
Adjuvant Therapy	0.443
Preoperative SCC-Ag	0.752
PALND	0.021

FIGURE 3: Multivariate analysis of clinicopathological factors for OS. FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; SCC-Ag: serum squamous cell carcinoma antigen; PALND: para-aortic lymph node dissection; OS: overall survival.

3.5. *Subgroup Analysis.* In subgroup analysis, subgroups were stratified by the variables known at the time of diagnosis, which included patient age, menopausal status, FIGO stage (2009 version), tumor size, and preoperative SCC-Ag value. As shown in Figure 5, the Kaplan–Meier method and log-rank test results showed that the OS of patients in cohort 2 was worse than that of patients in cohort 1 when they were aged  $\leq 47$  years ( $P = 0.033$ ), were premenopausal ( $P = 0.032$ ), were in stage IB ( $P = 0.009$ ), or had SCC-Ag  $< 6.5$  ( $P = 0.009$ ). A Cox regression analysis was conducted with various prognostic and clinicopathological factors in each subgroup, as shown in Figure S2. The multivariate analysis results showed that PALND was an independent risk factor for OS in patients aged  $\leq 47$  ( $P = 0.045$ ), those who were premenopausal ( $P = 0.045$ ),

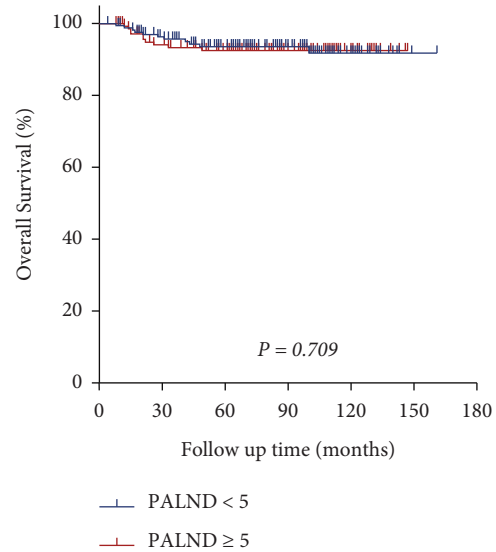


FIGURE 4: Kaplan–Meier estimates of OS according to the number of PALNs removed. OS: overall survival; PALN: para-aortic lymph nodes.

those in stage IB ( $P = 0.031$ ), and those with SCC-Ag  $< 6.5$  ( $P = 0.020$ ).

#### 4. Discussion

The survival rate of patients with early-stage cervical cancer is very high, and some patients can even be cured [17]. This study had an average of more than 80 months of long-term follow-up, and the patients’ survival rate was still higher than 90%. The pursuit of these patients is not only to live but also to live with quality. At present, a series of studies at our center have confirmed that patients with early cervical

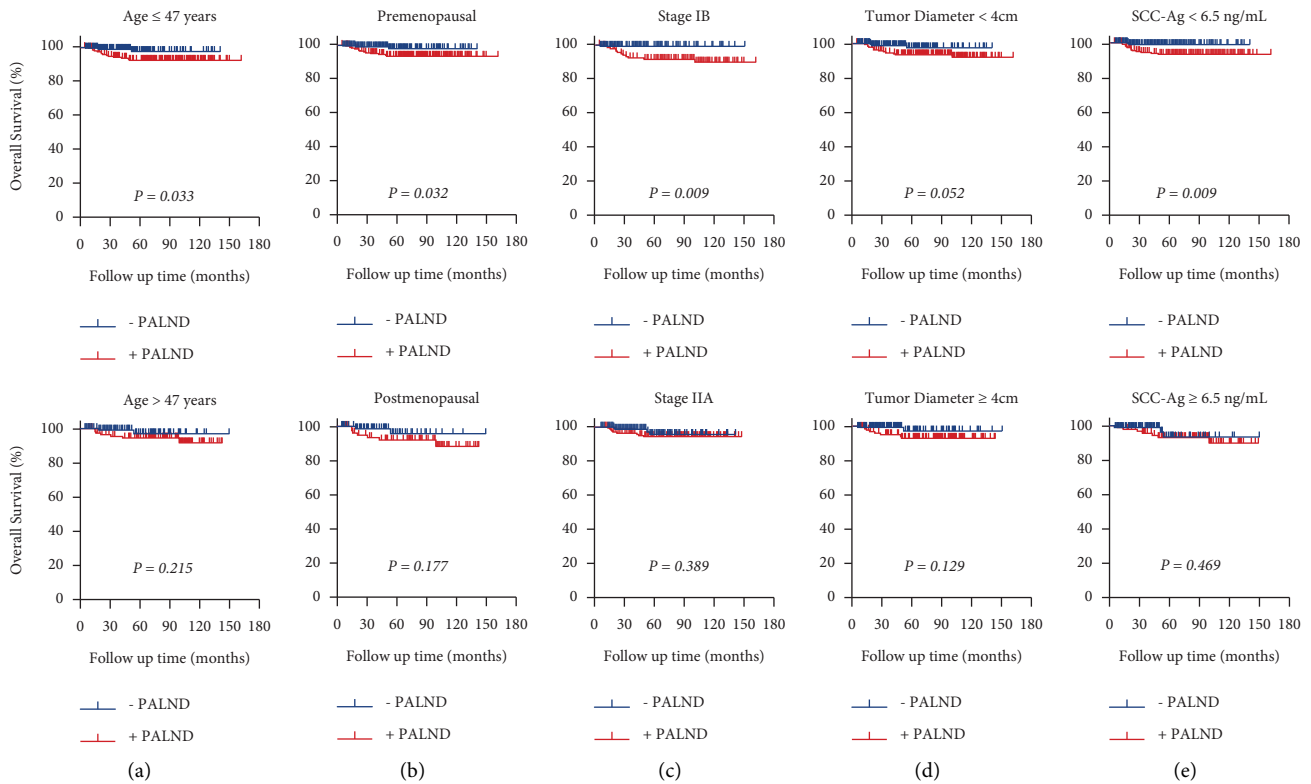


FIGURE 5: Kaplan-Meier estimates of OS stratified by patients' age (a), menopausal status (b), FIGO stage (c), tumor size (d), and preoperative SCC-Ag value (e). OS: overall survival; SCC-Ag: serum squamous cell carcinoma antigen; PALND: para-aortic lymph node dissection.

cancer can safely and effectively undergo radical trachelectomy, which preserves fertility [18–20]. This shows the great progress brought by precision medicine. Extensive lymph node resection, especially PALND, may cause serious complications. To determine whether the lymph nodes need to be removed, more research is needed.

Lymphadenectomy has always been regarded as a very important step during surgery for many kinds of malignant tumors [21, 22]. However, as medical technology becomes increasingly accurate, there is an increasing discussion about the necessity and extent of lymphadenectomy. A randomized controlled study conducted by Sasako et al. showed that treatment with D2 lymphadenectomy plus PALND does not improve the survival rate in curable gastric cancer compared with D2 lymphadenectomy alone [23]. Similar conclusions are gradually being reported in pancreatic neuroendocrine tumors [24], bladder cancer [25], and papillary thyroid cancer [26]. In gynecologic tumors, the famous LION study showed that for patients with advanced ovarian cancer who reach R0 and have no abnormal lymph nodes before and during the operation, compared with patients without lymph node dissection, lymph node dissection has no significant impact on OS or PFS but increases the incidence of postoperative complications [27]. In endometrial cancer, there is also a very authoritative randomized controlled study that found no evidence of a benefit in terms of OS or PFS for pelvic lymphadenectomy in women with early endometrial cancer [28]. However, no similar high-level

studies have been reported for cervical cancer. Our previous study showed that the number of positive lymph nodes truly affected the prognosis of patients with early-stage CSCC [29, 30]. The resection of too many “useless” lymph nodes may not have a significant effect on the prognosis of patients. The present study found that for patients with negative PALN, PALND may be “rubbing salt on the wound.” Taking the risk of complications may even further affect the patient's prognosis.

Actually, a small number of retrospective analyses have attempted to evaluate the therapeutic role of PALND in cervical cancer. Tsuruga et al. showed that indications for PALND in the surgical treatment of stage IB2, IIA2, or IIB cervical cancer need to be individualized. Patients with common iliac lymph node metastasis are possible candidates [10]. Gonzalez-Benitez et al. reported that the survival benefit of PALND in patients with advanced cervical cancer is lacking [31]. Del Carmen et al. emphasized that in patients undergoing RH and PLND for stage IA2-IB2 cervical cancer, PALND is not warranted based on the low risk of isolated metastatic disease and lack of survival benefit associated with the procedure [13]. The results of these studies indicate that patients with cervical cancer should be treated individually, and surgeons may choose not to remove the PALN in some special cases. However, in this study, we focused on patients with stage IB1-IIA2 CSCC who can undergo surgery and used the “ladder” rule of cervical cancer lymph node metastasis to accurately screen patients with negative PALNs.

Theoretically, this part of the population should include patients least able to benefit from PALND. Depending on whether PALND was performed, we divided the patients into two groups, and patient background was ideally balanced in the groups by matching; therefore, the comparison of –PALND and +PALND was considered reliable. Interestingly, the results showed that although there was no significant difference in PFS between the two groups, the OS of patients with PALND was worse. The results of the multivariate analysis also showed that PALND was an independent predictor of OS. At the same time, to verify whether the prognosis of patients is different due to an insufficient number of PALNs resected, we grouped the patients by the number of lymph nodes removed, and the results showed that there was no difference in the prognosis between the two groups. This result challenges conventional cognition and reminds surgeons that when treating patients with clinical PALN negativity, the options of “yes or no” may no longer be relevant since “absolutely not” may be a preferred option.

One of the reasons for this discrepancy may be that local immune function is damaged after lymph node removal. The lymphatic system is the first line of immune defense [32]. A recent study clearly showed that regional lymph nodes play an important role in antitumor immunity, particularly in microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) colorectal cancers with a high tumor mutational burden (TMB), requiring careful consideration of excessive nonmetastatic lymph node dissection in MSI-H/dMMR colorectal cancer patients [33]. Therefore, for patients with negative lymph nodes, maintaining the integrity of the lymphatic system as much as possible and protecting the patient’s immune function may improve the patient’s survival rate and quality of life, while blindly clearing the entire lymphatic system may be counterproductive.

Due to the uncertainty of the current guidelines, when the clinical evaluation of the PALN is negative, the surgeon will inevitably have subjective factors when selecting patients who need to undergo PALND. Sometimes patients who are young, are premenopausal, have a low BMI, and are not prone to postoperative complications may be more suitable. To help better select preoperative patients, our subjects were then stratified according to the variables known at the time of diagnosis, and the data were further analyzed. The results showed that for patients younger than 47 years, those who were premenopausal, those in FIGO stage IB, and those with SCC-Ag lower than 6.5, patients with PALND had worse survival. Furthermore, when multivariate analysis was performed, PALND was an independent factor. This reminds us that when treating these patients, if the clinical evaluation of the PALN is negative, we need to be very cautious when choosing PALND.

There are several limitations to this study, the most obvious being its retrospective nature at a single institution. Because of the nonrandomized nature of the study design and potential allocation biases arising from the retrospective comparison between groups, PSM was utilized to keep the patient characteristics of the two cohorts well-balanced, but unknown confounders still represent a source of bias.

Another shortcoming is the lack of statistical data on the occurrence of postoperative complications in this study. Whether PALND will increase the incidence of complications cannot be answered by this study, and it is doubtful whether the poor survival of patients with PALND is related to serious adverse events. In addition, the patients included in this study were only CSCC patients, and patients with cervical cancer of other pathological types were not included in this study. More studies are needed to determine the relationship between PALND and patient survival in these pathological types.

In summary, in contrast to other studies, our data showed that PALND had a negative impact on the OS of patients with early-stage CSCC. The pattern of recurrence was similar with and without PALND, and omitting PALND did not increase the rate of distant recurrence. For patients with cervical cancer who are clinically evaluated as PALN-negative, especially those who are younger, who are premenopausal, whose tumors are confined to the cervix (stage IB), and who have relatively low SCC, PALND needs to be selected with special care. The convention of feeling free to decide whether to perform PALND needs to be changed. It is recommended that we strive to find more accurate, convenient, and economical diagnostic methods for PALN metastasis. Nevertheless, whether PALND truly affects the OS of patients with cervical cancer and whether the guidelines need to clearly indicate which patients are not suitable for PALND require a higher level of evidence, that is, a prospective randomized controlled study, for verification.

### Data Availability

The data used to support the findings of this study will be made available on request to the corresponding author.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Authors’ Contributions

Qinhao Guo, Xingzhu Ju, and Xiaohua Wu conceptualised the study. Xingzhu Ju and Xiaohua Wu designed the study. Jun Zhu, Jiangchun Wu, Simin Wang, and Yong Wu handled data acquisition. Qinhao Guo and Jun Zhu were in charge of quality control of data and algorithms. Qinhao Guo, Jun Zhu, and Yong Wu handled data analysis and interpretation. Qinhao Guo, Jun Zhu, and Yong Wu were in charge of statistical analysis. Yong Wu, Xingzhu Ju, and Xiaohua Wu prepared the manuscript. Qinhao Guo and Jun Zhu edited the manuscript. All the authors reviewed the manuscript. Qinhao Guo, Jun Zhu, and Yong Wu contributed equally to this work.

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## Supplementary Materials

Table S1: site of first tumor recurrence. Figure S1: propensity scores of different groups (A). Distribution of the propensity scores (B). Figure S2: multivariate analysis of clinicopathological factors for OS in patients aged  $\leq 47$  years (A), patients who were premenopausal (B), patients with FIGO stage IB (C), and patients with SCC-Ag $<6.5$  ng/mL (D). (*Supplementary Materials*)

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