Jia *et al. Radiation Oncology* (2025) 20:73
https://doi.org/10.1186/s13014-025-02655-2

Radiation Oncology

RESEARCH Open Access

Risk stratification of node-positive early-stage cervical cancer treated with radical hysterectomy followed by chemoradiotherapy: a retrospective single-center study

Shuang-Zheng Jia[1†], Duan Yang[1†], Xue-Jiao Yang[1], Rui Wang[1], Xi Yang[1], Man-Ni Huang[1*†] and Ju-Sheng An[1*†]

Abstract

Background Limited data exist on the effectiveness of concurrent chemoradiotherapy (CRT) using intensity-modulated radiation therapy (IMRT) after radical surgery in patients with node-positive early-stage cervical cancer. This study aimed to identify prognostic factors and categorize patients into risk groups for personalized adjuvant therapy.

Methods The study included consecutive patients with pathologically confirmed node-positive cervical cancer who underwent radical hysterectomy and lymphadenectomy followed by CRT from January 2013 to October 2024 at our institute. Patients with parametrial invasion or positive resection margins were excluded. All patients received modern volumetric-modulated arc therapy with platinum-based concurrent chemotherapy. Data on clinicopathologic features, treatment details, and oncologic outcomes were collected. Univariate and multivariate Cox regression analyses were conducted to identify factors associated with disease-free survival (DFS) and overall survival (OS). Patients were further stratified into distinct risk categories for recurrence based on identified prognostic factors.

Results A total of 160 patients were included, with a median age of 44 years. The median number of lymph nodes retrieved was 33, and 11 patients presented with para-aortic lymph node metastasis (LNM). Over a median follow-up period of 39.7 months, 31 patients experienced disease progression, and 12 succumbed to the disease, yielding 3-year DFS and OS rates of 81.3% and 93.7%, respectively. Multivariate analysis identified non-squamous histotype (hazard ratio [HR]: 1.526, 95% confidence interval [CI]: 1.044–2.232, $p=0.029$) and LNM ≥ 4 (HR: 1.521, 95% CI: 1.027–2.252, $p=0.036$) as independent predictors of poorer DFS. Utilizing these prognostic factors for DFS, a risk stratification

†Shuang-Zheng Jia, Duan Yang, Man-Ni Huang and Ju-Sheng An contributed equally to this work.

*Correspondence:
Man-Ni Huang
huangmanni@csco.ac.cn
Ju-Sheng An
anmanman_0@126.com

Full list of author information is available at the end of the article

system was developed, categorizing patients into low-risk (no risk factors, $n=108$) and high-intermediate risk (one or two risk factors, $n=52$) groups. The high-intermediate-risk group exhibited significantly inferior DFS and OS compared to the low-risk group (3-year DFS: 67.4% versus 87.3%, HR: 1.697, 95% CI: 1.192–2.417, $p=0.002$; 3-year OS: 82.5% versus 98.8%, HR: 3.577, 95% CI: 1.668–7.667, $p<0.001$, respectively).

Conclusions Node-positive early-stage cervical cancer exhibits heterogeneous outcomes following radical hysterectomy and postoperative CRT. In patients with non-SCC histotype or ≥ 4 LNM, consolidation chemotherapy does not confer an additional survival benefit, indicating a need for innovative therapeutic strategies.

Keywords Cervical cancer, Radical hysterectomy, Lymph node metastasis, Chemoradiotherapy, Risk stratification

Background

Cervical cancer remains a significant global health challenge, with approximately 604,127 new cases and 341,831 deaths reported in 2020 [1]. For patients diagnosed with clinically early-stage cervical cancer, radical hysterectomy accompanied by pelvic lymph node dissection, followed by tailored adjuvant therapy, is a common therapeutic approach. However, approximately 25% of these patients are found to have pathologically confirmed lymph node metastasis (LNM) postoperatively [2–5], which represents the most critical adverse prognostic factor for early-stage cervical cancer. Currently, platinum-based concurrent chemoradiotherapy (CRT) remains the standard treatment for node-positive early-stage cervical cancer. Additionally, neoadjuvant chemotherapy followed by radical surgery is a feasible and effective option, particularly in contexts where radiotherapy resources are limited [6, 7]. However, the 5-year survival rate for these patients ranges from 46.8 to 82.5% [8–11], underscoring the necessity for survival risk stratification and the development of more personalized treatment strategies.

Nonetheless, there is a paucity of data regarding the prognosis and optimal management strategies for this particular subgroup. Several studies have demonstrated that certain histopathologic features are independently associated with survival in patients with node-positive cervical cancer following radical surgery. These characteristics include histologic subtype [8, 11–14], the number of metastatic lymph nodes [8, 12–18], parametrial involvement [12, 16], positive surgical margins [19], large tumor size [18, 20], lymphovascular space invasion (LVSI) [13], common iliac and/or para-aortic lymph node metastasis [15, 21], tumor-stroma ratio [18], and the metastatic lymph node ratio (the proportion of positive to total lymph nodes harvested) [11, 14, 19, 22, 23]. However, research is frequently constrained by relatively small sample sizes [16, 19, 21], limited lymph nodes removal (< 20) [19], heterogeneous treatment protocols [8, 12, 14, 15, 18, 19, 23, 24], and the inclusion of other confounding high-risk factors such as parametrial involvement or positive surgical margins [8, 11, 12, 14, 16–19, 21–24]. Besides, emerging evidence suggests that contemporary intensity-modulated radiation therapy (IMRT) is associated with improved survival outcomes and reduced radiation-induced non-hematologic toxicity in cervical cancer [25, 26].

Therefore, this study aims to address this gap by identifying prognostic factors related to survival in patients with node-positive early-stage cervical cancer who have undergone radical surgery followed by adjuvant CRT. Additionally, the study seeks to stratify these patients into distinct risk groups to enable tailored adjuvant therapy. To our knowledge, this case series is the first to focus specifically on node-positive early-stage cervical cancer without other high-risk features, treated with radical surgery followed by adjuvant CRT using volumetric-modulated arc therapy (VMAT).

Materials and methods

Participants

The study cohort was derived from a prospectively maintained database, encompassing patients treated between January 2013 to October 2024 at the Cancer Hospital, Chinese Academy of Medical Sciences. The eligibility criteria were: (1) histological diagnosis of squamous cell carcinoma (SCC), adenocarcinoma (ADC), or adenosquamous carcinoma (ASC) of the uterine cervix; (2) clinical FIGO 2009 stage Ib1-IIa uterine cervical cancer with pathologically confirmed lymph node metastasis after type III radical hysterectomy with pelvic and/or para-aortic lymphadenectomy. Patients with parametrial invasion or positive resection margin were excluded. Patient were also excluded if radical hysterectomy was aborted due to intraoperative identification of gross involvement of the parametria and/or pelvic lymph nodes.

Demographic, clinicopathologic and follow-up data were abstracted from patients' medical records. Histological findings including tumor size, LVSI, depth of cervical stromal invasion, vaginal involvement, number of dissected and positive lymph nodes, and location of metastatic LNs were also reviewed. LNs retrieved during surgery were labeled as parametrial, external iliac, internal iliac, obturator, common iliac and para-aortic for evaluation. Considering that all patients were node-positive, we

utilized the revised 2009 FIGO staging system to determine the stage of each participant [27].

The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences (IRB No. 24/290–4570). Informed consent was waived due to its retrospective nature.

Treatment and follow-up

According to our inclusion criteria, all patients underwent type III radical hysterectomy with pelvic LN dissection. Para-aortic LN sampling or dissection was performed in 70 patients (43.8%), and ovarian preservation was carried out in 65 patients (40.6%).

All patients received CRT after surgery. The median interval between surgery and the initiation of CRT was 41 days, ranging from 21 to 134 days. Postoperative external beam radiotherapy was delivered with 6-MV X-rays via VMAT. The clinical target volume comprised of regional lymph node regions (obturator, internal, external, presacral and common iliac nodal regions) and the upper vagina according to the RTOG guidelines. The median prescribed dose was 45 Gy, ranging from 45.0 to 50.0 Gy in 25 fractions to 50.4–56 Gy in 28 fractions (1.8–2.0 Gy daily, 5 fractions weekly). Twenty-one patients (13.1%) underwent para-aortic nodal irradiation due to positive paraaortic/common iliac node or more than three pelvic LN metastases. High-dose-rate intravaginal brachytherapy was given to 58 patients (36.3%) with close (≤ 5 mm) vaginal resection margin, with a total dose of 10–16 Gy following EBRT. Most of all patients (93.8%) received weekly platinum-based concurrent chemotherapy, and ten patients (6.3%) received doublet paclitaxel and cisplatin.

Fifty-five patients (34.4%) received paclitaxel/platinum-based doublet neoadjuvant chemotherapy for 1–3 circles before surgery, and 54 patients (33.8%) received 1 to 4 cycles of postoperative platinum-based doublet consolidation chemotherapy. These treatment decisions were made at the discretion of the responsible physician or patient preference.

After completion of treatments, patients were followed up every 3 months during the first 2 years and every 6 months thereafter or as clinically indicated.

Statistical analysis

The primary endpoint was disease-free survival (DFS), which was defined as the duration from surgery to the date of the first documented recurrence or the latest follow-up. Recurrences were analyzed according to the first site of recurrence, and defined as either locoregional (recurrence within the irradiated field) or distant recurrence (recurrence outside the irradiated field). Para-aortic nodal recurrence above the L4-L5 vertebral interspace was also regarded as a distant recurrence [28, 29]. We defined OS as the interval between surgery and death from any cause. Survival analysis was estimated using the Kaplan–Meier method and between-group comparisons were made using the log-rank tests. All variables with a p-value < 0.10 in univariate analysis were included in multivariate Cox regression analysis to determine independent prognostic factors for DFS and OS. Patients were further stratified into low-, intermediate- and high-risk groups for recurrence based on identified prognostic factor. DFS and OS of different risk groups were compared using log-rank test. Mann–Whitney U-test and the chi-square test were used when appropriate. A two-sided p-value of less than 0.05 was considered statistically significant. All statistical analysis was performed using SPSS software (version 26.0; Chicago, IL, USA).

Results

Patient characteristics

During the study period, 160 patients met our inclusion criteria for further analysis. The characteristics of these enrolled patients are shown in Table 1. The median age of the study population was 44 years (range, 24–73 years), and most patients were treated with abdominal radical hysterectomy (76.3%). The majority of patients had squamous cell histotype (n = 128, 80.0%), LVSI (n = 117, 73.1%), tumor size 2–4 cm (n = 84, 52.5%), and poorly differentiated (n = 89, 55.6%). Only one-eighth of the tumors invaded the inner layer of the cervix (n = 19, 11.9%), and vaginal involvement was found in 46 patients (28.8%). The majority of patients were classified as stage IB2 (n = 93, 58.2%) according to the FIGO 2009 staging system, followed by stages IIA1 (n = 27, 16.9%), IB1 (n = 22, 13.8%), and IIA2 (n = 18, 11.3%) Tables 2 and 3.

The median numbers of lymph nodes retrieved were 33 (range, 10–98), and the median number of metastatic LNs was 2 (range, 1–56). The most commonly involved LNs were the obturator LNs (n = 86, 53.8%), followed by the external iliac (n = 66, 41.2%), internal iliac (n = 39, 24.4%), parametrial (n = 27, 16.9%), common iliac (n = 17, 10.6%), para-aortic (n = 11, 6.9%) and presacral (n = 3, 1.9%) LNs. Patients with bilateral pelvic LNM accounted for 33.8% (n = 54) of all patients, and 26 patients (16.3%) had at least four positive LNs.

Survival analysis and prognostic analysis

After a median follow-up of 39.7 months (range, 3–110 months), 31 (19.4%) patients experienced recurrences, and 12 (7.5%) died. The 3-year DFS and OS were 81.3% and 93.7%, respectively. Distant metastasis alone, both distant and locoregional, and locoregional recurrence alone occurred in 19 (11.9%), 7 (4.4%), and 5 (3.1%) patients, respectively. Univariate analyses revealed that non-squamous histologic types and number of LNM ≥ 4

Table 1 Baseline characteristics of patients with node-positive early-stage cervical cancer

Characteristics	Values
Age (years)	44 (24–73)
≤44	83 (51.9%)
>44	77 (48.1%)
Body mass index (Kg/m^2)	23.0 (16.4–31.6)
≤23.0	80 (50.0%)
> 23.0	80 (50.0%)
Operation approach	
Open	122 (76.3%)
Laparoscopy	38 (23.8%)
Neoadjuvant chemotherapy	
No	105 (65.6%)
Yes	55 (34.4%)
Ovarian preservation	
No	95 (59.4%)
Yes	65 (40.6%)
Para-aortic lymph node resection	
No	90 (56.3%)
Yes	70 (43.8%)
Histology	
Squamous	128 (80.0%)
Non-squamous	32 (20.0%)
Tumor differentiation	
Well to moderate	71 (44.4%)
Poorly	89 (55.6%)
Stage (FIGO 2009)	
1B1	22 (13.8%)
1B2	93 (58.2%)
2A1	27 (16.9%)
2A2	18 (11.3%)
Tumor size (cm)	
≤2	20 (12.5%)
2–4	84 (52.5%)
>4	56 (35.0%)
Depth of invasion	
Inner layer	19 (11.9%)
Middle layer	60 (37.5%)
Outer layer	81 (50.6%)
Vaginal invasion	
Negative	114 (71.3%)
Positive	46 (28.8%)
Lymphovascular space invasion	
Negative	43 (26.9%)
Positive	117 (73.1%)
No. of lymph node resection	33 (10–98)
≤33	84 (52.5%)
≥34	76 (47.5%)
Number of LNM	2 (1–56)
≤3	134 (83.8%)
≥4	26 (16.3%)
Common iliac or para-aortic LNM	
Negative	143 (89.4%)
Positive	17 (10.6%)
Brachytherapy	
No	102 (63.8%)
Yes	58 (36.3%)
Consolidated chemotherapy	
No	106 (66.3%)
Yes	54 (33.8%)
Patterns of recurrence	
No evidence of disease	129 (80.6%)
Locoregional	5 (3.1%)
Distant and locoregional	7 (4.4%)
Distant	19 (11.9%)

LNM lymph node metastasis

were associated with impaired DFS in resectable node-positive cervical cancer patients. On multivariate analysis using forward Cox proportional hazards regression, non-squamous histotype (HR: 1.526, 95% CI: 1.044–2.232, $p = 0.029$) and number of LNM ≥ 4 (HR: 1.521, 95% CI: 1.027–2.252, $p = 0.036$) were independently associated with poor DFS (Fig. 1a and b).

Concerning recurrence patterns, among the 12 patients experiencing locoregional or both locoregional and distant recurrence, the majority ($n = 7$, 58.3%) exhibited multiple locations, followed by solitary vaginal vault ($n = 3$, 25.0%) and pelvic sidewall ($n = 2$, 16.7%) relapses. In contrast, among the 26 patients with distant or both locoregional and distant recurrence, 11 (42.3%) had multiple locations, followed by solitary lung ($n = 10$, 38.5%), para-aortic lymph node ($n = 3$, 11.5%), supraclavicular lymph node ($n = 1$, 3.8%), and liver ($n = 1$, 3.8%) involvement.

With respect to OS, univariate analyses revealed that there was a significant association between histology type, tumor differentiation, number of LNM ≥ 4, and bilateral pelvic LNM and OS outcomes. On multivariate analyses, non-squamous histotype (HR: 5.625, 95% CI: 1.750 -18.081, $p = 0.004$), poor tumor differentiation (HR: 5.017, 95% CI: 1.070 -23.522, $p = 0.041$), and number of LNM ≥ 4 (HR: 5.158, 95% CI: 1.530 -17.383, $p = 0.008$) were independently risk factors for decreased OS (Fig. 1c and e). The primary causes of mortality were identified as multiple organ dysfunction ($n = 7$) and bowel obstruction ($n = 5$).

Risk stratification

Using the identified prognostic factors for DFS, we generated a risk stratification for these patients. Patients with zero ($n = 108$), one ($n = 46$) or two ($n = 6$) risk factors were categorized as the low-risk ($n = 108$), high-intermediate-risk ($n = 52$) group, respectively. The DFS and OS in the high-intermediate-risk group were significantly worse compared to their low-risk group counterpart (3-year DFS: 67.4% versus 87.3%, HR: 1.697, 95% CI: 1.192–2.417,

Table 2 Factors associated with DFS in patients with node-positive early-stage cervical cancer

Characteristics	*n*	Univariable		Multivariable	
		HR, 95% CI	*p*-value	HR, 95% CI	*p*-value
Age (years)			0.963		
≤44	83	1			
> 44	77	0.983 (0.485–1.993)			
Body mass index (Kg/m^2)			0.054		0.119
≤23.0	80	1			
> 23.0	80	0.700 (0.484–1.013)			
Operation approach			0.433		
Open	122	1			
Laparoscopy	38	1.351 (0.634–2.879)			
Neoadjuvant chemotherapy			0.127		
No	105	1			
Yes	55	1.732 (0.849–3.534)			
Ovarian preservation			0.438		
No	95	1			
Yes	65	0.748 (0.358–1.563)			
Histology			0.014		0.029
Squamous	128	1		1	
Non-squamous	32	1.577 (1.081 -2.300)		1.526 (1.044–2.232)	
Tumor differentiation			0.075		0.052
Well to moderate	71	1			
Poorly	89	1.960 (0.922–4.167)			
Tumor size (cm)			0.461		
≤2	20	1			
2–4	84	0.610 (0.217–1.713)			
>4	56	0.936 (0.333–2.630)			
Depth of invasion			0.211		
Inner layer	19	1			
Middle layer	60	4.466 (0.589–33.856)			
Outer layer	81	5.204 (0.687–39.426)			
Vaginal invasion			0.654		
Negative	114	1			
Positive	46	1.188 (0.559–2.523)			
LVSI			0.834		
Negative	43	1			
Positive	117	1.084 (0.509–2.310)			
No. of LN resection			0.390		
≤33	84	1			
≥ 34	76	1.361 (0.672–2.756)			
No. of positive LN			0.018		0.036
≤3	134	1		1	
≥ 4	26	2.484 (1.140–5.416)		1.521 (1.027–2.252)	
Common iliac or para-aortic LNM			0.144		
Negative	143	1			
Positive	17	1.923 (0.788–4.694)			
Bilateral pelvic LNM			0.112		
Unilateral	106	1			
Bilateral	54	1.763 (0.869–3.579)			
Time interval to CRT			0.911		
≤6 weeks	90	1			
> 6 weeks	70	0.960 (0.465–1.983)			
Brachytherapy			0.724		
No	102	1			

Table 2 (continued)

Characteristics	n	Univariable		Multivariable	
		HR, 95% CI	p-value	HR, 95% CI	p-value
Yes	58	0.873 (0.411–1.856)			
Consolidated chemotherapy			0.737		
No	106	1			
Yes	54	1.134 (0.543–2.369)			

No. number, BMI body mass index, LVSI lymphovascular space invasion, LN lymph node, LNM lymph node metastasis

$p = 0.002$; 3-year OS: 82.5% versus 98.8%, HR: 3.577, 95% CI: 1.668–7.667, $p < 0.001$, respectively, Fig. 2a and b). We also conducted a comparative analysis of locoregional and distant DFS between the groups, with the results illustrated in our revised Fig. 2c and d. Our data analysis indicated that patients in the high-intermediate-risk group exhibited significantly poorer locoregional and distant DFS (3-year locoregional DFS: 86.1% compared to 96.8%, HR: 4.922, 95% CI: 1.413–17.15, $p = 0.008$; 3-year distant DFS: 71.8% compared to 88.3%, HR: 2.233, 95% CI: 0.946–5.269, $p = 0.0048$, respectively).

Besides, stratification analysis of our data revealed that consolidated chemotherapy had no influence on outcome in any of the risk groups (Fig. 3a and b).

Side effects

Due to the retrospective nature of our study, we were unable to accurately assess the incidence of digestive side effects. Regarding hematologic side effects, grade 3 or 4 adverse events were observed in 33 out of 160 participants, including leukopenia ($n = 30$), decreased neutrophil count ($n = 7$), anemia ($n = 3$), and thrombocytopenia ($n = 3$). No treatment-related deaths were recorded.

Discussion

The integration of nodal status into the revised 2018 FIGO staging system has significantly enhanced the ability to discriminate among women with clinically early-stage cervical cancer. Nonetheless, varying survival outcomes have been observed within this cohort, underscoring the necessity for further risk stratification. In this study, we recruited a relatively homogeneous cohort of patients diagnosed with FIGO 2009 stage 1B1-2A2 node-positive cervical cancer, who were free from other high-risk factors and underwent radical surgery followed by adjuvant CRT. Our findings indicate that a non-squamous histotype and the presence of four or more LNM are independently associated with decreased survival in these patients. Furthermore, we developed a straightforward scoring system based on these two factors to identify patients at ultra-high risk with poor prognoses. To our knowledge, this study is among the first to specifically focus on node-positive early-stage cervical cancer patients without additional high-risk characteristics, treated with radical surgery and adjuvant CRT utilizing modern VMAT technology.

Emerging evidence from diverse solid malignancies, including breast, gastric, and rectal cancers, highlights that the burden of nodal disease, rather than nodal status alone, profoundly influences patient outcomes. As in cervical cancer, several studies have demonstrated the prognostic value of the number of LNM (nLNM), albeit with varying cut-off values ranging from 2 to 5 across different studies [12–16, 23, 30]. An increase in the number of positive lymph nodes is associated with reduced survival rates [12, 15]. Recent analyses of the Chinese Cervical Cancer Clinical Research Database, which included 3,135 patients with FIGO 2018 stage IIICp cervical cancer, demonstrated that patients with four or more metastatic lymph nodes ($nMLN \geq 4$) had significantly poorer survival outcomes compared to those with three or fewer (OS: 76.8% vs. 67.9%, $p = 0.003$; DFS: 65.5% vs. 55.3%, $p < 0.001$) after propensity score matching [14]. A similar observation was reported by Olthof et al., where patients with four or more positive lymph nodes exhibited significantly reduced 5-year overall survival (58% vs. 79%, $p < 0.001$) [23]. In our study, the 3-year DFS and OS of patients with more than three LNM were significantly lower than those of patients with one to three LNM (64.0% vs. 84.7%, $p = 0.018$; 78.2% vs. 95.4%, $p < 0.001$, respectively). Furthermore, nearly all our patients with four or more LNM (88.5%, $n = 23/26$) exhibited bilateral node involvement, and over half of these patients (57.7%, $n = 15/26$) had common iliac or para-aortic LNM, indicating that higher LNM burden is a surrogate for systemic disease with microscopic tumor spread. These findings suggest that more intensive care is required for these ultra-high-risk patients, and the burden of lymph node involvement should be considered in future staging systems, as is done with other solid tumors.

In alignment with prior research, our findings indicate that non-SCC histology is independently correlated with reduced survival rates in patients with surgically treated node-positive cervical cancer. Specifically, patients with AC/ASC demonstrated a 1.186- to 4.11-fold increase in progression risk [8, 11, 13, 24, 31]. Furthermore, analyses utilizing the KROG 15 – 04 multicenter cohort and the SEER database revealed that patients with non-SCC histology experienced significantly poorer

Table 3 Factors associated with OS in patients with node-positive early-stage cervical cancer

Characteristics	*n*	Univariable		Multivariable	
		HR, 95% CI	*p*-value	HR, 95% CI	*p*-value
Age (years)			0.841		
≤44	83	1			
> 44	77	1.124 (0.359–3.521)			
BMI (Kg/m^2)			0.455		
≤23.0	80	1			
> 23.0	80	0.646 (0.204–2.050)			
Operation approach			0.953		
Open	122	1			
Laparoscopy	38	0.961 (0.258–3.583)			
Neoadjuvant chemotherapy			0.828		
No	105	1			
Yes	55	0.876 (0.265–2.895)			
Ovarian preservation			0.210		
No	95	1			
Yes	65	0.442 (0.119–1.639)			
Histology			< 0.001		0.004
Squamous	128	1		1	
Non-squamous	32	2.467 (1.389–4.380)		5.625 (1.750 -18.081)	
Tumor differentiation			0.041		0.041
Well to moderate	71	1		1	
Poorly	89	4.327 (0.939–19.925)		5.017 (1.070 -23.522)	
Tumor size (cm)			0.879		
≤2	20	1			
2–4	84	1.154 (0.138–9.664)			
>4	56	1.508 (0.173–13.115)			
Depth of invasion			0.102		
Inner layer	19	1			
Middle layer	60	16170.510			
Outer layer	81	44740.536			
Vaginal invasion			0.375		
Negative	114	1			
Positive	46	1.672 (0.530–5.279)			
LVSI			0.246		
Negative	43	1			
Positive	117	2.394 (0.523–10.955)			
No. of LN resection			0.086		0.382
≤33	84	1			
≥34	76	2.751 (0.826–9.167)			
No. of positive LN					0.008
≤3	134	1	< 0.001	1	
≥4	26	2.600 (1.435–4.710)		5.158 (1.53017.383)	
Common iliac or para-aortic LNM			0.463		
Negative	143	1			
Positive	17	1.762 (0.380–8.161)			
Bilateral pelvic LNM			0.040		0.752
Unilateral	106	1			
Bilateral	54	3.159 (0.991–10.065)			
Time interval to CRT			0.789		
≤6 weeks	90	1			
> 6 weeks	70	0.847 (0.252–2.844)			
Brachytherapy			0.960		
No		1			

Table 3 (continued)

Characteristics	*n*	Univariable		Multivariable	
		HR, 95% CI	*p*-value	HR, 95% CI	*p*-value
Yes	58	0.970 (0.292–3.225)			
Consolidated CT			0.249		
No	106	1			
Yes	54	1.924 (0.619–5.976)			

No. number, BMI body mass index, LVSI lymphovascular space invasion, LN lymph node, LNM lymph node metastasis

distant metastasis-free survival and DFS [13], as well as decreased OS and cancer-specific survival [31], in comparison to those with SCC histology among surgically treated node-positive cervical cancer patients. Notably, of the 10 patients with AC/ASC who experienced recurrence, 5 (50.0%) had locoregional recurrence or a combination of locoregional and distant recurrence, a rate that appears to be higher than that observed in SCC (33.3%, $n=7/21$), suggesting a potential resistance to radiotherapy in AC/ASC cases. Additionally, some researchers have raised concerns regarding the use of paclitaxel as a radiosensitizer, as opposed to cisplatin, for patients with AC/ASC [32]. In the study conducted by Huang et al. [33], patients with locally advanced AC/ASC who received paclitaxel-based concurrent CRT exhibited a significantly higher 5-year relapse-free survival rate compared to those treated with cisplatin-based regimens (53.8% vs. 41.7%). Therefore, additional research is necessary to determine the optimal radiotherapy dosage and to identify a more suitable radiosensitizer for patients with AC/ASC undergoing CRT.

It is noteworthy that several prognostic factors previously identified for early cervical cancers, such as LVSI, bulky tumor size, and deep cervical stromal invasion, did not exhibit a significant impact on survival outcomes in our study. These factors have predominantly been derived from surgical series designed to establish criteria for adjuvant treatment [34]. As a result, suitable prognostic indicators for early cervical cancers with high-risk features remain elusive when standard treatments, including radical surgery and postoperative CRT, are employed [13]. Our findings indicate that the prognostic factors influencing survival in this specific context may differ from those identified in surgical series and warrant distinct definition.

Based on the prognostic factors for DFS, we developed a simple risk model for patients with node-positive early-stage cervical cancer treated with CRT after radical surgery, dividing them into low-risk (67.5%) and high-intermediate risk (32.5%) groups. The low-risk group demonstrated favorable 3-year DFS and OS rates of 87.3% and 98.8%, in contrast to the 5-year OS rate of 66.0% observed with curative CRT from SEER database analysis [35]. This suggests that CRT following surgery is particularly effective for patients of reproductive age with SCC and ≤ 3 LNM, as it aids in preserving gonadal function and reduces the risk of vaginal fibrosis and shortening. In contrast, the high-intermediate risk group demonstrated inferior outcomes, with 3-year DFS and OS rates of 67.4% and 82.5%, respectively. This group also experienced a significantly elevated risk of locoregional failure and distant metastasis, particularly the latter, with 3-year locoregional and distant DFS rates of 86.1% and 71.8%, respectively. These results suggest that short durations of concurrent chemotherapy in CRT may be inadequate for effectively eradicating potential undetected distant micro-metastases [12]. Consequently, these findings highlight the necessity for more intensive treatment strategies, such as neoadjuvant or consolidation therapy. Nonetheless, stratification analysis of our data indicated that neither neoadjuvant nor consolidation chemotherapy provided additional benefits. Conversely, a retrospective study conducted by Zhong et al. involving 138 patients with surgically treated node-positive cervical cancer found that three cycles of platinum-based consolidation chemotherapy following surgery and CRT were significantly correlated with improved survival in patients with ≥ 4 LNM or those with ≥ 3 LNM combined with LVSI or outer layer stromal invasion [36]. Besides, the ongoing international EMBRACE II studies are currently exploring the efficacy of limited para-aortic nodal irradiation (up to L2) in patients with ≥ 3 LNM or a single common iliac node [37]. Notably, the global, randomized, phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial demonstrated that the addition of pembrolizumab to CRT significantly improves PFS and OS in patients with FIGO 2018 stage III-IVa, particularly among those with a higher tumor burden [38]. Therefore, there is an urgent need for further investigation into innovative treatment strategies, such as concurrent CRT combined with immunotherapy or consolidation systemic therapy that integrates chemotherapy and immunotherapy in these ultra high-risk subjects.

We are aware that our study has several limitations. Firstly, as this is a retrospective study conducted at a single center, inherent biases are present. Nevertheless, the relative homogeneity of the study population and treatment protocols may mitigate these biases. Despite this, further external validation using cohorts from diverse hospitals or ethnic groups is necessary. Secondly, a small

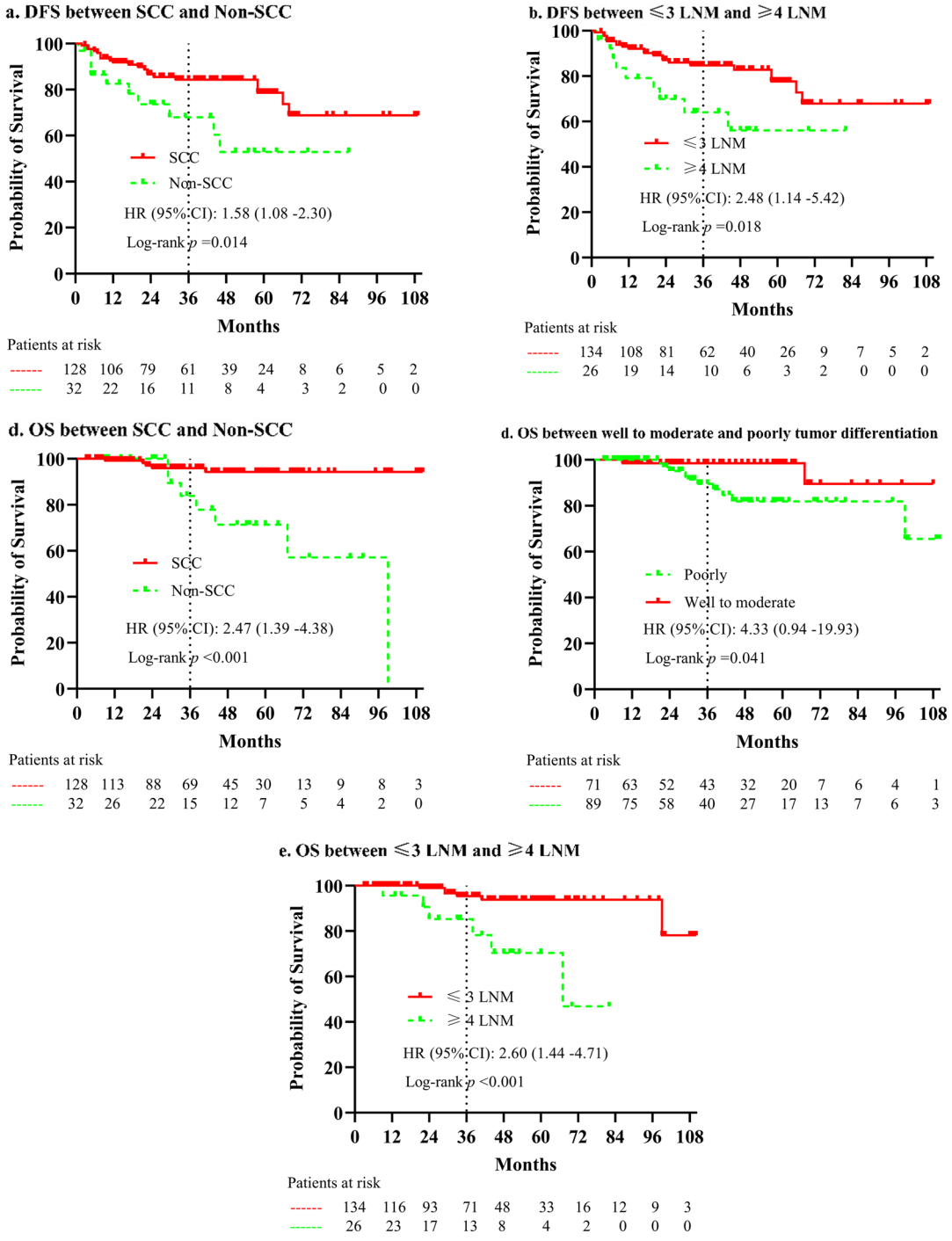

Fig. 1 Kaplan–Meier plots of survival in different subgroups for node-positive early-stage cervical cancer treated with radical hysterectomy followed by chemoradiotherapy

subset of patients in this study received either neoadjuvant or consolidation chemotherapy. While a uniform treatment cohort would have been ideal, we included all these patients to better reflect real-world data for this specific population. Moreover, our analysis revealed that neither neoadjuvant nor consolidation chemotherapy was associated with survival outcomes. Thirdly, the follow-up period has not been sufficient to report on the 5-year survival rate of our patients. Nevertheless, in alignment with previous research, we observed a median recurrence interval of 15 months, with over 80% of patients experiencing recurrences within the first 3 years post-treatment. Fourthly, we did not incorporate LNR into our analysis, as both the total number of resected

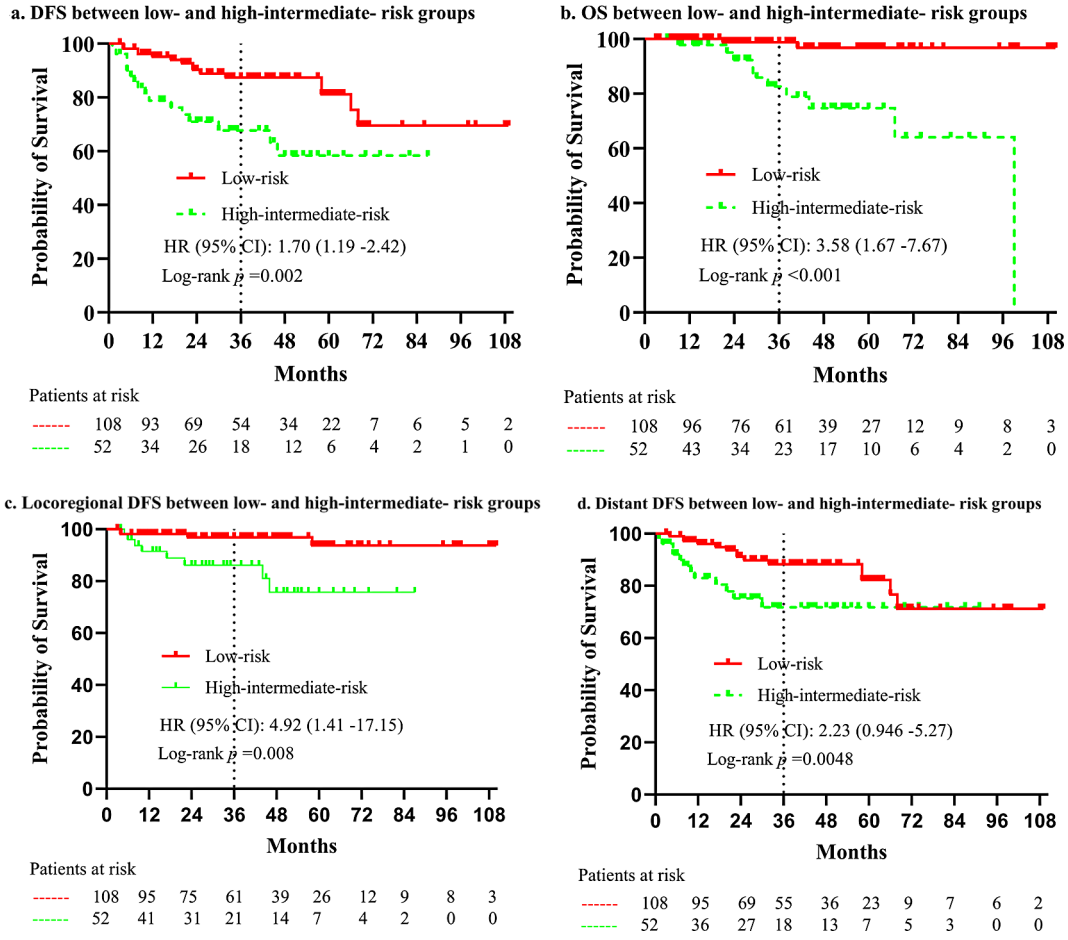

Fig. 2 Kaplan–Meier plots of survival between low- and high-intermediate- risk groups

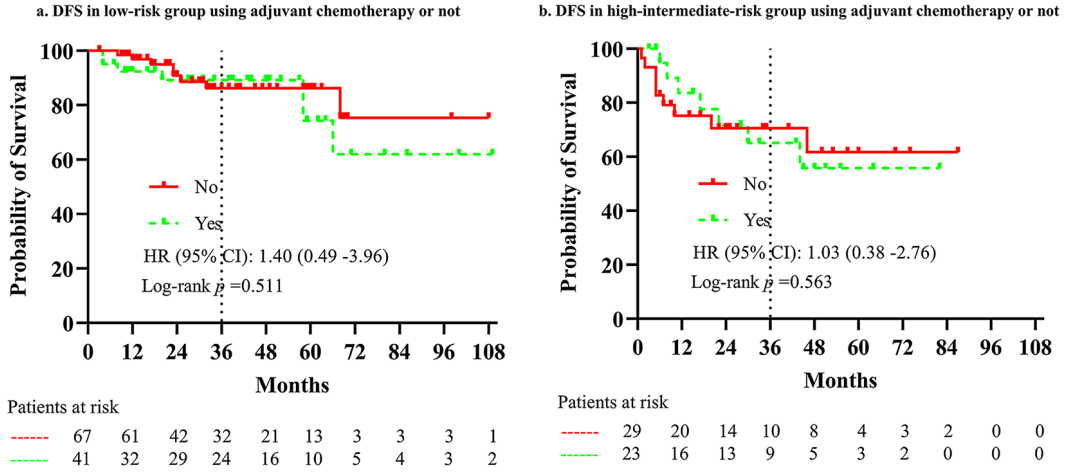

Fig. 3 Kaplan–Meier plots of DFS in different risk groups using adjuvant chemotherapy or not

lymph nodes and the number of metastatic lymph nodes are contingent upon the thoroughness with which pathologists examine the surgical specimens. Although all surgical procedures were conducted by experienced gynecologic oncologists and all pathology specimens were assessed by two cancer pathologists at our institution, which may mitigate potential bias. Finally, the generalizability of our study is constrained. All patients in our study were treated with VMAT at the National Cancer Center of China. This is in contrast to the majority

of cervical cancer cases, which occur in underdeveloped countries or rural areas with limited resources. Nonetheless, similar findings have been reported by Aoki et al., who studied 59 patients treated with a parallel opposing portal technique using 60Co for EBRT. They found that having ≥ 2 LNM was significantly associated with decreased survival in patients undergoing surgery and adjuvant radiotherapy [16]. Nonetheless, to the best of our knowledge, this study is among the first to specifically investigate node-positive early-stage cervical cancer patients without additional high-risk characteristics who were treated with radical surgery and adjuvant CRT utilizing contemporary VMAT technology.

In conclusion, this study introduces a straightforward risk stratification system incorporating non-SCC histotype and ≥ 4 LNM in patients with node-positive early-stage cervical cancer undergoing radical hysterectomy followed by CRT. To our knowledge, this scoring system represents the first predictive model specifically addressing node-positive early-stage cervical cancer, devoid of other high-risk features, treated with radical surgery and subsequent adjuvant CRT using contemporary VMAT technology. Our results emphasize that radical hysterectomy followed by CRT yields favorable survival outcomes for patients with SCC histotype and ≤ 3 LNM. However, for patients with non-SCC histotype or ≥ 4 LNM, there is a need for innovative therapeutic approaches, such as concurrent CRT combined with immunotherapy or consolidation systemic therapy that integrates chemotherapy and immunotherapy.

Abbreviations

CRT	Chemoradiotherapy
IMRT	Intensity-modulated radiation therapy
DFS	Disease-free survival
OS	Overall survival
LNM	Lymph node metastasis
LVSI	Lymphovascular space invasion
VMAT	Volumetric-modulated arc therapy
SCC	Squamous cell carcinoma
ADC	Adenocarcinoma
ASC	Adenosquamous carcinoma
nLNM	Number of lymph node metastasis

Acknowledgements
The authors thank the patients and their families for their acceptance to participate in this study.

Author contributions
Concept and design: SJ, DY, JA, MH. Provision of study materials or patients: MH, JA. Acquisition, analysis or interpretation of data: SJ, DY, RW, XY. Drafting and revision of manuscript: all authors. Supervision: JA.

Funding
This work was supported by grants from CAMS Innovation Fund for Medical Sciences (2023-I2M-C&T-B-079) to Shuang-Zheng Jia.

Data availability
The datasets utilized in the present study can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences (IRB No. 24/290–4570). Informed consent was waived due to its retrospective nature.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gynecologic Oncology, National Cancer Center / National Clinical Research Center for Cancer / Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P. R. China

Received: 1 March 2025 / Accepted: 30 April 2025
Published online: 13 May 2025

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