Lymph nodes metastasis in cervical cancer: Incidences, risk factors, consequences and imaging evaluations

Rongxu Du | Lei Li | Shuiqing Ma | Xianjie Tan | Sen Zhong | Ming Wu

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Lei Li and Ming Wu, Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Shuifu Yuan No. 1, Dongcheng District, Beijing 100730, China.
Email: lileigh@163.com; drwuming@sina.com

Abstract

Aim: The aim of this study was to determine the incidence, risk factors, consequences and accuracy of imaging evaluation of lymph node (LN) metastasis in a cohort of 406 patients treated with radical hysterectomy (RH), lymphadenectomy of pelvic LN (PLN) and para-aortic LN (PALN), which was performed primarily by one physician.

Methods: From February 2001 to November 2015, patients with cervical cancer of FIGO stage IB were included, if they received RH of class III or type C performed by Dr. M. Wu in Peking Union Medical College Hospital. Follow-up ended in December 2016. Incidences and accuracy of imaging evaluation of LN metastasis were described, and predictive factors of LN metastasis and its impact on survival outcomes were determined in univariate and multivariate models.

Results: Among 406 patients with clinical stage IB, 57 (14.0%) had lymphatic metastasis. In multivariate model, positive parametrium was independent factor for general LN metastasis (odds ratio [OR] 5.1; 95% confidence interval [95% CI], 2.1–12.1) and PLN metastasis (OR 5.3; 95% CI, 2.2–12.8). Positive PLN was independent factor for metastasis to common iliac LN and PALN. After adjusted with clinico pathologic factors, general and site-specific LN metastases were independent risk factors of progression-free survival and overall survival (all \( P \) values <0.05). Preoperative imaging evaluation had low sensitivity but high specificity for predicting LN metastasis. Various imaging methods had similar predictive accuracy.

Conclusion: Lymphatic metastasis was significantly related to the clinico pathologic characters and survival of cervical cancer. More sensitive preoperative evaluation is needed for predicting the LN metastasis.

KEYWORDS
cervical cancer, lymph node metastasis, radical hysterectomy

1 | INTRODUCTION

Cervical cancer has the highest incidence and mortality in female genital tract cancers in China.1 For patients with early-stage cervical cancers, lymph nodes (LN) metastasis has been proved to be a critical risk factor related to the survival of cervical cancer.2,3 Previous studies have suggested that the 5-year overall survival (OS) of patients with early-stage cervical cancers could decrease by approximately 30% as the LN metastasis occurs.4 Pelvic lymphadenectomy has integrated into the surgical treatment for young patients with early-stage cervical cancer,5,6 whereas the role of lymphadenectomy of para-aortic LN (PALN) is still controversial,7 because of its invasive characteristic, potential severe complications and requirement for high skill.8,9 There were also few reports about relevant clinico pathologic factors predicting LN metastasis. In this study, we aim to elucidate incidence, relevant clinico pathologic factors of LN metastasis and their impact on survival outcomes in patients of stage IB cervical cancer treated with radical hysterectomy (RH) from a tertiary teaching hospital, which were performed primarily by one physician, and all patients received lymphadenectomy of pelvic LN (PLN) and PALN. Besides, various presurgical imaging methods were evaluated for the predictive accuracy of LN metastasis.
METHODS

Treatments

Statistical analysis

Presurgical imaging evaluation

Patients

Study design

This is a retrospective study conducted at Department of Obstetrics and Gynecology, Peking Union Medical College Hospital (PUMCH). The Institutional Review Board of PUMCH has approved this study. The registration number is NCT03291236 (clinicaltrials.gov). All patients signed consents before surgeries.

All patients with cervical cancer of stage IB admitted to PUMCH from February 2001 to November 2015 were included, if they received RH of class III or type C performed primarily by Dr. M Wu. All patients were followed in outpatient clinics up to December 31, 2016. Recurrence was validated by imaging examination and/or biopsy. Mortality was confirmed by reviewing medical records and interviews over telephone or email.

The primary measurements are incidences of LN metastasis in general and in specific sites (pelvic cavity, common iliac vessels and para-aorta) proved by pathologic examination. Risk factors of LN metastasis and survival outcomes (OS and progression-free survival [PFS]) were determined by univariate and multivariate analyses. Accuracy of preoperative imaging was compared with practical LN involvement.

Patients

Data of eligible patients were collected by searching and reviewing medical records. Inclusion criteria consist of following conditions: histopathologically proven primary cervical cancer; FIGO stage IB diagnosed by pelvic examinations of two experienced physicians of gynecologic oncology; primary surgical physician was Dr. M. Wu; surgical procedures belonged to RH of class III or type C with lymphadenectomy of PALN. Patients were excluded if they had distant metastasis in presurgical imaging.

Presurgical imaging evaluation

All patients received presurgical imaging evaluations including contrast-enhancement computed tomography (CT), gadolinium-containing contrast-enhancement magnetic resonance imaging (MRI) and 18F-FDG positron emission tomography (PET)/CT for thoracic, abdominal and pelvic cavities within 4 weeks before RH. The results were interpreted by corresponding imaging specialists. For patients suspicious of distant metastasis in CT or MRI, a PET-CT would be given for the analysis of metabolism status of the suspicious lesions. We included the last prescribed modality for the analysis of accuracy of presurgical imaging.

Treatments

Surgical treatment consists of RH, bilateral salpingo-oophorectomy, lymphadenectomy of PLN and PALN. For young patients with requirement of preserving ovaries, salpingectomy was undertaken along with suspension of the ovaries to the peritoneum at the level of the anterior superior spine. All RH procedures were primarily performed by one surgeon (Dr. M. Wu) according to class III or Meigs’ surgeries of Piver–Rutledge–Smith classification (before 2011) and later according to type C of the Q-M classification (after 2011). Type C1, that is nerve-sparing RH, requires separation of two parts of the dorsal parame- tria: the medial part, which entails recto-uterine and recto-vaginal ligaments, and the lateral laminar structure, also called mesouteretum, which contains the hypogastric plexus, whereas type C2 surgery indicates RH without preservation of autonomic nerves. The paracervix is transected completely, including the part located caudal to the deep uterine vein. RH was performed through laparotomy or laparoscopy.

In procedure of RH, removed LNs were placed and sealed in bags made up of sterile gloves, and were taken out together with excised uterus. The caudal extension of LN removal was bounded by deep circumflex iliac vein, whereas PALNs were removed along the aorta and inferior vena cava up to the level of inferior mesenteric artery, and to the renal vein level when the metastasis was suspicious. LNs of external, internal iliac vessels and obturator were always removed as conternumious tissues. LNs of common iliac vessels and para-aorta were dissected specially for analysis of metastasis. Skeletonization of major vessels was labeled as thoroughness of lymphadenectomy, and the numbers of LN were recorded to guarantee the quality of lymphadenectomy.

Complications related with RH within 3 months were reviewed and collected from medical records as adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. All histological specimens underwent thorough pathologic examinations. Pathologic characters include pathologic subtypes, lymph-vascular space invasion (LVSI), invasion depth of the stroma, lymphatic metastasis, involvement of uterus or parametrium and status of vaginal margin.

Conization is performed in some patients to specify diagnosis or staging. Neoadjuvant chemotherapy (NAC) is given to a group of patients with stage IB2, LVSI in specimens of biopsy or conization. Regimens of NAC consist of palitaxel/carboplatin, palitaxel/cisplatin (in a cycle of 21 days) or fluorouracil/cisplatin (in a cycle of 28 days). Postoperative adjuvant therapies, including systematic chemotherapy, radiotherapy, concurrent chemoradiotherapy (CCRT) or a combination of them, were provided for patients with risk factors of recurrence according to National Comprehensive Cancer Network guideline. Systematic chemotherapy has similar plans as NAC. CCRT consists of radiotherapy and concurrent chemotherapy of cisplatin or palitaxel if patient had hypersensitivity reaction to cisplatin. Radiotherapy consists of conventional external-bean fractionation and low-dose rate (40–70 cGy/h) brachytherapy. For PALN metastasis, additional extending radiation therapy is given to achieve curable treatment.

Statistical analysis

SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was applied for statistical analysis. Risk factors related to LN metastasis were determined by univariate analysis and multivariate model of logistic regression, with $P < 0.05$ used to indicate statistical significance. The Kaplan–Meier method as univariate analysis and Cox proportional hazards regression model as multivariate analysis were used to determine the impact of the clinico pathologic characteristics on survival outcomes.
### Table 1
Median lymph nodes harvested and metastasis status of lymph nodes in various stages and regions

| Stage | Pelvic LN | Common iliac LN | Para-aortic LN |
|-------|-----------|----------------|---------------|
|       | Median no. (range) | Positive cases (%) | Median no. (range) | Positive cases (%) | Median no. (range) | Positive cases (%) |
| IB1 (n = 277) | 28 (6–58) | 33 (11.9) | 3 (0–11) | 8 (2.9) | 12 (1–25) | 10 (3.6) |
| IB2 (n = 129) | 25 (10–53) | 22 (17.0) | 3 (0–9) | 6 (4.7) | 12 (1–25) | 9 (7.0) |
| Total (n = 406) | 26 (6–58) | 55 (13.5) | 3 (0–11) | 14 (3.4) | 12 (1–25) | 19 (4.7) |

LN, lymph nodes.

*Pelvic lymph nodes indicate lymph nodes of external, internal iliac vessels and obturator.

# RESULTS

### 3.1 Epidemiological, clinico pathologic characters and survival outcomes of patients

A total of 406 patients with clinical stage IB accepted RH by Dr. M. Wu during study period, and 371 cases (91.4%) were included in the analysis of survival outcomes. The median age of all 406 patients was 42 years (range 21–65). There were 277 (68.2%) and 129 (31.8%) cases of stage IB1 and IB2, with tumors having median diameter of 3.0 cm (range 1.0–7.0). Squamous, adenoma and adenosquamous carcinomas were seen in 336 (82.8%), 55 (13.5%) and 15 cases (3.7%), respectively. Grades 1–3 were seen in 203 (50.0%), 145 (35.7%) and 58 (14.3%) cases.

### Invasion depth of stroma

Invasion depth of <1/3, 1/3–2/3 and >2/3 of the stroma was seen in 180 (44.3%), 115 (28.3%) and 111 (27.3%) cases, respectively. There were 162 (39.9%), 331 (81.5%), 24 (5.9%), 3 (0.7%) and 57 (14.3%) cases with positive LVSI, involvement of the uterine, involvement of the parametrium, positive vaginal margin and metastasis to LN, respectively. Severe (grade 3/4) complications occurred in 28 patients (6.9%).

### Distribution of lymphatic metastasis

Among 371 patients with definite survival outcomes, 70 cases (17.2%) had recurrence proved by imaging or pathologic examinations, and explicit death due to cancer occurred in 38 (9.4%) patients. Median PFS was 45.8 months (range 6–189), and 5- and 10-year PFS was 80% and 73%, respectively. Median OS was 48.5 months (range 12–189), and 5- and 10-year OS was 88% and 84%, respectively.

### Predictive factors of lymphatic metastasis

Univariate analysis results of significant relevant factors of lymphatic metastasis are listed in Table 2. In multivariate analysis, parametrial involvement was an independent risk factor for metastasis to general LN (odds ratio [OR] 5.1; 95% confidence interval [95% CI], 2.1–12.1; P < 0.001) and for metastasis to PLN (OR 5.3; 95% CI, 2.2–12.8; P < 0.001); positive PLN was an independent risk factor for metastasis to common iliac LN (OR 108.3; 95% CI, 13.8–849.1; P < 0.001); positive PLN (OR 85.8; 95% CI, 10.5–699.7, P < 0.001) and positive common iliac LN (OR 13.9; 95% CI, 3.1–61.0; P = 0.001) were independent risk factors for metastasis to PALN.

### Impacts of lymphatic metastasis on survival outcomes

In multivariate analysis, general LN metastasis (hazard ratio [HR] 2.0; 95% CI, 1.1–3.6; P = 0.017), stage IB2 (HR 2.0; 95% CI, 1.2–3.2; P = 0.005) and positive vaginal margin (HR 9.2; 95% CI, 2.6–33.0; P = 0.001) were independent risk factors of higher recurrence; general LN metastasis (HR 3.6; 95% CI, 1.8–7.1; P < 0.001), RH before year of 2011 (HR 2.8; 95% CI, 1.3–6.0; P = 0.010) and stage IB2 (HR 3.6; 95% CI, 1.9–6.9; P < 0.001) were independent risk factors of higher mortality. However, neoadjuvant therapy and postoperative adjuvant therapy as a whole or definite regimens (chemotherapy or radiotherapy) had no impact on the recurrence or mortality in univariate or multivariate analysis (all P values >0.05).

As shown in Table 3, in univariate analysis, LN metastasis to specific sites all resulted in higher recurrence and higher mortality. After adjusted with FIGO stages, status of vaginal margin for recurrence, surgical year for mortality a LN metastasis to specific sites remained independent risk factors of survival outcomes (all P values <0.05).

### Predictive value of presurgical imaging

Within 4 weeks before RH, imaging evaluation of CT, MRI and PET-CT were prescribed for 368, 22 and 16 patients, respectively. Imaging and pathological assessment about LN metastasis are listed in Table 4. There were 81 cases of LN metastasis in presurgical imaging, which is greater than practical involved cases (57 cases). There were no significant differences of accuracy of three imaging modalities (all P values <0.05) either for PLN or PALN.

For predicting LN metastasis of iliac vessels, imaging evaluation had a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 0.250, 0.808, 0.173 and 0.871, respectively. For predicting metastasis to PALN, imaging evaluation had a sensitivity, specificity, PPV and NPV of 0.579, 0.964, 0.440 and 0.979, respectively.
TABLE 2  Univariate analysis of risk factors for metastasis to lymph nodes in cervical cancer

|                      | General LN | Pelvic LN | Common iliac LN | Para-aortic LN |
|----------------------|------------|-----------|-----------------|----------------|
|                      | OR (95% CI)| P         | OR (95% CI)     | P              |
| Conization           |            |           |                 |                |
| No                   | 0.036      | 0.047     | 0.510           | 0.967          |
| Yes                  | 0.4 (0.2–0.9) | 0.4 (0.2–1.0) | 1.5 (0.4–4.9) | 1.0 (0.3–3.0) |
| Differentiation      |            |           |                 |                |
| G1                   | Reference  | Reference | Reference       | Reference       |
| G2                   | 2.4 (1.3–4.5) | 0.005     | 2.6 (1.4–4.8)   | 0.003           |
| G3                   | 1.8 (0.8–4.2) | 0.186     | 1.6 (0.7–4.0)   | 0.273           |
| Invasion depth of stroma | 0.012 | 0.019 | 0.068 | 0.030 |
| <1/3                 | Reference  | Reference | Reference       | Reference       |
| >1/3 but <2/3        | 1.8 (0.8–3.7) | 0.121     | 1.6 (0.8–3.7)   | 0.179           |
| >2/3                 | 2.8 (1.4–5.6) | 0.003     | 2.7 (1.3–5.3)   | 0.005           |
| Parametrial involvement | <0.001    | <0.001    | 0.022           | 0.001          |
| No                   | Reference  | Reference | Reference       | Reference       |
| Yes                  | 5.1 (2.1–12.1) | 5.3 (2.2–12.8) | 4.8 (1.2–18.6) | 6.9 (2.2–21.2) |
| Positive pelvic LN   |            |           |                 |                |
| No                   | Reference  | Reference | Reference       | Reference       |
| Yes                  | 108.3 (13.8–849.1) | 170.3 (22.1–1312.1) | 106.4 (28.0–404.1) |<0.001 |
| Positive common iliac LN |          |           |                 |                |
| No                   | Reference  | Reference | Reference       | Reference       |
| Yes                  | Reference  | Reference | Reference       | Reference       |

95% CI, 95% confidence interval; LN, lymph node; OR, odds ratio.

*Pelvic LNs indicate lymph nodes of external and internal iliac vessels and obturator but no lymph nodes of common iliac vessels.

TABLE 3  Univariate analysis of metastasis of lymph nodes on the survival outcomes

| Sites of LN | PFS HR (95% CI) | P | OS HR (95% CI) | P |
|-------------|-----------------|---|----------------|---|
| General     | Reference       |   | Reference       |   |
| Negative    | 2.5 (1.4–4.3)   | 0.001 | 3.6 (1.8–7.1) | <0.001 |
| Positive    | 2.5 (1.5–4.4)   | 0.001 | 3.7 (1.8–7.2) | <0.001 |
| External/internal iliac vessels and obturator | Reference |   | Reference       |   |
| Negative    | 2.5 (1.5–4.4)   | <0.001 | Reference       | <0.001 |
| Positive    | 6.2 (2.8–13.6)  | <0.001 | 7.9 (3.0–20.5) | <0.001 |
| Common iliac vessels | Reference |   | Reference       |   |
| Negative    | 4.1 (2.0–8.4)   | <0.001 | Reference       | <0.001 |
| Positive    | 5.1 (2.1–12.2)  | <0.001 | Reference       | <0.001 |

95% CI, 95% confidence interval; HR, hazard ratio; LN, lymph node; OS, overall survival; PFS, progression-free survival.

4 | DISCUSSION

Lymphatic metastasis is the most important risk factor of survival outcome in cervical cancer, which could make the recurrence increase to 25–30%. The incidence of PLN metastasis in cervical cancer patients staged IA2–IB2 ranges from 3.7% to 21.7%, and could be 30% higher than PALN metastasis. Berman et al. reported the relativity between PALN and advanced stage, with incidence of PALN metastasis of 5% for stage IB, 16% for stage II and 25% for stage III. RH with pelvic lymphadenectomy is the standard surgical treatment for young women with early-stage cervical cancer. In this retrospective study, we provided detailed relationship with lymphatic metastasis and other clinico pathologic factors and survival outcomes in a large cohort of patients with relative uniform surgical principles and extension. Previous studies suggested the low 5-year OS or 5-year PFS in patients with PLN metastasis or PALN metastasis. In our study, general
or site-specific LN metastasis all had significant impact on survival outcomes as well, even adjusted by various clinico pathologic factors, further specifying the significance of lymphatic metastasis, systematic lymphadenectomy and related presurgical imaging evaluation. Further, we revealed that adjuvant therapy had no potential impact on the survival outcomes. The possible reasons included the wide application of adjuvant therapy (244 of 406 patients, 60.1%) in the study cohort and the limited size of patients. Despite of numerous reports guaranteeing the safety and effectiveness profile about NAC, evidences from randomized controlled trials and meta-analysis suggested NAC had no improvement in the survival outcomes of locally advanced cervical cancer. A rigorous prospective study of adjuvant treatment is needed to specify the influence on the survival outcomes of the patients with lymphatic metastasis and other high-risk factors.

Few reports explored the predictive factors of LN metastasis. For cervical cancer of IA–IIB, invasion depth of stroma and involvement of parametrium may be independent risk factors associated with lymphatic metastasis in multivariate analysis. The PALN metastasis was considered to be correlated with PLN metastasis, whereas the rate of skip metastasis was lower than 4% in most of previous studies, and negative common iliac LN may indicate a relative low risk of PALN metastasis. However, the status of general LN was only related to the status of parametrium, whereas positive parametrium is a just mis-judgment of clinical stage. Although positive common iliac LN strongly suggested the status of PALN, it is worth noting that negative common iliac LN did not necessarily guarantee negative PALN. In our study, there was one isolated metastasis in common iliac vessels LN and PALN separately. Therefore, based on above discussion and data, complete and systematic lymphadenectomy of PLN and PALN should be an integrated part of RH for cervical cancer of IB.

So far, locating lymphatic metastases in patients with cervical cancer is still based on imaging technology, which determines possible metastases mainly according to the size of the LN, thus have a high diagnostic accuracy for evaluating enlarged LN, but a poor accuracy for regular-sized LN. Although the application of laparoscopic lymphadenectomy and sentinel LN biopsy was discussed in some studies, Lee et al. evaluated the value of para-aortic lymphadenectomy before further treatment in 2015, and these authors found results from nodal staging surgery of the patients using PET/CT, which showed that no PALN metastasis before definite chemoradiotherapy could be cost effective. Scans using CT, MRI and PET are routinely used in presurgical examinations. But the discussion about the most useful imaging method for detecting lymphatic metastasis has not reached a consensus. There has been a study reporting that for LN of a certain size, CT could achieve a specificity higher than 90% and a sensitivity ranges from 45% to 80%; FDG-PET has a higher sensitivity and is able to detect different kinds of distant metastases including PALN metastasis. Choi et al. described PET/CT as the most advantageous method in presurgical assessment of cervical cancer in a meta-analysis. However, it still has a false-negative rate of 12%. In general, the sensitivity and specificity of imaging methods are not entirely satisfactory, which could also be recognized in our study, due to lots of factors resulting in the enlargement of LN, and 10–15% patients whose image shows no lymphatic metastasis might be proved to have LN metastasis in a pathological analysis.

The main limitations of our study consist of recall bias and selection bias as a retrospective study. Lack of consistent criterion of pathologic examinations and imaging evaluation were the most important confounding factors in our study. The limited sample size of positive common iliac LN and PALN restricted extrapolation of related conclusions.

### 5 | CONCLUSION

Lymphatic metastasis was significantly related to the clinico pathologic characters and survival of cervical cancer. Preoperative imaging evaluation had low sensitivity but high specificity for predicting LN metastasis. Various imaging methods, such as CT, MRI and PET-CT, had similar accuracy of prediction for lymphatic metastasis.

### CONFLICT OF INTEREST

All the authors have no conflicts of interest to declare.

### ORCID

Lei Li http://orcid.org/0000-0001-8723-3461

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