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Para-aortic and pelvic lymphadenectomy in locally advanced cervical cancer with pelvic lymph node metastasis

Wei Jiang[1†], Mei-ling Zhong[1†], Su-lan Wang[2], Yan Chen[3], Ya-nan Wang[1], Si-yuan Zeng[1] and Mei-rong Liang[1,4*]

Abstract

Objective This study sought to explore the efficiency of para-aortic and pelvic lymphadenectomy in the treatment of locally advanced cervical cancer (LACC) with pelvic lymph node (PLN) metastasis.

Methods A total of 171 LACC patients with imaging-confirmed pelvic lymph node metastasis were included in this study. These patients were divided into two groups: the surgical staging group, comprising 58 patients who had received para-aortic and pelvic lymphadenectomy (surgical staging) along with concurrent chemoradiation therapy (CCRT), and the imaging staging group, comprising 113 patients who had received only CCRT. The two groups' progression-free survival (PFS), overall survival (OS) and treatment-related complications were compared.

Results The surgical staging group started radiotherapy 10.2 days (range 9–12 days) later than the imaging staging group. The overall incidence of lymphatic cysts was 9.30%. In the surgical staging group, para-aortic lymph node metastasis was identified in 34.48% (20/58) of patients, while pathology-negative PLN was observed in 12.07% (7/58). Over a median follow-up period of 52 months, no significant differences in PFS and OS rates were found between the two groups ($p > 0.05$). Subgroup analysis of patients with lymph node diameters of ≥ 1.5 cm revealed a five-year PFS rate of 75.0% and an OS rate of 80.0% in the surgical staging group, compared to 41.5% and 50.1% in the imaging staging group, respectively, showing statistically significant differences ($p = 0.022$, HR:0.34 [0.13, 0.90] and $p = 0.038$, HR: 0.34 [0.12,0.94], respectively for PFS and OS). Additionally, in patients with two or more metastatic lymph nodes, the five-year PFS and OS rates were 69.2% and 73.1% in the surgical staging group, versus 41.0% and 48.4% in the imaging staging group, with these differences also being statistically significant ($p = 0.025$, HR: 0.41[0.19,0.93] and $p = 0.046$, HR: 0.42[0.18,0.98], respectively).

Conclusion Performing surgical staging before CCRT is safe and delivers accurate lymph node details crucial for tailoring radiotherapy. This approach merits further investigation, particularly in women with pelvic lymph nodes measuring 1.5 cm or more in diameter or patients with two or more imaging-positive PLNs.

Keywords Surgical staging, Locally advanced cervical cancer, Positive pelvic lymph node

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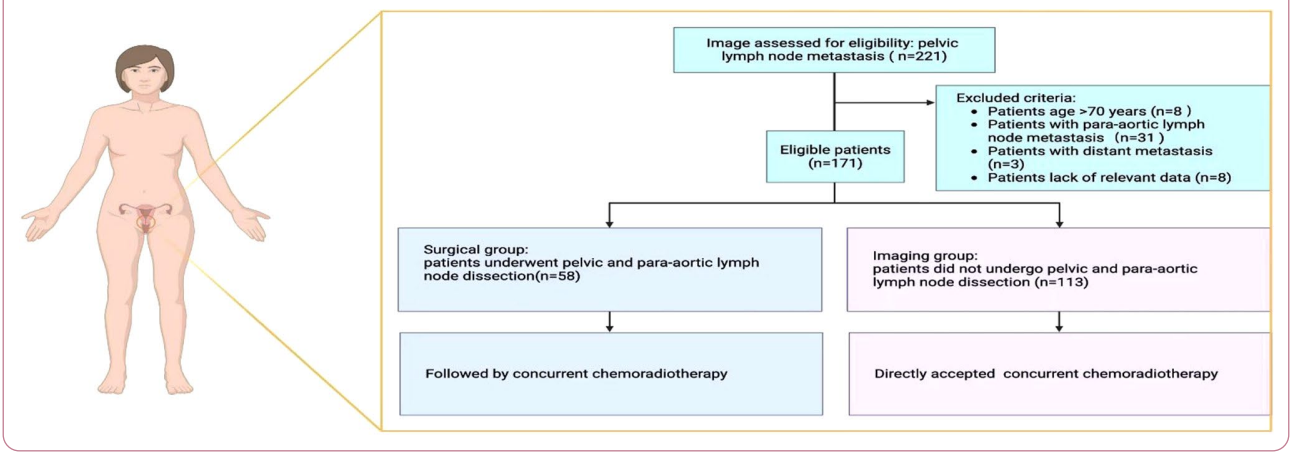
Graphical Abstract



Introduction

Lymph node metastasis stands as an independent prognostic risk factor in cervical cancer and has been classified as a distinct substage, Stage IIIC, according to the revised 2018 FIGO staging system [1]. For patients with para-aortic lymph node (PALN) metastasis, where recurrence is common, and prognosis is poor, extended-field radiotherapy is advised [2, 3]. The likelihood of PALN metastasis increases with the stage of the disease, ranging from 2 to 7% in Stage IB, 7.2–25% in Stage II, and 21–37% in Stage III [4–6]. Lymph node status can be assessed through imaging or surgical staging, with computed tomography (CT) and magnetic resonance imaging (MRI) having detection accuracies of about 60% and 80% respectively. Positron emission tomography CT (PET-CT) offers improved detection capabilities but still yields a 10% false-negative rate [7–10]. These inaccuracies can result in either insufficient treatment or overtreatment during imaging-based CCRT.

The National Comprehensive Cancer Network (NCCN) guidelines (2B category) recommend surgical staging of PALN before CCRT to accurately determine lymph node involvement. However, surgical staging is associated with risks such as lymphatic cysts, potential delays in radiotherapy, increased hospitalization costs, and mixed evidence regarding survival benefits [11–13]. Para-aortic lymphadenectomy is generally unnecessary for patients with negative pelvic lymph nodes (PLNs) due to the low risk of PALN metastasis. In contrast, it is more appropriate for those with preoperative positive PLN, as surgical staging can lead to modified treatment plans in over 25% of cases [14, 15].

This study aims to investigate the survival benefits and treatment-related complications of combining para-aortic and pelvic lymphadenectomy in patients with LACC who have pelvic lymph node metastasis.

Materials and methods

Patients

We conducted a retrospective review of medical records from patients with LACC treated at six different inpatient departments of Jiangxi Maternal and Child Health Hospital between January 2014 and December 2018. The selection criteria for the study included: (1) patients under the age of 70; (2) histological subtypes of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; (3) FIGO 2009 stages IB2, IIA2, or IIB-IVA; (4) presence of imaging-positive pelvic lymph nodes; (5) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with normal cardiac function, adequate blood cell counts, and normal liver and kidney function; and (6) availability of complete follow-up data. Patients who had previously received abdominal radiotherapy or had imaging-confirmed para-aortic lymph node or distant metastases were excluded from the study (Fig. 1).

The enrolled patients were divided into two groups: the surgical staging group and the imaging staging group. Those in the surgical staging group underwent para-aortic and pelvic lymphadenectomy prior to the initiation of CCRT. In contrast, patients in the imaging staging group received CCRT based solely on imaging findings. Surgical staging procedures were exclusively conducted in inpatient area A, meaning all patients from the surgical staging group were treated there, while the imaging staging group comprised patients from the other inpatient areas.

CT evaluation

Each patient underwent a CT scan to assess lymph node status. Lymph nodes were classified as imaging-positive if they met the following criteria: a minimum axial diameter of ≥1.0 cm, or a round shape with a diameter between 8 and 10 mm, exhibiting central necrosis or a signal intensity within the node similar to the tumor, as

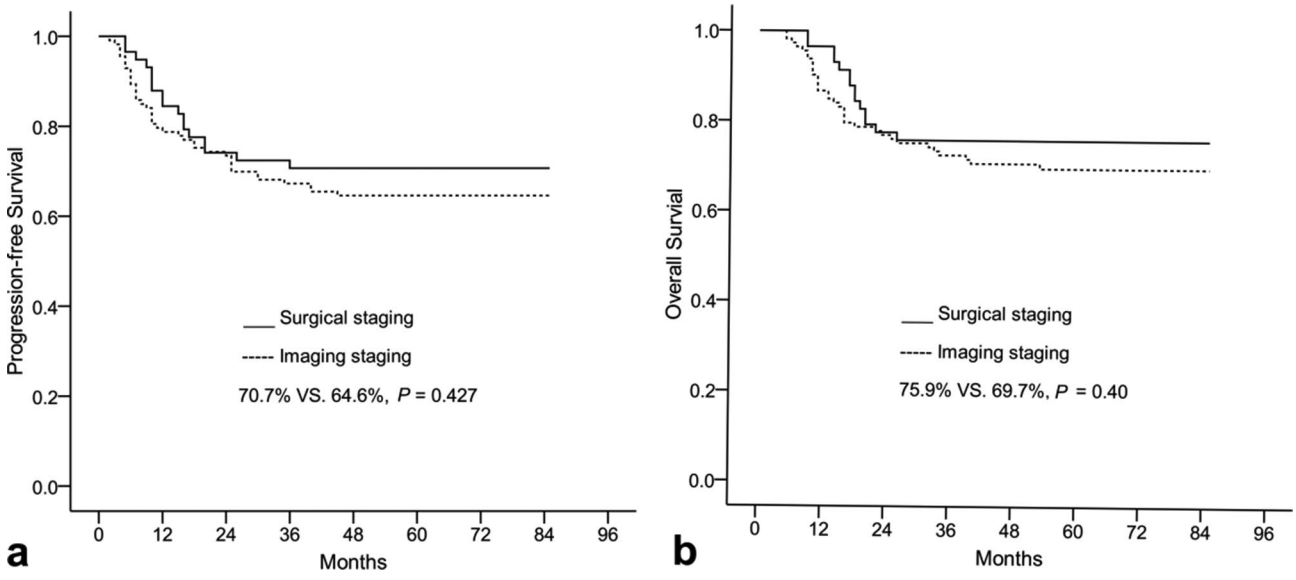


Fig. 1 The five-year progression-free survival (PFS) and overall survival (OS) rates of patients in the surgical staging group ($n=58$) and imaging staging group ($n=113$)

well as evidence of tumor extension beyond the nodal capsule [7].

Para-aortic plus pelvic lymphadenectomy

Surgical staging was performed using laparoscopy to dissect pelvic and para-aortic lymph nodes, and adnexectomy was also conducted in this group. The dissection extended caudally from the intersection of the deep circumflex iliac vein and the external iliac artery to cranially include the inferior mesenteric artery. If the para-aortic lymph nodes at the level of the inferior mesenteric artery appeared enlarged or tested positive—characterized by the nodes merging together, appearing gray-white, or feeling hard—the dissection extended up to the level of the left renal vein. The excised lymphatic tissues were submitted for hematoxylin-eosin staining, with samples cataloged based on their anatomical location.

Concurrent chemoradiotherapy

All patients underwent radical concurrent chemoradiotherapy combined with brachytherapy. Pelvic external beam radiotherapy was delivered using intensity-modulated radiation therapy (IMRT) to a total dose of 45–50.4 Gy. Additionally, high-dose brachytherapy ranging from 30 to 40 Gy was administered to the primary cervical tumors in fractions of 5–7 Gy. The total dose at point A was 80 Gy for small-volume cervical tumors and ≥85 Gy for large-volume tumors.

Concurrent chemotherapy was administered weekly during external beam radiation therapy (EBRT). This included intravenous liposome paclitaxel (60 mg/m^2) or docetaxel (25 mg/m^2) in combination with carboplatin [area under the curve (AUC)=2.0] or nedaplatin (30 mg/m^2).

Follow-up

The decision to keep a patient under surveillance depended on both the patient's risk of recurrence and their personal preferences. The basic guidelines included taking the patient's medical history, performing physical examinations, and conducting additional auxiliary tests every 3–6 months during the first two years, every 6–12 months over the subsequent three years, and annually after that. Patients with high-risk diseases were monitored more frequently. Instances of local recurrence or distant metastasis were documented based on follow-up imaging or pathological evaluations. Late treatment-related adverse events were assessed according to the criteria established by the Radiation Therapy Oncology Group (RTOG) [16].

Statistical analysis

Frequency distributions for the groups were analyzed using either the $\chi 2$ test or Fisher's exact test, as appropriate. OS and PFS were estimated using the Kaplan–Meier method. The log-rank test was employed to compare survival curves between groups. Both univariate and multivariate analyses were conducted using the Cox proportional hazards regression model. P-value<0.05 was considered statistically significant.

Results

Patient characteristics

A total of 171 eligible patients were included in this study: 58 in the surgical staging group and 113 in the

Table 1 Patients characteristics

Characteristics/groups	Imaging Staging (*n* = 113)	Surgical Staging (*n* = 58)	*p* value
Age(years)	49.61 ± 7.74	48.15 ± 8.58	0.178
ECOG status			
0	96	50	
1	15	7	0.975
2	2	1	
Histological subtypes			
SCC	104	53	0.882
ADC/ASC	9	5	
Tumor size			
< 4 cm	23	7	
4–4.9 cm	30	13	
5–5.9 cm	27	17	0.425
≥ 6 cm	33	21	
Pelvic wall involved			
Yes	63	28	0.354
No	50	30	
LN-diameter			
1.0–1.49 cm	72	38	0.816
≥ 1.5 cm	41	20	
No. of positive LN			
1	74	32	0.188
≥ 2	39	26	
Adjuvant chemotherapy			
yes	67	37	0.568
No	46	21	

Abbreviation: ADC: adenocarcinoma; ASC: adenosquamous carcinoma; SCC: squamous cell carcinoma; LN: lymph node

imaging staging group. The median age at diagnosis was 49 years (range: 31–69 years). The characteristics of the two patient groups are presented in Table 1.

For the surgical staging group, the average operation time was 120 min (range, 90–180 min), and the average blood loss was 50 ml (range, 20–100 ml). Radiotherapy began 10.2 days (range, 9–12 days) later for this group compared to the imaging staging group. The incidence of lymphatic cysts was 9.30%, and one patient experienced bowel obstruction post-operatively. Among the surgical staging group, 34.48% (20 out of 58 patients) had para-aortic lymph node metastasis, while 12.07% (7 out of 58) had pathology-negative pelvic lymph nodes.

Treatment outcomes and survival

The median follow-up period was 52 months (range, 5–85 months). During this time, 48 patients passed away: 14 from the surgical staging group and 34 from the imaging staging group. The five-year PFS rates were 70.7% for the surgical staging group and 64.6% for the imaging staging group, a difference that was not statistically significant ($p = 0.427$, HR: 0.80 [0.45, 1.41]). Similarly, the five-year OS rates were 75.9% for the surgical staging group and 69.7% for the imaging staging group, with no statistically significant difference ($p = 0.40$, HR: 0.77 [0.41, 1.43]).

A subgroup analysis was conducted on patients whose tumors extended to the pelvic wall or who had multiple LN metastases. For patients with LN-diameter ≥ 1.5 cm or greater, the five-year PFS and OS rates in the surgical staging group were 75.0% and 80.0%, respectively, compared to 41.5% and 50.1% in the imaging staging group. These differences were statistically significant ($p = 0.022$, HR: 0.34 [0.13, 0.90] for PFS and $p = 0.038$, HR: 0.34 [0.12, 0.94] for OS) (Fig. 2). Additionally, for patients with two or more metastatic LNs, the five-year PFS and OS rates were 69.2% and 73.1% in the surgical staging

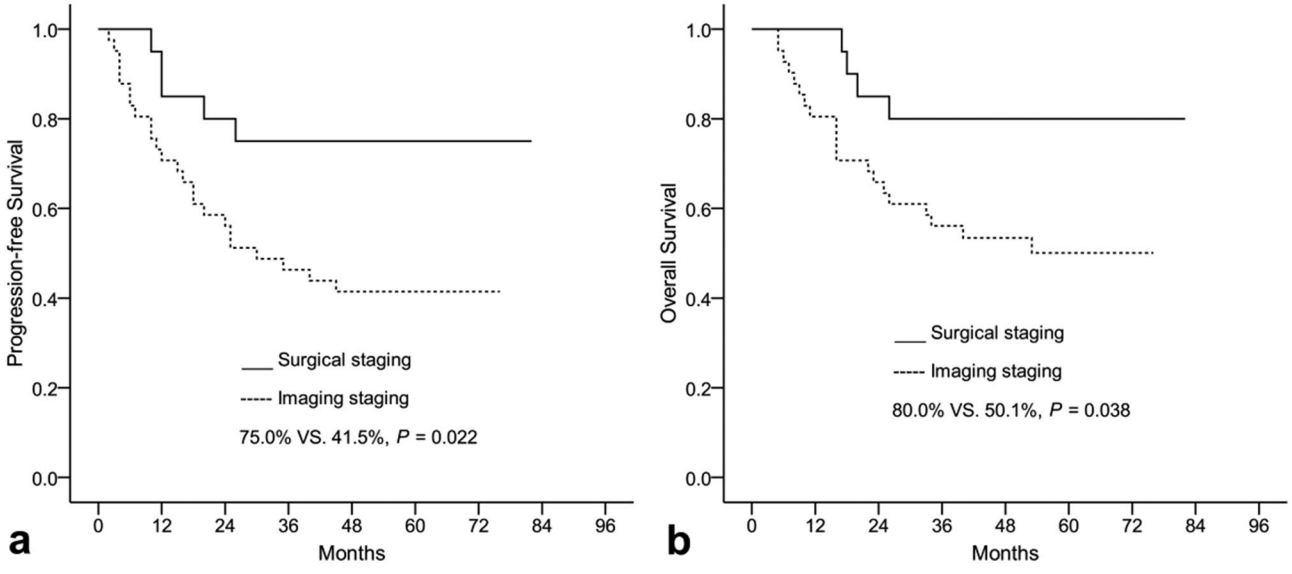


Fig. 2 The five-year PFS and OS rates of patients with LN-diameter ≥ 1.5 cm in the surgical staging group (*n* = 20) and imaging staging group (*n* = 41)

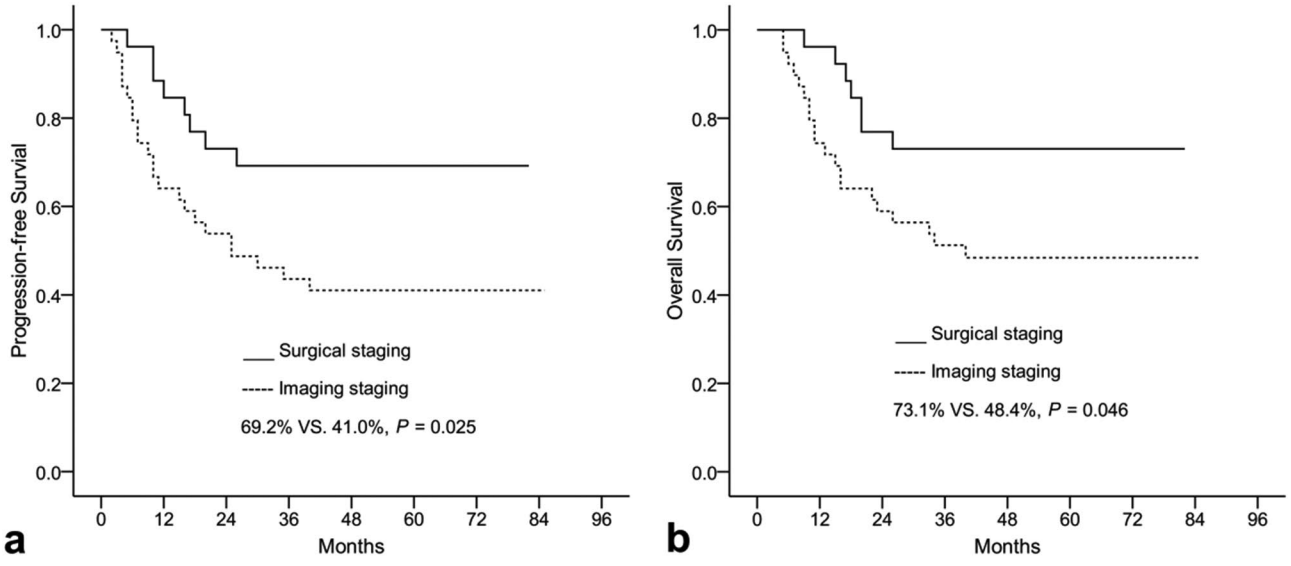


Fig. 3 The five-year PFS and OS rates of patients with two or more metastatic LNs in the surgical staging group ($n=26$) and imaging staging group ($n=39$)

Table 2 Benefit of surgical staging by subgroups according to risk factors

Risk factors /groups	No.	5-year PFS				5-year OS			
		Imaging	Surgical	*p*-value	HR (95%CI)	Imaging	Surgical	*p*-value	HR (95%CI)
Pelvic-wall involved									
yes	91	57.1%	67.9%	0.34	0.69 (0.33,1.48)	64.5%	75.0%	0.33	0.66(0.28,1.54)
No	80	74.0%	73.3%	0.97	1.02 (0.42,2.46)	76.0%	76.7%	0.94	0.96(0.38,2.45)
Histological subtypes									
SCC	157	64.4%	69.8%	0.50	0.82(0.46,1.47)	69.9%	75.5%	0.47	0.79(0.41,1.51)
ADC/ASC	14	66.7%	80.0%	0.65	0.59(0.06,5.71)	66.7%	80.0%	0.65	0.59(0.06,5.71)
Diameter of LN									
1–1.49 cm	110	77.8%	68.4%	0.31	1.46(0.69,3.09)	80.6%	73.7%	0.45	1.36(0.61,3.07)
≥ 1.5 cm	61	41.5%	75.0%	0.022	0.34(0.13, 0.90)	50.1%	80.0%	0.038	0.34(0.12,0.94)
No. of metastatic LN									
1	106	77.0%	71.9%	0.53	1.29(0.58,2.9)	80.8%	78.1%	0.71	1.19(0.48,2.94)
≥ 2	65	41.0%	69.2%	0.025	0.41(0.19,0.93)	48.4%	73.1%	0.046	0.42(0.18,0.98)

Abbreviation: ADC: adenocarcinoma; ASC: adenosquamous carcinoma; SCC: squamous cell carcinoma; LN: lymph node

group, versus 41.0% and 48.4% in the imaging staging group, also showing statistically significant differences ($p=0.025$, HR: 0.41 [0.19, 0.93] for PFS and $p=0.046$, HR: 0.42 [0.18, 0.98] for OS) (Fig. 3). However, patients in the surgical staging group with only one positive LN measuring < 1.5 cm had slightly poorer clinical outcomes compared to those in the imaging staging group. The therapeutic value of surgical staging is detailed in Table 2.

Prognostic factor analysis

Univariate analyses indicated that tumor size, lymph node diameter, and the number of lymph nodes were significantly correlated with five-year PFS and OS rates (all $p<0.05$). Multivariate analysis further identified tumor size ($p=0.001$, HR: 1.65 [1.24, 2.19] for PFS; $p=0.016$, HR: 1.51 [1.12, 2.05] for OS) and the number of metastatic lymph nodes ($p=0.01$, HR: 2.09 [1.17, 3.76] for PFS; $p=0.01$, HR: 2.32 [1.22, 4.40] for OS) as independent predictors of five-year PFS and OS. Table 3 provide detailed results of the univariate and multivariate analyses.

Adverse events

The incidence rates of Grade 3/4 myelosuppression, Grade 3/4 acute gastrointestinal disorders, Grade 3/4 chronic gastrointestinal disorders, and lower limb edema in the surgical staging group were 41.4%, 8.6%, 5.2%, and 10.3%, respectively. In comparison, the imaging group had incidence rates of 35.4% for myelosuppression, 6.2% for both acute and chronic gastrointestinal disorders, and 6.2% for lower limb edema. None of these differences were statistically significant ($p=0.44$, 0.56, 0.79, and 0.20, respectively). Details of treatment-related complications for both groups are presented in Table 4.

Table 3 Univariate and multivariate analyses of factors affecting OS and PFS

Variables	Univariate analyses				Multivariate analyses			
	five-year PFS		five-year OS		five-year PFS		five-year OS	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age	1.04(0.75,1.46)	0.81	1.09(0.76,1.570	0.63	1.01(0.72,1.42)	0.94	1.05(0.72,1.52)	0.81
Tumor size	1.68(1.28, 2.22)	0.000	1.53(1.15,2.05)	0.004	1.65(1.24,2.19)	0.001	1.51(1.12,2.05)	0.007
Histological subtypes	0.94(0.34, 2.59)	0.90	1.15(0.42,3.21)	0.78	0.99(0.35,2.76)	0.98	1.27(0.45,3.56)	0.65
Pelvic wall involved	1.61(0.95,2.77)	0.08	1.40(0.79,2.50)	0.25	1.42(0.82,2.46)	0.21	1.21(0.67,2.19)	0.52
LN-diameter	2.08(1.24,3.50)	0.006	1.96(1.11,3.45)	0.02	1.32(0.74,2.35)	0.35	1.21(0.64,2.28)	0.56
LN-number	2.32(1.38, 3.91)	0.002	2.46(1.39,4.36)	0.002	2.09(1.17,3.76)	0.01	2.32(1.22,4.40)	0.01
Surgical staging	0.80(0.45, 1.41)	0.43	0.77(0.41, 1.43)	0.40	0.61(0.34,1.10)	0.10	0.59(0.31,1.12)	0.11

Table 4 Treatment related complications in surgical staging group and imaging group

toxicities \group	surgical (*n* = 58)	imaging (*n* = 113)	*p*-value
Grade3/4 myelosuppression	24(41.4%)	40(35.4%)	0.44
Grade3/4 acute gastrointestinal disorder	5(8.6%)	7(6.2%)	0.56
Grade3/4 chronicgastrointestinal disorder	3(5.2%)	7(6.2%)	0.79
lower limb edema	6(10.3%)	7(6.2%)	0.33

Discussion

PALN metastasis is a common pattern of treatment failure, and some studies suggest that prophylactic extended-field radiotherapy (EFRT) can help control PALN and distant metastasis[17, 18]. However, the survival benefits of EFRT are debated, and it may be associated with adverse effects [17–20]. Accurate assessment of lymph node status is crucial for effective treatment. Imaging examinations often result in false positives and false negatives. In this study, PALN metastasis was found in 34.48% (20/58) of patients, while 12.07% (7/58) showed pathology-negative PLN despite having imaging-positive PLN and imaging-negative PALN. Consequently, almost half (27/58) of the patients required modifications to their radiation treatment plans. The Uterus-11 trial, a prospective randomized study, reported upstaging (imaging-negative but pathology-positive para-aortic lymph nodes) in 33% (39/120) of patients in the surgical staging group [21]. Thus, detecting metastatic PALN is essential for tailoring chemoradiation plans to each patient.

Studies examining the therapeutic efficacy of surgical staging prior to concurrent chemoradiation therapy (CCRT) have produced conflicting results. Lai CH et al. [22] conducted a prospective randomized controlled trial evaluating 61 patients with LACC who were staged either through imaging or lymphadenectomy. Their findings indicated that the surgical staging group had significantly worse PFS rates compared to the imaging group (HR 3.13, $p=0.005$), leading to early termination of the study. However, this outcome may have been influenced by the fact that the surgical group included more patients with Stage IIIB disease or adenosquamous carcinoma and fewer who received CCRT compared to the imaging group. Conversely, a Spanish multicenter retrospective study involving 922 patients found comparable OS and PFS rates between patients who underwent imaging staging and those who underwent surgical staging [23]. This finding was supported by the Uterus-11 international multicenter study, which randomized 255 patients with LACC into surgical (130 patients) and clinical staging groups (125 patients), followed by primary platinum-based CCRT. After a median follow-up of 90 months (range 1–123 months), no significant differences were observed in PFS ($p=0.084$) and OS ($p=0.071$) rates [24]. In contrast, Dabi Y et al. [25] conducted a retrospective multicenter cohort analysis of 644 patients with LACC, showing that surgical staging was significantly associated with better (DFS) than clinical staging ($p<0.001$). It also emerged as an independent prognostic factor for DFS (OR 0.64, CI 95% 0.46–0.89, $p=0.008$) and OS (OR 0.43, CI 95% 0.27–0.68, $p<0.001$) in multivariate analysis. Additionally, Gold et al. [12] analyzed data from GOG 85, GOG 120, and GOG 165 trials and found that surgical staging enhanced PFS (50% vs. 36%) and OS (54% vs. 40%), particularly for Stage III/IV compared to Stage II. However, these trials did not perform subgroup analyses. Therefore, certain subtypes of LACC might specifically benefit from surgical staging.

In our study, no significant differences were observed in PFS and OS between the surgical and imaging groups ($p>0.05$). However, subgroup analysis revealed that surgical staging improved PFS (50% vs. 36%) and OS (54% vs. 40%) in patients with LN diameters ≥ 1.5 cm and those with two or more metastatic LNs. Consistent with previous findings, both the size and number of LNs are significant prognostic factors for OS and DFS in patients with LACC [26, 27]. Our results align with those of Marnitz S et al. [28], who found that removing tumor-involved LNs provided a survival benefit, with survival rates in patients having more than five resected positive nodes comparable to those with negative nodes. Similarly, a retrospective analysis by Coin et al. [29] demonstrated that excising macroscopically metastatic LNs significantly enhances clinical outcomes.

It is understood that doses exceeding 60 Gy are needed to eradicate metastatic LNs larger than 1 cm, with even higher doses necessary for nodes larger than 1.5 cm. However, such high-dose delivery is challenging due to dose limitations imposed by organs at risk, particularly near para-aortic LNs. Favorable local control can be achieved with much lower doses if the large tumor-involved LN is surgically removed, thereby reducing the likelihood of chronic gastrointestinal dysfunction by minimizing the radiation dose and field.

A common concern with surgical staging is that it can lead to surgical complications and delay the initiation of radiotherapy. During para-aortic lymphadenectomy, particularly when dealing with bulky lymph node dissection, it is crucial to avoid intraoperative vascular injuries, as these can be fatal or affect patient outcomes. A thorough examination of pre-operative imaging is essential to prevent such complications. If bulky LNs are fused with the inferior vena cava or aorta, they may be nearly unresectable, warranting a re-evaluation of the risks or even the decision to forgo surgery. Additionally, using an ultrasonic knife to expose normal tissue before debulking the enlarged LN is a critical step to minimize the risk of severe vascular injury. In our study, all para-aortic and pelvic lymphadenectomy procedures were performed laparoscopically to reduce postoperative complications. The average operation time was 120 min, with an average blood loss of 50 ml. The incidence of lymphatic cysts was 9.30%, and there was one case of bowel obstruction post-surgery, figures that are consistent with previously reported data [30]. Furthermore, we observed no differences between patients who underwent surgical staging and those who did not regard acute and chronic gastrointestinal disorders, which is in line with findings from other studies [23–31].

As our study was retrospective, limitations include a heterogeneous patient population, and the selection bias typically associated with retrospective designs. However, we attempted to mitigate this bias by randomly assigning patients to one of six independent treatment groups within our oncology department. Surgical staging was infrequently employed in five of these groups but was more commonly used in one, leading to a quasi-randomized condition. Additionally, the number of patients with LN diameters ≥ 1.5 cm, or with two or more metastatic LNs, was too small to allow for definitive conclusions. Lastly, we used CT imaging to evaluate LN status rather than PET-CT, which is often the preferred preoperative examination method in many centers. Further investigation is needed to assess the value of surgical staging in this specific patient group.

Conclusion

Performing surgical staging before concurrent chemoradiation therapy proved to be safe and offered precise information about patients' lymph node status, which is crucial for planning radiation therapy. This approach has the potential to enhance survival outcomes, particularly for patients with lymph nodes measuring ≥ 1.5 cm in minimum axial diameter and for those with two or more imaging-positive lymph nodes.

Author contributions

Wei Jiang: writing, editing and revising the article.Meiling-Zhong: editing and revising the articleSu-lan Wang: editing and revising the article.Yan Chen: data analysis.Ya-nan Wang: collecting the data of patients. Si-yuan Zeng: supervising, editing and revising.Mei-rong Liang: supervising, editing and revising.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the ethics committee of Jiangxi Maternal and Child Health Hospital (No.EC-KT-202230). An exemption of requiring written informed consent has been granted by the ethics committee of Jiangxi Maternal and Child Health Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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