Risk Factors of Pelvic Lymph Node Metastasis and Recurrence in Patients with Early Cervical Cancer

Xinmei Wang (wangxinmei1983@tmu.edu.cn)
Tianjin Central Hospital of Gynecology and Obstetrics

Hongyuan Zhang
Tianjin Central Hospital of Gynecology and Obstetrics

Juan Xu
Tianjin Central Hospital of Gynecology and Obstetrics

Pengpeng Qu
Tianjin Central Hospital of Gynecology and Obstetrics

Research Article

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

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1041771/v1

Abstract

Background: Pelvic lymph node metastasis (PLNM) is one of the critical factors affecting the postoperative prognosis of patients with cervical cancer. Preoperative identification of risk factors for PLNM can optimize preoperative treatment plans and prognostic assessments.The purpose of this study was to investigate the risk factors for PLNM and its recurrence in patients undergoing radical hysterectomy for cervical cancer.

Methods: Medical records of 245 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 between January 2010 and December 2015 were reviewed. Clinicopathological risk factors were retrospectively analyzed. All patients were followed up for 5–10 years. Multivariate analysis was performed using a logistic regression model for the analysis of risk factors for PLNM.

Results: Preoperative hemoglobin level, FIGO stage, LVSI, parametrial infiltration, and tumor diameter differed significantly between the two groups ($P<0.05$).Multivariate analysis revealed preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, parametrial infiltration, and tumor diameter ≥4 cm as significant risk factors for PLNM and recurrence of cervical cancer after surgery ($P<0.05$). PLNM was identified as the independent risk factor for recurrence in patients with cervical cancer after surgery ($P<0.05$).

Conclusions: Patients with PLNM have a high recurrence rate, and postoperative follow-up should be closely followed to ensure timely detection of recurrence and treatment. For patients at high risk of PLNM, intraoperative careful and comprehensive pelvic lymph node resection should be performed to avoid missing metastatic lymph nodes and affecting the prognosis. 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.

Background

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 cervical cancer have lymph node metastasis [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 cervical cancer. By preoperatively

identifying the risk factors for PLNM, preoperative treatment planning and prognosis evaluation may be optimized.

The purpose of this retrospective study was to identify the risk factors for PLNM and recurrence, then provide insights into the treatment and prognosis of cervical cancer.

Methods

Clinical data

The clinical data of 245 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,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. 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 cervical cancer,3) patients who received radiotherapy or neoadjuvant chemotherapy before surgery, and 4) cases complicated by malignant tumors in other organ systems.

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 (Figure 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 ≥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 (November 1, 2020). Recurrence was defined as disease found at any time after surgery.

Patient anonymity was preserved as the data were collected from the hospital's electronic medical records. The research ethics committee of Tianjin Central Hospital of Gynecology and Obstetrics waived the requirement for ethics approval and informed consent because the study used previously stored data.

The study were performed in accordance with the Declaration of Helsinki.

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 $P<0.05$.

Results

The 245 patients included in the study were 27–70 (45.31±6.42) years old, of whom 185 (75.51%) had no PLNM, whereas 60 (24.49%) had PLNM. All patients were followed up for 5–10 years, and 39 (16.25%) patients relapsed.

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 ≥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 the PLNM(+) and PLNM(-) groups;. (Table 1).

Table 1
Characteristics associated with PLNM

Characteristic	Patients (n)	PLNM(+) (n=60, 24.49%)	PLNM(-) (n=185, 75.51%)	*Chi-square*	*P-value*
Age (years)					
<45	119	25 (41.67)	94 (50.81)	0.775	0.424
≥45	126	35 (58.33)	91 (49.19)		
HPV infection					
Yes	165	39 (65.00)	126 (68.11)	0.019	0.899
No	80	21 (35.00)	59 (31.89)		
Preoperative hemoglobin level (g/L)					
<110	75	34 (56.67)	41 (22.16)	5.998	0.015
≥110	170	26 (43.33)	144 (77.84)		
FIGO stage					
I	122	13 (21.67)	109 (58.92)	8.113	0.005
II	123	47 (78.33)	76 (41.08)		
Deep stromal invasion					
Yes	133	50 (82.76)	83 (44.86)	15.394	0.000
No	112	10 (18.33)	102 (55.14)		
harvested lymph nodes					
<15	138	32 (53.33)	106 (57.30)	0.244	0.621
≥15	107	28 (46.67)	79 (42.70)		
LVSI					
Yes	63	49 (81.67)	14 (7.57)	19.304	0.000
No	182	11 (18.33)	171 (92.43)		
Parametrial infiltration					
Yes	53	45 (75.00)	8 (4.32)	22.676	0.000

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

Characteristic	Patients (n)	PLNM(+) (n=60, 24.49%)	PLNM(-) (n=185, 75.51%)	*Chi-square*	*P-value*
No	192	15 (25.00)	177 (95.68)		
Pathological type					
SCC	214	52 (86.67)	162 (87.57)	0.000	0.989
Non-SCC	31	8 (13.33)	23 (12.43)		
Tumor diameter (cm)					
<4	157	27 (45.00)	130 (70.27)	4.647	0.034
≥4	88	33 (55.00)	55 (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

Logistic regression analysis of risk factors for PLNM

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

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	0.000	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; FIGO, International Federation of Gynaecology and Obstetrics; LVSI, lymphovascular space invasion;B,Regression coefficient;SE,Standard erro;OR: Odds ratio;

Characteristics associated with recurrence

All patients were followed up for 5–10 years, and 39 (16.25%) patients relapsed. The number of patients with preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration, tumor diameter ≥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).

Table 3
Characteristics associated with recurrence

Characteristic	Patients (n=245)	No recurrence (n=206, 84.08%)	Recurrence (n=39, 15.91%)	*Chi-square*	*P-value*
Age (years)					
<45	119	104 (50.49)	15 (38.46)	1.974	0.160
≥45	126	102 (49.51)	24 (61.54)		
HPV infection					
Yes	165	144 (69.90)	21 (53.84)	2.861	0.092
No	80	62 (30.10)	18 (46.15)		
Preoperative hemoglobin level (g/L)					
<110	75	50 (24.27)	25 (64.10)	5.449	0.021
≥110	170	156 (75.73)	14 (35.90)		
FIGO stage					
I	122	111 (53.88)	11 (28.21)	5.217	0.029
II	123	95 (46.12)	28 (71.79)		
Deep stromal invasion					
Yes	133	101 (49.03)	32 (82.05)	8.185	0.004
No	112	105 (50.97)	7 (17.95)		
harvested lymph nodes					
<15	138	113 (54.85)	25 (64.10)	1.168	0.280
≥15	107	93 (45.15)	14 (35.90)		
LVSI					
Yes	63	33 (16.02)	30 (76.92)	17.29	0.000
No	182	173 (83.98)	9 (23.08)		
Parametrial infiltration					
Yes	53	25 (12.14)	28 (71.29)	13.974	0.002

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

Characteristic	Patients (n=245)	No recurrence (n=206, 84.08%)	Recurrence (n=39, 15.91%)	*Chi-square*	*P-value*
No	192	181 (87.86)	11 (28.21)		
Pathological type					
SCC	214	195 (37.31)	19 (30.77)	0.605	0.437
Non-SCC	31	11 (62.69)	20 (69.23)		
Tumor diameter (cm)					
<4	157	146 (70.87)	11 (28.21)	6.217	0.034
≥4	88	60 (29.13)	28 (71.79)		
PLNM					
Yes	60	29 (14.08)	31 (79.49)	18.219	0.000
No	185	177 (85.93)	8 (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					

Logistic regression analysis of risk factors for recurrence

Logistic regression analysis used to identify independent predictors for PLMN revealed preoperative

hemoglobin <110 g/L, FIGO stage II, LVSI, deep stromal invasion, parametrial infiltration, tumor diameter ≥4 cm, and PLMN as independent risk factors for recurrence of cervical cancer (OR≥1 and P<0.05) (Table 4).

Table 4
Logistic regression analysis of risk factors for recurrence

Characteristic	B	SE	Wald	*P-value*	O R (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	0.000	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;B,Regression coefficient;SE,Standard erro;OR: Odds ratio; CI: Confidence interval

Discussion

Radical hysterectomy and bilateral pelvic lymphadenectomy are still the primary clinical treatment methods for patients with early-stage cervical cancer. PLNM is the main metastatic route of cancer cell proliferation and an essential determinant of prognosis [8, 9]. The incidence of PLNM after cervical cancer surgery has been reported to range from 15 to 30% in patients with Stage IA–IIA cervical cancer. [6, 7]. In this study, the incidence of PLNM was 24%. The clinicopathologic data from 245 patients with FIGO IA-IIA cervical cancer treated by radical surgery were retrospectively analyzed. It was found that preoperative hemoglobin <110 g/L, FIGO stage II, LVSI, parametrial infiltration, and tumor diameter ≥4 cm as significant risk factors for PLNM and recurrence of cervical cancer after surgery.

The hemoglobin level reduces commonly in the perioperative period [10]. Moreover, anemia occurs in more than one-third of cancer patients, and severe anemia is a risk factor for death in such patients [11–13]. 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 [14, 15]. 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 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.

Tumor staging is a defining index of tumor growth and the extent of its spread. 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, 16]. PLNM rates of Ia, Ib, IIa, and IIb stages are reported to be 10.5%,13.1%, 27.1%, and 50.0%, respectively [17], confirming that LNM increases with advanced FIGO stages. 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). This finding is consistent with previously reported results.

LVSI, deep stromal invasion, parametrial infiltration, and tumor diameter are closely related to PLNM and the recurrence of early cervical cancer [18, 19]. LVSI is pathologically confirmed by the presence of malignant tumor cells between two layers of vascular endothelial tissue and is an important prognostic index of cervical cancer. Vascular infiltration is an independent risk factor for PLNM [20, 21]. 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 [22, 23]. Consistent with previous studies, in our study, 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).

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]. 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 [18, 24, 25]. 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 [26]. 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, 23]. Thus, the postoperative survival rate tends to decrease [27, 28]. Pelvic lymph node dissection can effectively remove metastatic lymph nodes, reduce the tumor load, prevent PLNM, and reduce the risk of distant recurrence [29, 30]. 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=0.000). 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.

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

Declarations

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.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

The project name: Establishment and clinical application of early diagnosis system for cervical precancerous lesions caused by HPV E6 and E7

Contract no.: 19YFZCSY00600

Authors’ contributions

XmW: project development, data collection, manuscript writing.

HyZh: data collection and data analysis.

JY: data collection and data analysis.

PpQ: project development.

All authors have read and approved the final manuscript.

Acknowledgment

We thank all participants in the study for their invaluable contribution.

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Figures

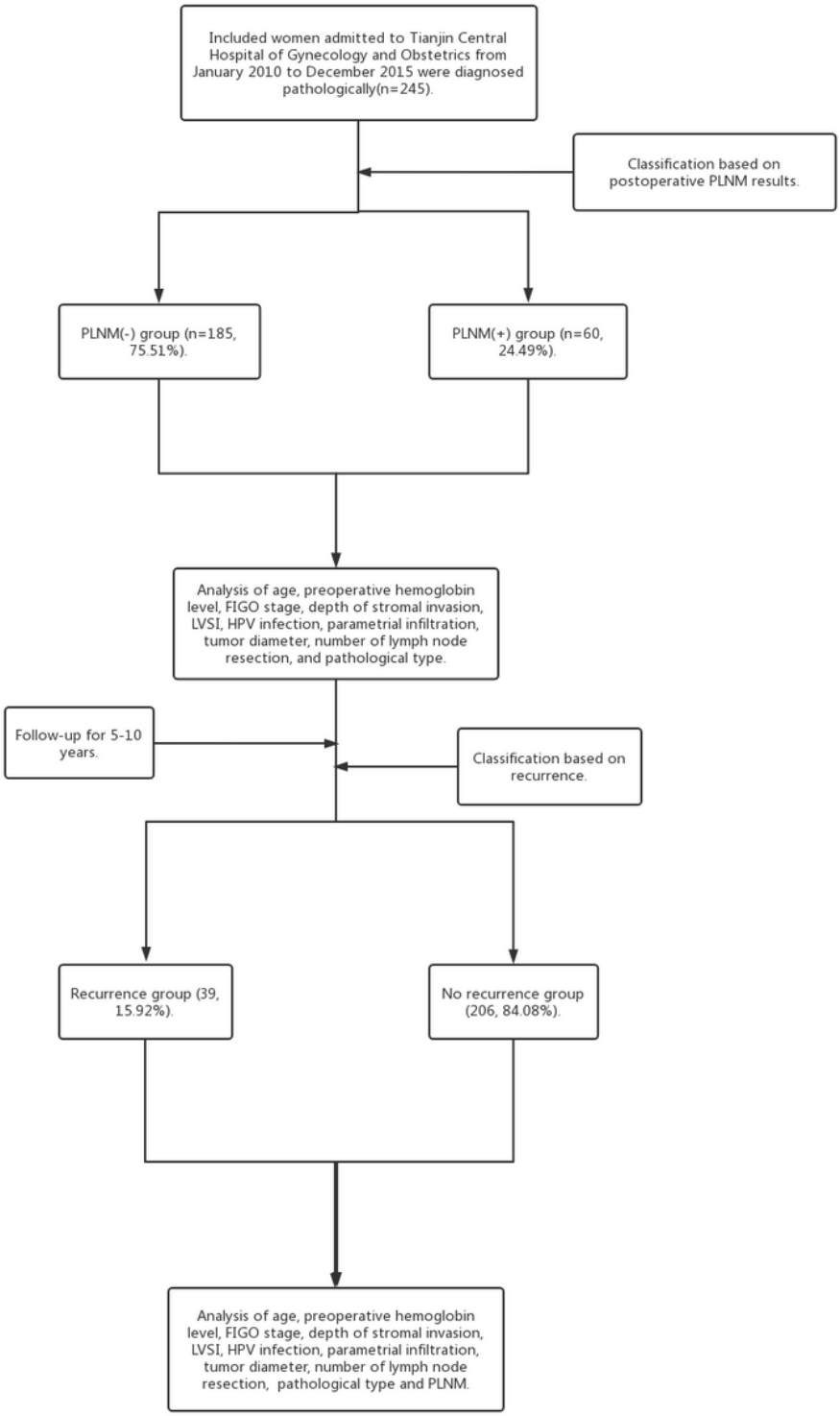

Figure 1

Study flow chart