

Prognostic Factors of Cervical Adenocarcinoma With Positive Pelvic Lymph Node Metastases Without Preoperative Lymph Node Enlargement Treated With Radical Hysterectomy

TOSHIAKI WATANABE, NATSUKI TAMASHIRO, YUKO SHIMOJI, YOSHIHISA ARAKAKI, YUSUKE TAIRA, TOMOKO NAKAMOTO, WATARU KUDAKA and YOICHI AOKI

Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

Abstract. *Background/Aim:* Pelvic lymph node (LN) metastases are found histopathologically after radical hysterectomy (RH) in some cases of cervical adenocarcinoma with no enlarged LNs on preoperatively. The aim was to clarify whether LN metastasis is a prognostic factor in these patients, and whether any postoperative therapy is advisable. *Patients and Methods:* Sixty-one patients with stage I-II cervical adenocarcinoma [International Federation of Obstetrics and Gynecology (FIGO) 2008] with no enlarged pelvic LNs on preoperative imaging evaluation who underwent RH at our institution were retrospectively examined for clinicopathological, treatment, and prognosis-related factors. *Results:* The median age was 47 years. FIGO stages were IB1 in 44 patients, IB2 in 10, IIA in 4, and IIB in 3. Seventeen patients (27.9%) had positive pelvic LNs. The multivariate analysis for both overall (OS) and disease-free (DFS) survival showed only pelvic LN metastasis was an independent prognostic factor. In a multivariate analysis of LN-positive cases, multiple LN metastases was an

independent prognostic factor for poorer DFS. OS rates were 100%, 83.3%, and 30.0%, and DFS rates were 85.5%, 83.3%, and 12.5% for patients with no LN metastasis, single metastasis, and multiple metastases, respectively, showing a significant difference. Eight recurrences were observed in 10 patients with multiple node-positive disease, and six (75%) had an intrapelvic recurrence. *Conclusion:* Among patients who underwent RH for cervical adenocarcinoma with no preoperative enlarged LN and positive pelvic LNs confirmed postoperatively, multiple positive pelvic LNs are an independent poor prognostic factor. Because pelvic recurrence is common, concurrent chemoradiotherapy, possibly using paclitaxel and cisplatin, should be considered as adjuvant therapy.

The proportion of cervical adenocarcinoma in Japan was only a few percent in the 1960s but has gradually been increasing, with adenocarcinoma accounting for 1,791 (22.4%) out of 7983 cervical cancer cases in 2019 (1). Adenocarcinoma has a longer cell cycle than squamous cell carcinoma, a lower percentage of radiosensitive G₂M and G₁ stage cells, and biological characteristics such as a lower oxygen effect ratio in radiotherapy, resulting in resistance to radiotherapy (2). Although there are scattered reports of superior outcomes associated with surgical treatment for cervical adenocarcinoma, there are no randomized controlled trials comparing surgery and radiotherapy, specifically for adenocarcinoma (3-5). Given the radioresistance of adenocarcinoma in stages I-II, radical hysterectomy (RH) is considered reasonable if complete tumor removal is possible. Pelvic lymph node (LN) metastasis is a poor prognostic factor in cervical adenocarcinoma, however, superior radiotherapy results have been reported in LN metastasis-positive cases (4, 5). The National Comprehensive Cancer Network Guidelines broadly categorize indications for

Correspondence to: Yoichi Aoki, Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus 207, Uehara, Nishihara, Okinawa 903-0215, Japan. Tel: +81 988951177, Fax: +81 988951426, e-mail: yoichi@med.u-ryukyu.ac.jp

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radical radiation therapy by the presence or absence of enlarged pelvic LNs, rather than by histological type. Concurrent chemoradiotherapy (CCRT) is recommended for patients with enlarged pelvic LNs (6).

In some cases, pelvic LN metastases are found on histopathological evaluation after RH in patients who had no enlarged pelvic LNs on preoperative imaging evaluation. The aim of this study was to clarify whether LN metastasis is also a prognostic factor in these patients, and whether any postoperative therapy is advisable.

Patients and Methods

From April 2004 to July 2019, 61 patients with stage I-II cervical adenocarcinoma by the 2009 International Federation of Obstetrics and Gynecology classification (7) with no enlarged pelvic LNs on preoperative imaging evaluation who underwent RH at our Institution were retrospectively examined for clinicopathological, treatment, and prognosis-related factors. For preoperative evaluation of pelvic LNs, significant enlargement was defined as a short diameter of 10 mm or more on pelvic magnetic resonance imaging.

For statistical analyses, Kaplan-Meier and log-rank tests were used for determination of overall (OS) and disease-free (DFS) survival, and Cox proportional hazards regression analysis was used for multivariate analysis of prognostic factors.

This retrospective study was conducted according to the principles stated in the 1964 Declaration of Helsinki and subsequent revisions and was approved by the Institutional Review Board of our university in September 2022 (#2000). We used the opt-out method to obtain consent from the patients.

Results

The clinicopathological backgrounds of the 61 eligible patients with cervical adenocarcinoma are shown in Table I. The median age was 47 (range: 28-68) years. International Federation of Obstetrics and Gynecology stages were IB1 in 44 patients, IB2 in 10, IIA in 4, and IIB in 3. Most patients had usual-type endocervical adenocarcinoma (38 cases) or endometrioid carcinoma (12 cases). The median diameter of the cervical tumor was 30 (range=5-62) mm. Two patients (3.2%) had parametrial invasion, 26 patients (42.6%) had lymphovascular space involvement, 28 patients (45.9%) had more than 2/3 depth of cervical stromal invasion, and 17 patients (27.9%) had positive pelvic LNs. The median observation period was 62.8 (7.9-168.1) months.

OS and DFS according to clinicopathological factors are shown in Table II. OS and DFS were significantly poorer in patients with parametrial invasion, lymphovascular invasion, and those with pelvic LN metastasis. Table III shows the multivariate analysis of prognostic factors for OS and DFS; only pelvic LN metastasis was an independent prognostic factor for both of these endpoints.

Additional analysis of the influence of pelvic LN metastasis was performed for the number of metastases,

Table I. Clinicopathological background (N=61).

Variable	Value
Median age (range), years	47 (28-68)
Clinical stage*	
IB1	44 (72.1%)
IB2	10 (16.4%)
IIA	4 (6.6%)
IIB	3 (4.9%)
Histological subtype, n (%)	
Endocervical (usual type)	38 (62.3%)
Endometrioid	12 (19.7%)
Mucinous	2 (3.3%)
Adenosquamous	9 (14.8%)
Median tumor diameter (range) mm	30 (5-62)
Parametrial invasion, n (%)	2 (3.2%)
Lymphovascular space involvement, n (%)	26 (42.6%)
Stromal invasion (>2/3), n (%)	28 (45.9%)
Pelvic lymph node metastasis, n (%)	17 (27.9%)
Median follow-up period (range), months	62.8 (7.9-168.1)

*International Federation of Obstetrics and Gynecology classification (7).

extra-nodal invasion, and the maximum diameter of intra-nodal metastases. Of the 17 patients with positive pelvic LNs, 10 (16.4%) had multiple metastases, 9 (14.8%) had extra-nodal extension, and 8 (13.1%) had intra-nodal metastases greater than 5 mm. In a multivariate analysis of LN-positive cases, the presence of multiple metastases was an independent prognostic factor ($p=0.048$) for poorer DFS (Table IV), although it did not significantly affect OS ($p=0.100$).

Based on these results, we examined prognosis for three groups: Patients with negative pelvic LNs (n=44), single metastasis (n=7), and multiple metastases (n=10). The groups showed no significant differences in age, clinical stage, histology, tumor size, and pelvic LN enlargement. Sixteen out of the 17 patients with positive LNs received postoperative adjuvant therapy (chemotherapy in 15 and radiation therapy in one). OS rates were 100%, 83.3%, and 30.0% ($p<0.001$), and DFS rates were 85.5%, 83.3%, and 12.5% ($p<0.001$) for the three groups, respectively, showing a significant difference (Figure 1 and Figure 2). The only comparison that failed to reach significance was between the LN-negative and single-metastasis groups in DFS ($p=0.390$).

Table V shows the recurrence frequency and site in cases with negative LN s, single LN metastasis, and multiple LN metastases. Six (13.6%) out of 44 node-negative patients and two (28.6%) out of seven single node-positive patients experienced recurrence. However, eight (80.0%) recurrences in 10 multiple node-positive patients were observed, with six (75%) being an intrapelvic recurrence (all six patients received postoperative adjuvant chemotherapy). Regarding treatment after recurrence, five cases were treated with

Table II. Univariate analysis for overall survival (OS) and disease-free survival (DFS) at 5 years.

Variable	Subgroup	n	OS, %	p-Value	DFS, %	p-Value
Age	≥47 Years	31	84.8	0.438	76.8	0.885
	<47 Years	30	89.0		71.9	
Tumor diameter	≥40 mm	49	90.9	0.340	75.9	0.556
	<40 mm	12	73.3		65.6	
Parametrial invasion	No	59	90.3	<0.0001	76.6	0.0120
	Yes	2	0		0	
LVSI	No	35	92.7	0.0467	85.1	0.0123
	Yes	26	79.0		59.0	
Stromal invasion	≤2/3	33	85.6	0.407	78.3	0.459
	>2/3	28	88.3		69.1	
Pelvic LN metastasis	Negative	44	100	<0.0001	85.5	0.0001
	Positive	17	52.9		41.8	

LN: Lymph node; LVSI: lymphovascular space involvement.

Table III. Multivariate analysis for overall survival (OS) and disease-free survival (DFS) at 5 years.

Variable		OS		DFS	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	<47 Years	0.957 (0.214-4.292)	0.955	1.187 (0.392-3.589)	0.762
Tumor diameter	≥40 mm	4.000 (0.086-185.2)	0.479	1.121 (0.218-5.771)	0.892
Parametrial invasion	Yes	6.238 (0.425-91.6)	0.182	2.024 (0.236-17.40)	0.521
LVSI	Yes	1.262 (0.258-3.881)	0.774	1.576 (0.417-5.964)	0.503
Deep stromal invasion	Yes	2.998 (0.0106-10.48)	0.532	1.105 (0.284-4.293)	0.886
Pelvic LN metastasis	Yes	57.99 (1.731-1943.1)	0.0234	4.300 (1.130-16.36)	0.0324

CI: Confidence interval; HR: hazard ratio; LN: lymph node; LVSI: lymphovascular space involvement.

Table IV. Multivariate analysis for overall survival (OS) and disease-free survival (DFS) at 5 years in patients with lymph node (LN) metastasis.

Variable	OS		DFS	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Multiple LN metastases	6.901 (0.688-69.2)	0.100	6.392 (1.032-58.75)	0.048
LN metastasis ≥5 mm	1.136 (0.074-17.48)	0.927	2.173 (0.079-59.85)	0.646
Extra-nodal invasion	2.252 (0.171-29.70)	0.537	1.215 (0.0480-30.72)	0.906

CI: Confidence interval; HR: hazard ratio.

radiation alone, after four were dead of disease and only one had no evidence of disease (NED). Another five cases were treated with CCRT using paclitaxel and cisplatin (TP-CCRT) and achieved NED. The remaining two cases were treated with CCRT using cisplatin but died of their disease. Four cases were treated with systemic chemotherapy, resulting in one with NED, one alive with disease, and two died of disease. In the remaining two cases, one underwent surgical removal of the LN recurrence, and the other received best supportive care.

Discussion

We examined 17 patients with pelvic LN metastases and no enlarged pelvic LNs (*i.e.*, with short diameters of <10 mm on preoperative pelvic magnetic resonance imaging). Positron-emission tomography/CT detects LN metastases of 5 mm or larger (8). Tumors that occupy a high percentage of the excised LNs are more likely to be detected (8, 9). Even with the increased accuracy of positron-emission tomography/CT in detecting LN metastases, there are still

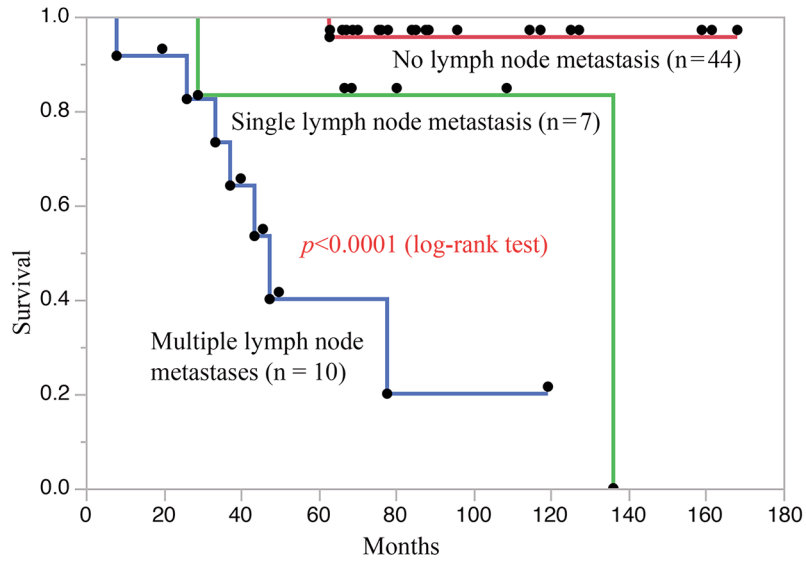


Figure 1. Kaplan-Meier curves for overall survival (OS) of patients with lymph node-negative, single-lymph node (LN) metastasis, and multiple LN metastases. 5-Year OS rates were 100%, 83.3%, and 30.0% ($p<0.001$), respectively, for the three groups. The only comparison that failed to reach significance was between the LN-negative and single metastasis groups in DFS.

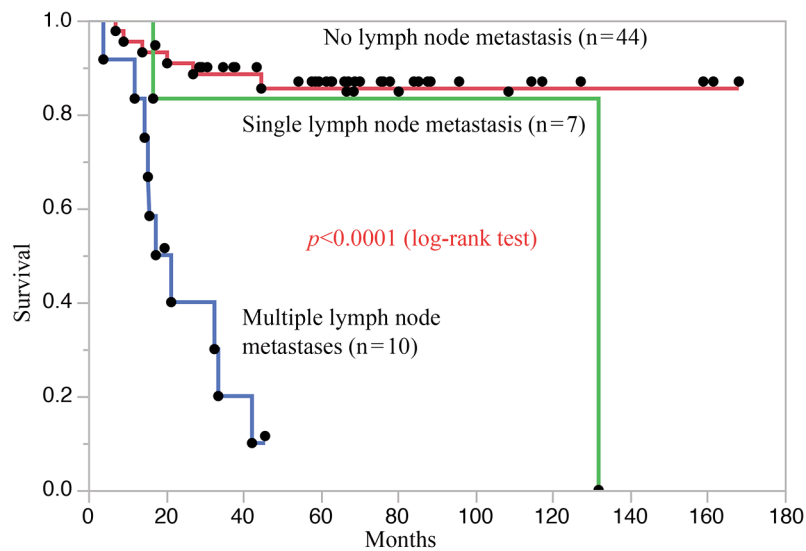


Figure 2. Kaplan-Meier curves for disease-free survival (DFS) of patients with lymph node-negative, single-lymph node (LN) metastasis, and multiple LN metastases. 5-Year DFS rates were significantly different at 85.5%, 83.3%, and 12.5% ($p<0.001$), respectively, for the three groups.

false-positive and false-negative cases. For these patients, histopathological diagnosis is the most accurate. Our study provides important information about managing these borderline cases.

We examined risk factors for cervical cancer recurrence. We evaluated pelvic LN metastases for the number of metastases, the presence of extra-nodal invasion, and the maximum diameter of metastases. Importantly, only multiple

LN metastases emerged as an independent prognostic factor. Regarding the number of LN metastases, Ishikawa *et al.* reported that 5-year OS rates for 193 cases of cervical adenocarcinoma with 0, 1-2, and ≥ 3 LN metastases were 89.2%, 61.3%, and 13%, respectively; the 5-year DFS rates were 85%, 51%, and 13%, respectively (10). Multiple LN metastasis was previously identified as a strong risk factor in 243 patients undergoing RH and pelvic lymphadenectomy

Table V. Site of recurrence by the number of lymph node metastases.

Recurrence	LN metastasis, n (%)		
	None (n=44)	Single (n=7)	Multiple (n=10)
Total number	6 (13.6%)	2 (28.6%)	8 (80.0%)
Site of recurrence			
Intra-pelvic	2 (33%) 1: Vaginal stump 1: PLN		6 (75%) 3: Vaginal stump 3: PLN
Intra-/extra-pelvic	3 (50%) 1: PLN+ILN 1: Vaginal stump+lung 1: Vaginal stump+AW	1 (50%), PLN+PAN	
Extra-pelvic	1 (17%), PAN	1 (50%), PM+bone	2 (25%), Lung

LN: Lymph node; AW: abdominal wall; ILN: inguinal lymph node; PAN: para-aortic lymph node; PLN: pelvic lymph node; PM: psoas muscle.

with positive pelvic lymph nodes, parametrial involvement, or positive surgical margins (11). Although we only examined patients with adenocarcinoma of the cervix, five out of the seven patients with no postoperative recurrence had a single pelvic LN metastasis. This finding suggests that the number of pelvic LNs is important in identifying high-risk groups for postoperative recurrence. OS and DFS rates were significantly different among the three groups. The only comparison that failed to reach significance was between the LN-negative and single metastasis groups in DFS.

Our Institute currently uses chemotherapy (paclitaxel plus carboplatin) as postoperative adjuvant treatment for patients at high risk of recurrence. This approach considers the possibility that radiotherapy after RH may impair long-term quality of life due to adverse effects such as radiation cystitis and colitis (12). In the present study, there was no significant difference in prognosis between LN-negative cases and cases with a single metastasis. Therefore, postoperative chemotherapy improves DFS in cases with a single metastasis. The prognosis was clearly poor in patients with multiple LN metastases, with 70% (7/10) of patients with pelvic recurrence. These results suggest that chemotherapy alone is insufficient for local control, and CCRT should be considered, as Matsuo *et al.* previously reported (13). TP-CCRT for cervical adenocarcinoma is superior to both distant control by multi-agent chemotherapy and local control by radiation therapy and may improve prognosis in patients with multiple metastases (14, 15).

Regarding radiotherapy outcomes after recurrence, Haasbeek *et al.* reported OS rates of 45% and 28% for pelvic wall recurrence and 93% and 63% for central recurrence at 2 and 5 years, respectively (16). Other reports have shown the usefulness of intensity-modulated radiation therapy and high-dose-rate interstitial brachytherapy; however, these studies were not limited to adenocarcinoma (17, 18). Refinement of

radiotherapy methods has improved treatment outcomes. Whether radiotherapy should be combined with chemotherapy in patients with pelvic recurrence is debatable (19). CCRT is considered when the intensity of radiation-only treatment is insufficient, such as when recurrent lesions are widely distributed throughout the pelvis, or in cases with a large tumor volume. Our Department does not have fixed criteria and cases are considered individually. In this study, five patients received radiation therapy alone for recurrent disease. Outcomes were four deaths and only one case with NED. Another five cases were treated with CCRT; three cases treated with TP-CCRT achieved NED, and the remaining two cases treated with cisplatin-CCRT died of their disease. TP-CCRT for recurrent cervical adenocarcinoma might be promising and should be considered (14, 15).

Conclusion

Among patients with no preoperative enlarged LNs who underwent RH for cervical adenocarcinoma and had positive pelvic LNs confirmed postoperatively, multiple positive pelvic LNs are an independent poor prognostic factor. Because pelvic recurrence is common, CCRT, possibly TP-CCRT, should be considered as adjuvant therapy for such patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

The work presented herein was carried out in collaboration among all Authors. TW and YA made substantial contribution to the conception, designed methods, interpreted the results, and wrote the article. TW, NT, YS, YA, YT, TN, WK, and YA engaged in data

acquisition and analyzed the data. TW and YA substantively revised the article. All Authors treated patients, read the article, and approved this submission.

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