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ORIGINAL RESEARCH

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Necessity of systematic pelvic lymphadenectomy for early-stage cervical cancer

Xinmei Wang[1,*], Hongyuan Zhang[1], Juan Xu[1], Pengpeng Qu[1]

[1]Department of Gynecological Oncology, Tianjin Central Hospital of Gynecology and Obstetrics, 300100 Tianjin, China

***Correspondence**
wangxinmei1983@tmu.edu.cn
(Xinmei Wang)

Abstract

To explore the risk factors for pelvic lymph node metastasis (PLNM) and recurrence in early-stage cervical cancer, then individualized management of patients with different risk levels can be carried out. Medical records of 735 patients who underwent radical hysterectomy and bilateral pelvic lymphadenectomy as primary treatment for the International Federation of Gynaecology and Obstetrics (FIGO, 2009) stage IA–IIA cervical cancer were reviewed. Clinical and pathological risk factors include age, FIGO stage, preoperative hemoglobin level, depth of stromal invasion, lymphovascular space invasion (LVSI), human papillomavirus (HPV) infection, and parametrial infiltration, tumor diameter, harvested lymph nodes, and pathological type were retrospectively analyzed. All patients were followed up for 5–10 years. Preoperative hemoglobin $<$110 g/L, FIGO stage II, LVSI, parametrial infiltration, and tumor diameter $\geq$4 cm were risk factors for PLNM and recurrence of early-stage cervical cancer after surgery ($p < 0.05$). PLNM was the independent risk factor for recurrence ($p < 0.05$). For patients with risk factors for PLNM, careful and systematic pelvic lymphadenectomy should be performed. Patients with PLNM have a high recurrence rate, and postoperative follow-up should be closely followed to ensure timely detection of recurrence and treatment Given the many complications of pelvic lymph node dissection for the low-risk population, further research is needed to determine whether pelvic lymphadenectomy should be attempted only in high-risk individuals.

Keywords

Cervical cancer; Pelvic lymph node metastasis; Radical hysterectomy; Lymphovascular space invasion; Pelvic lymphadenectomy; Hemoglobin

1. Introduction

Cervical cancer is one of the most common malignant tumors leading to death in women worldwide, and approximately 280,000 patients die from this disease each year [1, 2]. Radical hysterectomy and bilateral pelvic lymphadenectomy are standard treatments for most early-stage cervical cancers. Surgery can not only eliminate the disease, but also provide accurate pathological staging information that clinicians can use to target adjuvant therapy. Pelvic lymph node metastasis (PLNM) is the primary route of metastasis in cervical cancer, directly affecting cervical cancer treatment and prognosis [3–5].

However, only 15%~30% of patients with early-stage cervical cancer have PLNM [6, 7]. It means that more than 70% of patients with early-stage cervical cancer may have received unnecessary lymphadenectomy, which can lead to many postoperative complications. Therefore, it is essential to study risk factors affecting PLNM for the clinical treatment of early-stage cervical cancer.

The purpose of this study was to investigate the risk factors of PLNM and recurrence in patients with early cervical cancer, and to provide evidence for the individualized management of patients with cervical cancer.

2. Methods

2.1 Clinical data

The clinical data of 735 patients with cervical cancer at Tianjin Central Hospital of Gynecology and Obstetrics between January 2010 and December 2015 were retrospectively analyzed using the hospital medical records.

The inclusion criteria in our study were as follows: (1) Patients had squamous, adenocarcinoma or adenosquamous carcinoma of the cervix who were diagnosed by pathology. (2) Patients had FIGO (2009) stage: IA–IIA cervical cancer, and (3) Patients who received primary radical surgical treatment consisting of radical hysterectomy and bilateral pelvic lymphadenectomy. (4) Patients with complete clinical data and follow-up results. The exclusion criteria were as follows: (1) Patients with small-cell neuroendocrine carcinoma, cervical sarcoma, cervical lymphoma, cervical melanoma and other cervical nonepithelial tumors, (2) preoperative metastatic cer-

vical cancer, (3) patients who received radiotherapy or neoadjuvant chemotherapy before surgery, and (4) cases complicated by malignant tumors in other organ systems. (5) Patients with severe heart, liver, kidney and lung diseases. (6) Patients with severe mental diseases. (7) Patients with incomplete clinical data.

According to the presence or absence of PLNM, the patients were divided into two groups: (1) PLNM (−) group: patients without PLNM, and (2) PLNM (+) group: patients with PLNM. All patients were followed up for 5–10 years, and based on follow-up data, they were divided into two groups: (1) Recurrence group: patients with recurrence, and (2) no recurrence group: patients without recurrence. Age, preoperative hemoglobin level, FIGO stage, depth of stromal invasion, lymphovascular space invasion (LVSI), human papillomavirus (HPV) infection, parametrial infiltration, tumor diameter, harvested lymph nodes, and pathological type were retrospectively analyzed. Patients in both groups were divided into two levels depending on the above parameters (Fig. 1).

Two gynecologic pathologists reviewed the pathological slides of each patient to confirm tumor diameter, LVSI, depth of cervical stromal invasion, parametrial invasion, harvested lymph nodes, and pathological type. The largest dimension was recorded as tumor diameter by the pathologist. The deep stromal invasion was defined as the depth of cervical stromal invasion $\geq$1/2. In general, patients with postoperative pathologic findings of LVSI, pelvic LNM or parametrial invasion were advised to undergo postoperative adjuvant irradiation and/or concurrent cisplatincontaining chemotherapy for four cycles. The followup period was calculated from the date of surgery to the date of last followup (01 November 2020). Recurrence was defined as disease found at any time after surgery.

2.2 Statistical analysis

SPSS version 21.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The two-by-two or fourfold contingency table (chi-square) test employing exact probabilities was used. Multivariate analysis was performed using a logistic regression model. All tests were two-sided, and the level of significance was set at $p < 0.05$.

3. Results

The 735 patients included in the study were 27–70 (45.31 $\pm$ 6.42) years old, of whom 555 (75.51%) had no PLNM, whereas 180 (24.49%) had PLNM. All patients were followed up for 5–10 years, and 117 (15.92%) patients relapsed.

3.1 Characteristics associated with PLNM

Patients in both groups were subdivided into two levels, depending on age, HPV infection, preoperative hemoglobin level, FIGO stage, depth of stromal invasion, LVSI, parametrial infiltration, tumor diameter, harvested lymph nodes, and pathological type. The number of patients with preoperative hemoglobin <110 g/L, FIGO stage II, deep stromal invasion, LVSI, parametrial infiltration and tumor diameter $\geq$4 cm in the PLNM (+) group was significantly higher than that in the PLNM (−) group ($p < 0.05$). However, age, HPV infection, number of lymphadenectomies, and pathological type did not differ significantly between the PLNM (+) and PLNM (−) groups (Table 1).

3.2 Logistic regression analysis of risk factors for PLNM

Logistic regression analysis was used to identify independent predictors for PLNM, and preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration, and tumor diameter $\geq$4 cm were found to be independent risk factors for postoperative PLNM of cervical cancer ($p < 0.05$) (Table 2).

3.3 Characteristics associated with recurrence

All patients were followed up for 5–10 years, and 117 (15.92%) patients relapsed. The number of patients with preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration, tumor diameter $\geq$4 cm, and PLNM in the recurrence group was significantly higher than that in the non-recurrence group ($p < 0.05$). Age, HPV infection, harvested lymph nodes, and pathological type did not differ significantly between the two groups (Table 3).

3.4 Logistic regression analysis of risk factors for recurrence

Logistic regression analysis used to identify independent predictors for PLNM revealed preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration, tumor diameter $\geq$4 cm, and PLNM as independent risk factors for recurrence of cervical cancer (OR $\geq$1 and $p < 0.05$) (Table 4).

4. Discussion

The incidence of PLNM after cervical cancer surgery is reported to be 15–30% in patients with stage IA–IIA cervical cancer [6–8]. The 5-year overall survival rate of patients with PLNM is about 50%, while the survival rate of patients without PLNM is more than 90% [9, 10]. Lymph node metastasis is closely related to surgical methods and the prognosis of patients [11, 12]. Extensive lymphadenectomy for cervical cancer patients without lymph node metastasis may lead to unnecessary complications such as infection, nerve injury, lymphocytic cyst formation, vascular injury, venous thromboembolism, and lymphedema of lower extremities, affecting the quality of life of patients. Therefore, accurate preoperative or intraoperative pelvic lymph node metastasis assessment is an urgent clinical issue.

Many experts and scholars have studied the correlation between the clinicopathological factors of cervical cancer and lymph node metastasis, but the results were different. This study retrospectively analyzed the clinicopathologic data from 735 patients with FIGO IA–IIA cervical cancer treated by radical surgery. It was found that preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, parametrial infiltration and

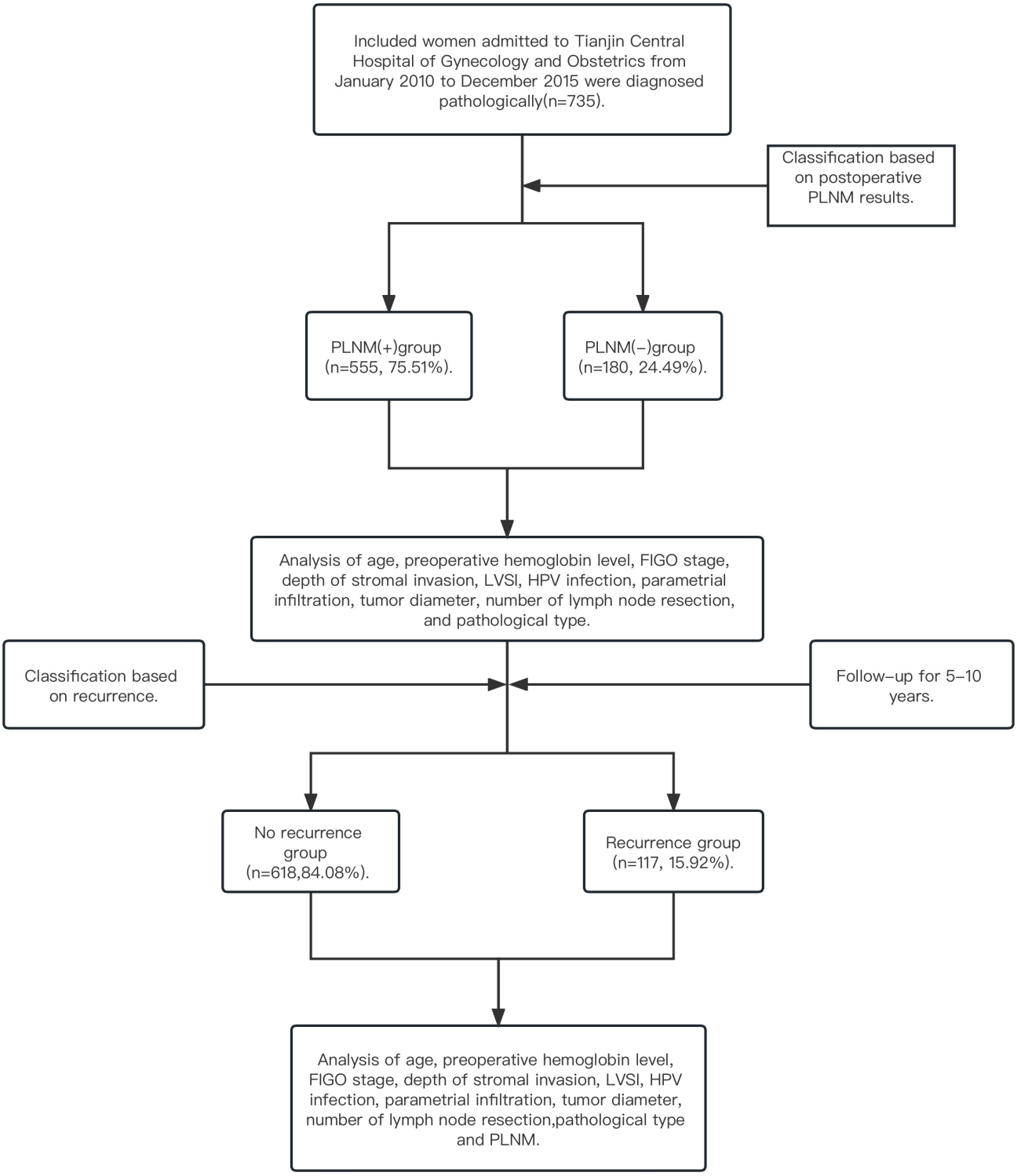

FIGURE 1. The flowchart of study. PLNM: pelvic lymph node metastasis; FIGO: International Federation of Gynaecology and Obstetrics; LVSI: lymphovascular space invasion; HPV: human papillomavirus.

tumor diameter $\geq$4 cm as significant risk factors for PLNM and recurrence of cervical cancer after surgery.

The hemoglobin level reduces commonly in the perioperative period [13]. Moreover, anemia occurs in more than one-third of cancer patients, and severe anemia is a risk factor for death in such patients [14–16]. The level of hemoglobin, the primary oxygen carrier, directly affects the oxygen supply and oxygen content of the tumor. Preoperative blood transfusion and other strategies do not improve prognosis in cervical cancer patients, and in patients complicated with anemia, the tumor is highly aggressive, further deteriorating the prognosis [17, 18]. In this study, the number of patients with preoperative hemoglobin $<$110 g/L was significantly higher in the PLNM (+) group than in PLNM (−) group ($p < 0.02$). And the

TABLE 1. Characteristics associated with PLNM.

Characteristic	Patients (n)	PLNM (+) (n = 180, 24.49%)	PLNM (−) (n = 555, 75.51%)	Chi-square	*p*-value
Age (yr)					
<45	357	75 (41.67)	282 (50.81)	0.775	0.424
≥45	378	105 (58.33)	273 (49.19)		
HPV infection					
Yes	495	117 (65.00)	378 (68.11)	0.019	0.899
No	240	63 (35.00)	177 (31.89)		
Preoperative hemoglobin level (g/L)					
<110	225	102 (56.67)	123 (22.16)	5.998	0.015
≥110	510	78 (43.33)	432 (77.84)		
FIGO stage					
I	366	39 (21.67)	327 (58.92)	8.113	0.005
II	369	141 (78.33)	228 (41.08)		
Deep stromal invasion					
Yes	399	150 (82.76)	249 (44.86)	15.394	<0.001
No	336	30 (18.33)	306 (55.14)		
Number of lymphadenectomies					
<15	414	96 (53.33)	318 (57.30)	0.244	0.621
≥15	321	74 (46.67)	237 (42.70)		
LVSI					
Yes	189	147 (81.67)	42 (7.57)	19.304	<0.001
No	546	33 (18.33)	513 (92.43)		
Parametrial infiltration					
Yes	159	135 (75.00)	24 (4.32)	22.676	<0.001
No	576	45 (25.00)	531 (95.68)		
Pathological type					
SCC		156 (86.67)	486 (87.57)	0.000	0.989
Non-SCC		24 (13.33)	69 (12.43)		
Tumor diameter (cm)					
<4	471	81 (45.00)	390 (70.27)	4.647	0.034
≥4	264	99 (55.00)	165 (29.73)		

PLNM: pelvic lymph node metastasis; FIGO: International Federation of Gynaecology and Obstetrics; LVSI: lymphovascular space invasion; HPV: human papillomavirus; SCC: squamous cell carcinoma.

TABLE 2. Logistic regression analysis of risk factors for PLNM.

Characteristic	B	SE	Wald	*p*-value	OR (95% CI)
Preoperative hemoglobin level	0.741	0.313	5.390	0.015	2.115 (1.143–3.914)
FIGO stage	0.986	0.355	7.647	0.006	2.687 (1.334–5.414)
Deep stromal invasion	1.198	0.254	15.129	<0.001	3.612 (2.388–5.997)
LVSI	1.610	0.421	15.132	<0.001	4.952 (2.212–11.089)
Parametrial infiltration	1.161	0.427	3.879	0.001	2.614 (2.241–4.249)
Tumor diameter	0.656	0.311	4.474	0.034	1.926 (1.049–3.535)

PLNM: pelvic lymph node metastasis; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval; FIGO: International Federation of Gynaecology and Obstetrics; LVSI: lymphovascular space invasion; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

TABLE 3. Characteristics associated with recurrence.

Characteristic	Patients (n = 735)	No recurrence (n = 618, 84.08%)	Recurrence (n = 117, 15.91%)	Chi-square	*p*-value
Age (yr)					
<45	357	312 (50.49)	45 (38.46)	1.974	0.160
≥45	378	306 (49.51)	72 (61.54)		
HPV infection					
Yes	495	432 (69.90)	63 (53.84)	2.861	0.092
No	240	184 (30.10)	54 (46.15)		
Preoperative hemoglobin level (g/L)					
<110	225	150 (24.27)	75 (64.10)	5.449	0.021
≥110	510	468 (75.73)	42 (35.90)		
FIGO stage					
I	266	333 (53.88)	33 (28.21)	5.217	0.029
II	369	285 (46.12)	84 (71.79)		
Deep stromal invasion					
Yes	399	303 (49.03)	96 (82.05)	8.185	0.004
No	336	345 (50.97)	21 (17.95)		
Number of lymphadenectomies					
<15	414	339 (54.85)	75 (64.10)	1.168	0.280
≥15	321	279 (45.15)	42 (35.90)		
LVSI					
Yes	189	99 (16.02)	90 (76.92)	17.291	<0.001
No	546	519 (83.98)	27 (23.08)		
Parametrial infiltration					
Yes	159	75 (12.14)	84 (71.29)	13.974	0.002
No	576	543 (87.86)	33 (28.21)		
Pathological type					
SCC	642	585 (37.31)	57 (30.77)	0.605	0.437
Non-SCC	93	33 (62.69)	60 (69.23)		
Tumor diameter (cm)					
<4	471	438 (70.87)	33 (28.21)	6.217	0.034
≥4	264	180 (29.13)	84 (71.79)		
PLNM					
Yes	180	87 (14.08)	93 (79.49)	18.219	<0.001
No	555	531(85.93)	24 (20.51)		

PLNM: pelvic lymph node metastasis; FIGO: International Federation of Gynaecology and Obstetrics; LVSI: lymphovascular space invasion; HPV: human papillomavirus; SCC: squamous cell carcinoma.

TABLE 4. Logistic regression analysis of risk factors for recurrence.

Characteristic	B	SE	Wald	*p*-value	OR (95% CI)
Preoperative hemoglobin level	0.822	0.358	5.272	0.022	2.275 (1.128–4.590)
LVSI	1.600	0.411	15.131	<0.001	4.952 (2.212–11.089)
Deep stromal invasion	0.912	0.138	8.268	0.001	1.825 (1.675–3.111)
Parametrial infiltration	1.032	0.423	5.714	0.011	1.620 (1.366–2.124)
Tumor diameter	0.685	0.612	5.308	0.008	1.744 (1.187–3.146)
FIGO stage	1.195	0.439	7.412	0.006	3.303 (1.397–7.807)
PLNM	1.104	0.367	9.030	0.003	3.016 (1.468–6.195)

PLNM: pelvic lymph node metastasis; FIGO: International Federation of Gynaecology and Obstetrics; LVSI: lymphovascular space invasion.

number of patients with preoperative hemoglobin <110 g/L was significantly higher in the recurrence groups than in the no-recurrence groups ($p < 0.03$). Moreover, preoperative hemoglobin <110 g/L was identified as an independent risk factor for postoperative PLNM and recurrence of cervical cancer after surgery. This finding was consistent with the results of previous studies.

Previous studies have shown that tumor staging, LVSI, deep stromal invasion, parametrial infiltration and tumor diameter are closely related to PLNM and the recurrence of early cervical cancer [19–21]. PLNM rates of Ia, Ib, IIa and IIb stages are reported to be 10.5%, 13.1%, 27.1% and 50.0%, respectively [22]. As the tumor stage increases, the depth and extent of tumor invasion to the surrounding tissue, the aggressiveness and malignancy of the tumor, and the recurrence rate increase significantly [3, 19, 23]. When cancer cells invade the lymphatic space, they can promote the formation of tumor thrombosis and invade local lymph nodes through the lymphatic vessels, thus inducing parametrial infiltration and PLMN [24, 25]. In this study, the number of FIGO stage II cervical cancer patients with PLNM was higher than the number of FIGO stage I cervical cancer patients with PLNM ($p = 0.005$), and the proportions of patients with LVSI (81.67%) and parametrial infiltration (75%) in the PLNM (+) group were significantly higher than those of patients in the PLNM (−) group ($p < 0.005$), which was consistent with previously reported results.

The tumor diameter can reflect the tumor growth time as tumor growth is a continuous invasion and proliferation process. The longer the growth time, the more likely is the lymph node metastasis [6, 7, 26]. With an increase in tumor diameter and a prolonged growth period, the depth of stromal invasion tends to increase. The contact area between tumor tissue and lymphatic vessels and the risk of LNM also tend to significantly increase [20, 27, 28]. A study on the prognosis of 93 patients with early cervical cancer after surgery found that a tumor diameter ≥4 cm is a risk factor for PLNM and recurrence of cervical cancer [29]. In this study, the number of patients with tumor diameter ≥4 cm and deep stromal invasion differed significantly between the two groups ($p < 0.005$ and $p < 0.05$), consistent with previous studies.

Besides preoperative hemoglobin <110 g/L, LVSI, deep stromal invasion, parametrial infiltration and tumor diameter ≥4 cm, it was shown that PLNM is an independent risk factor for the recurrence of cervical cancer. PLNM is more likely to occur in advanced cervical cancer. Postoperative invasion, metastasis, and recurrence are prone to occur in patients with PLNM [21]. Thus, the postoperative survival rate tends to decrease [30, 31]. Pelvic lymph node dissection can effectively remove metastatic lymph nodes, reduce the tumor load, prevent PLNM, and reduce the risk of distant recurrence [32, 33]. For patients with positive pelvic lymph nodes, the interval between recurrence is significantly shorter than for those with negative lymph nodes, and the risk of recurrence is relatively higher [6]. In this study, the proportion of patients with PLNM in the recurrence group was (79.47%) significantly higher than that in the non-recurrence group ($p < 0.001$). PLNM was therefore identified as an independent risk factor for recurrence in patients with cervical cancer after radical hysterectomy and bilateral pelvic lymphadenectomy.

The main strength of this study was that patients with recurrence after surgery were from the same group of patients with PLNM, thereby reducing bias and achieving more accurate results.

This study also has unavoidable limitations due to its retrospective design. First, we could not assess all variables potentially associated with residual lesions in this single-center study. Furthermore, because the study population was from one hospital, the external validity of our results may be low. Further prospective studies with a larger sample size and a broader context are needed.

5. Conclusions

In this study, we found that hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration and tumor diameter ≥4 cm are independent risk factors for postoperative PLNM and cervical cancer recurrence. Furthermore, PLNM is an independent risk factor for the postoperative recurrence of cervical cancer. LNM is an important prognostic indicator for the clinical treatment of cervical cancer. A comprehensive preoperative evaluation is strongly recommended to improve the curative effect and prognosis of cervical cancer and avoid PLNM. For patients with risk factors for PLNM, careful and systematic pelvic lymphadenectomy should be performed. Patients with PLNM have a high recurrence rate, and postoperative follow-up should be closely followed to ensure timely detection of recurrence and treatment. Given the many complications of pelvic lymph node dissection for the low-risk population, further research is needed to determine whether pelvic lymphadenectomy should be attempted only in high-risk individuals.

ABBREVIATIONS

PLNM, Pelvic lymph node metastasis; LVSI, Lymphovascular space invasion; FIGO, International Federation of Gynaecology and Obstetrics; HPV, Human papillomavirus; SCC, Squamous cell carcinoma.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XMW—project development, data collection, manuscript writing; HYZ—data collection and data analysis; JY—data collection and data analysis; PPQ—project development. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective analysis was exempt from ethics committee approval at Tianjin Medical University, Tianjin Central Hospital of Gynecology and Obstetrics because the committee

did not consider approval was necessary for a retrospective chart review. The data were collected through the institution's electronic medical records while preserving patient anonymity. The research ethics committee waived the requirement for informed consent because the study used previously stored data. Administrative permissions were not required to access and use the medical records described in our study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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