

Prognostic significance of the number of metastatic lymph nodes in early cervical cancer: a retrospective study

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Summary

Purpose of Investigation: To determine the significance of positive pelvic lymph node (PLN) metastasis for progression-free survival (PFS) and overall survival (OS) of patients with early cervical cancer alone and in combination with known poor prognostic factors. **Materials and Methods:** This study was a retrospective analysis of 245 patients with Stage IA-IIA cervical cancer with radical hysterectomy from 1998-2014. Age, FIGO (*International Federation of Gynecology and Obstetrics*) Stage, histologic type, tumor size, stromal invasion depth, PLN metastasis, metastatic PLN numbers, lymphovascular space invasion (LVSI), parametrial invasion, and vaginal resection margin status were collected. PFS and OS were evaluated in accordance with each parameter. **Results:** Tumor size, LVSI, and metastatic PLN numbers were independently associated with PFS. The metastatic PLN number was associated with both PFS and OS and was an important factor for poor prognosis. **Conclusion:** These findings may contribute to PFS and OS assessment and treatment modality decisions.

Key words: Uterine cervical neoplasms; Prognosis; Radical hysterectomy; Metastatic lymph nodes; Lymph node status.

Introduction

Cervical cancer is the second most common cancer in women worldwide [1, 2]. Due to the advent of the cervical cancer screening system, the majority of patients are diagnosed at early stages [3]. Patients with early cervical cancer usually undergo a radical hysterectomy and pelvic lymph node (PLN) dissection with or without adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) depending on their prognostic risks to prevent tumor recurrence [4-6]. However, despite early detection and intervention, the recurrence risk after surgery for Stages I and II is 15-30% [7, 8]. Therefore, evaluating risk factors for recurrence is important to determine a more appropriate treatment plan for each patient.

Various studies have been conducted to evaluate individual risk factors for prediction of a poor prognosis. The tumor size, depth of cervical stromal invasion, presence of lymphovascular space invasion (LVSI), PLN metastasis, parametrial involvement, histological type, and positive surgical resection margins have been reported to have significance for prognostic predictions [4, 8-12]. Assuming that these risk factors are correlated, several investigators have also proposed various prognostic scoring systems by grouping poor prognostic risk factors using multivariate analysis. Kamura *et al.* categorized patients into three groups based on the presence of risk factors, namely PLN metastasis, the histological type, and the tumor diameter [11]. Sevin *et al.* proposed a prognostic scoring system based on the depth of invasion, LVSI, PLN metastasis, and age [4]. Additionally, some investigators developed a

nomogram to predict the individual recurrence risk in patients with early cervical cancer who undergo surgery. This nomogram includes four prognostic factors from multivariate analyses: the FIGO Stage, depth of invasion, parametrial involvement, and number of positive lymph nodes [13].

Studies have evaluated the clinical significance of the number of positive lymph nodes. Sakuragi *et al.* reported that the prognosis of patients with only one positive lymph node was not significantly different from that of node-negative patients; however, the five-year survival rates of patients with one or two or more positive lymph nodes were 84.9% and 26.5%, respectively [14]. In contrast, Ditto *et al.* reported that even one metastatic lymph node had a negative effect on progression-free survival (PFS) and overall survival (OS) [15]. Although lymph node metastasis is known to be an important prognostic factor for patients with early cervical carcinoma, the relationship between the number of positive lymph nodes and the prognosis of early cervical cancer remains controversial.

This study aimed to investigate the relationship between the number of positive lymph nodes and PFS and OS in patients with early cervical cancer. The authors also evaluated the ability of other factors known to be associated with a poor prognosis in early cervical cancer to predict disease prognosis.

Materials and Methods

A total of 255 patients diagnosed with Stage IA-IIA cervical cancer from 1998-2014 were enrolled in this study. Institutional Review Board approval was obtained. Data for

Table 1. — Patient characteristics.

| Characteristics | Number of cases | |
|---------------------------------|-----------------|-----------|
| | n = 245 | % |
| Stage | IA1-IA2 | 26 10.61 |
| | IB1-IB2 | 193 78.78 |
| | IIA-IIA2 | 26 10.61 |
| Size | ≤ 2 | 103 42.04 |
| | 2-4 | 95 38.78 |
| | > 4 | 47 19.18 |
| Size | 0-4 | 198 80.82 |
| | > 4 | 47 19.18 |
| Stromal invasion | < 1/3 | 105 42.86 |
| | ≥ 1/3 - < 2/3 | 66 26.94 |
| | ≥ 2/3 | 74 30.2 |
| Pelvic lymph node metastasis | Negative | 206 84.08 |
| | Positive | 39 15.92 |
| Number of lymph node metastasis | 0 | 206 84.08 |
| | 1 | 15 6.12 |
| | ≥ 2 | 24 9.8 |
| Number of lymph node metastasis | 0 | 206 84.1 |
| | 1 and ≥ 2 | 39 15.9 |
| Number of lymph node metastasis | 0 and 1 | 221 90.2 |
| | ≥ 2 | 24 9.8 |
| Number of lymph node metastasis | Negative | 142 57.96 |
| | Positive | 103 42.04 |
| Parametrial invasion | Negative | 217 88.57 |
| | Positive | 28 11.43 |
| Vaginal margin | Negative | 226 92.24 |
| | Positive | 19 7.76 |

each patient were retrospectively analyzed. Nine patients with insufficient pathologic results and one patient with co-existent lung cancer were excluded. Hence, the remaining 245 patients were included as the sample. All patients underwent a radical hysterectomy and either unilateral or bilateral salpingo-oophorectomy depending on their age and tumor stage. PLN dissection was performed when the nodes appeared suspicious for malignancy on radiologic evaluation or clinical examination. Adjuvant therapy was decided according to the patient's risk factors and physician's judgment. Patients with at least one of three high-risk factors (microscopic parametrial invasion, positive tumor resection margins, and positive PLNs) generally underwent adjuvant radiotherapy or platinum-based CCRT. Adjuvant radiotherapy alone was performed in patients who had at least two of three intermediate-risk factors [LVSI, stromal invasion of more than half of the cervix or one-third of the outer cervix, and a large tumor size (≥ 4 cm)].

After surgery, all specimens were reviewed by pathologists at our institution. Data were collected for the following parameters: age, FIGO Stage, histologic type, tumor size, depth of stromal invasion, PLN metastasis, number of metastatic PLNs, LVSI, parametrial invasion, vaginal resection margin status, type of adjuvant therapy, and date of

death or last follow-up. PFS was defined as the period from initial treatment to recurrence of cervical cancer, whereas OS was the period from initial treatment to the last follow-up or death due to cervical cancer.

The authors used the Kaplan-Meier method to assess OS and PFS and Cox proportional hazards regression to determine the univariate and multivariate hazard ratios for PFS and OS. All prognostic parameters that were determined to be significant in the univariate analysis were included in the multivariate analysis. A result was defined as significant when the p -value was < 0.05 . The data analysis was performed using the SPSS software, version 18.0.

Results

The clinicopathological characteristics of the 245 patients are summarized in Table 1. Among them, 26 patients had clinical Stage IA, 193 had Stage IB, and 26 had Stage IIA disease. The tumor size was ≤ 2 cm in 103 patients, 2-4 cm in 95 patients, and > 4 cm in 47 patients. A total of 105 patients had a $< 1/3$ stromal invasion depth, 66 had between $1/3$ and $2/3$, and 74 had $\geq 2/3$. Of the 245 patients, 39 had PLN metastasis (15 had one metastatic PLN, and 24 had more than two metastatic PLNs). Furthermore, 103 patients had LVSI, 28 had parametrial invasion, and 19 had positive resection margins.

The univariate analysis of prognostic factors for early cervical cancer is shown in Table 2. The tumor stage, tumor size, stromal invasion, number of metastatic PLNs, and LVSI were significantly associated with both PFS and OS. PLN metastasis was significantly associated only with OS ($p = 0.0215$). The number of metastatic PLNs was significantly associated with both PFS and OS in patients with zero or one metastatic PLN and in those with two or more metastatic PLNs ($p = 0.0378$ and 0.0007 , respectively).

The multivariate analysis of prognostic factors for early cervical cancer is presented in Table 3. The tumor size ($p = 0.0198$), number of metastatic PLNs ($p = 0.0005$), and LVSI ($p = 0.0429$) were significantly associated with PFS, whereas the number of metastatic PLNs ($p = 0.0044$) and stromal invasion ($p = 0.0427$) were significantly associated with OS. Notably, the presence of PLN metastasis was not significantly associated with either PFS or OS; however, when the number of metastatic PLNs was specified, a significant association with both PFS and OS was identified.

Discussion

The FIGO staging system has been used to assess the prognosis of cervical cancer and suggest treatment options for each stage. However, numerous studies have shown that clinical FIGO staging can lead to understaging for up to 20% early cervical cancer cases [16, 17]. Moreover, because of differences in clinicopathological characteristics among patients, prediction of accurate recurrence and survival rates is challenging. Therefore, a FIGO staging-dependent treatment could result in over- or undertreatment of patients. Several studies have investigated risk factors to

predict the prognosis of cervical cancer more accurately. These factors include the depth of the cervical stroma, tumor size, presence of LVSI, PLN metastasis, parametrial involvement, histological type, and positive surgical resection margins [4, 8-12]. In this study, risk factors including the tumor size, number of metastatic PLNs, and LVSI showed a significant association with PFS, whereas stromal invasion and the number of metastatic PLNs were significantly associated with OS in the multivariate analysis.

Lymphatic channel dissemination is a common mechanism of cervical cancer spread [18]. When lymph node metastases are present, the five-year survival rate declines from 85% to 50% [19]. Thus, the prognosis becomes worse when the number of positive lymph nodes increases [20, 21]. This finding was consistent with the present finding that the number of metastatic PLNs was positively correlated with both PFS and OS in the multivariate analysis. Additionally, in the univariate analysis, patients with two or more metastatic PLNs had poorer PFS ($p = 0.0378$) and OS ($p = 0.0007$) than patients with zero or one metastatic PLN. This result implies that cervical cancer with only one metastatic PLN is still a localized disease, whereas two or more positive PLNs may indicate systemic spread. Multiple lymph node metastasis demands postoperative adjuvant CCRT. Radiation targets the intrapelvic tumor, whereas cytotoxic agents eliminate micrometastasis and tumors outside the field of radiation. Furthermore, chemotherapy works as a radiosensitizer that improves the outcome of radiotherapy and reduces the risk of exposing normal tissues to radiation. Several studies found similar outcomes with adjuvant CCRT, with a year- year PFS rate of 70-80% and a five-year OS rate of 80-85% [22-24].

The strength of this study was that the patients were from a single institution and underwent a standardized treatment protocol. A limitation of this study was that the authors could not control the number of dissected PLNs, which was easily influenced by the accuracy of the pathologic test and the surgical technique. This sample had varying numbers of dissected PLNs, with a range from 3 to 23. Therefore, the concept of lymph node density (LND), which is the ratio of metastatic lymph nodes to the number of positive lymph nodes, has emerged. Polterauer *et al.* reported a strong association between the LND and both PFS and OS [25]. They reported that the OS of patients with a LND $\leq 10\%$ was comparable to that of patients without lymph node involvement and concluded that a LND $> 10\%$ indicated a poor prognosis.

Conclusion

In conclusion, the authors found that the tumor size, presence of LVSI, and number of metastatic PLNs were independently associated with recurrence of early cervical cancer after surgical treatment. In particular, the number of metastatic PLNs in early cervical cancer was significantly associated with both PFS and OS. These findings can help with assessment of PFS and OS and contribute to decision-

making regarding the treatment modality for each patient. Future prospective studies are required to validate and expand our findings.

Author contribution

All authors contributed to the manuscript at all stages including design, planning, data abstraction, and manuscript writing.

Ethics approval and consent to participate

The protocol was approved by the Ethics committee of DAUHIRB (approval number: TEMP-20-121).

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Conflict of interest

We have no conflicts of interest to declare.

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