

Original Article

Distribution of pelvic lymph nodes as well as preoperative and surgical pathologic factors associated with nodal metastases in women with cervical cancer

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Abstract: We sought to evaluate the distribution pattern of lymph node (LN) metastasis and to identify preoperative and surgical pathologic factors, which predict positive lymph nodes in patients with cervical carcinoma treated with radical hysterectomy and lymph node dissection (RHND). 365 patients with cervical carcinoma treated by RHND at a single cancer center from 1995 to 2005 were included. 87 patients were found to be with positive lymph nodes. Univariate analysis showed factors impacting node metastasis were FIGO stage, histological type, serum level of squamous cell carcinoma antigen (SCC-Ag) before treatment, preoperative radiotherapy, invasive depth of vaginal portion of the cervix and cervical canal. In a multivariate analysis, FIGO stage, SCC-Ag and the invasive depth of cervical canal were the stronger predictors of positive pelvic lymph nodes. In receiver-operating characteristics (ROC) curves analysis, the "best" cutoff of SCC-Ag was 2.85 ng/mL. The 5-year survival time of patients with positive lymph node was relatively shorter compared with the negative ones (94±1% vs. 67±5%, *P*-value <0.001). Patients with lymph node (including abdominal aorta or common iliac lymph node metastasis) group had poorer prognosis compared with pelvic lymph node (excluding common iliac lymph node metastasis) group (61±16% vs. 69±6% *P*<0.001). For patients with cervical carcinoma treated with RHND, FIGO stage, SCC-Ag and the invasive depth of cervical canal emerged to be the most significant predictors of positive lymph nodes. The "best" cutoff of SCC-Ag was 2.85 ng/mL and its real value needs further study.

Keywords: Cervical carcinoma, prognostic factors, SCC-Ag, lymph nodes, survival analysis

Introduction

Lymph node metastasis is one of the most important prognostic factors in patients with cervical cancer [1]. Pelvic lymphadenectomy should be done systematically at the time of radical hysterectomy. The current International Federation of Gynecology and Obstetrics (FIGO) [2] staging system for cervical cancer does not take into account pelvic LN status, which is the key to determine the prognosis and treatment of cervical cancer. Identifying the distribution of lymph node metastasis and its survival prognosis so as to establish appropriate management is particularly important [3]. Meanwhile, it is of great necessity to predict lymph node metastasis of cervical cancer

with analysis of the association between tumor markers, pathologic factors, clinical risk factors and lymph node metastasis.

Women at low risk of lymph node metastasis might be eligible for conservative therapy, including radical trachelectomy, and women at high risk might require more extensive lymph node evaluation at the time of radical hysterectomy to determine whether adjuvant treatment is needed.

Therefore, the purpose of this study was to report the distribution and status of pelvic lymph nodes and to identify whether preoperative and surgical pathologic factors were correlated with positive pelvic lymph nodes and sur-

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Table 1. Distribution of lymph node metastases of cervical carcinoma

Location	Left side	Right side	Total (cases, %)
Common iliac	9	10	19 (10.16%)
Internal iliac	12	13	25 (13.37%)
External iliac	14	16	30 (16.04%)
obturator	24	29	53 (28.34%)
Obturator fossae	21	34	55 (29.41%)
Deep inguinal	2	3	5 (2.67%)
Total	82	105	187 (100%)

vival prognosis in patients with cervical carcinoma treated with RHND. Therefore, we could establish a better mode of predicting the risk of lymph node involvement.

Materials and methods

365 consecutive patients with FIGO stages (Ia2-IIb) cervical cancer were determined from the Cancer Center of Sun Yat-sen University during Nov 1995 and Dec 2000. All Patients had been treated by RHND with a median average follow-up time of 92 months (range, 2-149 months). The surgical technique of RHND was consistent with a Class-III extended hysterectomy as described by Piver (3). 319 patients (the data of 46 cases were missing) were tested by SCC-Ag routinely with a microparticle enzyme-immunoassay system before primary treatment. And among those patients with bulky tumors, 205 received preoperative intravaginal brachytherapy, 31 with cisplatin-based neoadjuvant chemotherapy and 29 with the methods combined.

All patients were classified based on the definition of clinical staging system by the International Federation of Gynecology and Obstetrics (FIGO) in 1989, whereas our histological classification was performed according to the World Health Organization. Histopathological findings were retrieved from the files of the patients: tumor size (<4 cm or ≥4 cm), FIGO stage, SCC-Ag before treatment, histological type (squamous cell carcinoma or other histological types including adenosquamous carcinoma, adenocarcinoma and clear cell carcinoma), grade (G1 or G2 or G3), invasive depth of vaginal portion of the cervix and cervical canal, preoperative chemotherapy, preoperative radiotherapy, and status of pelvic lymph nodes.

Continuous variables are reported as the “mean ± SD”, or the median and first and third quartile, while categorical variables were described using proportions. Group differences were determined with t-tests, or the Chi squared test. The follow-up intervals were calculated in months and defined as the time between the date of diagnosis and date of the event (death, recurrence) or last follow-up. Kaplan-Meier survival Curves were performed, and the log-rank test was employed to test the difference between groups. All statistical analysis was performed with the aid of SPSS 16.0 software.

Results

365 patients were examined for LN status. The mean age of these patients was 42 (19-75) years. 87 (23.84%) patients were found to be with at least one positive pelvic lymph node. Distribution of lymph node metastases of cervical carcinoma is shown in **Table 1**. The metastasis rate of the obturator and the obturator fossa (57.75%) is the highest, followed by external iliac (16.04%), and internal iliac lymph nodes (13.37%). And the lymph node metastasis of 49 patients (56.32%) was limited to one site, including obturator (18), obturator fossa (18), external iliac (6), internal iliac (4), common iliac (2), and deep inguinal (1). There were 36 cases (73.47%) of a single group of lymph node metastasis in obturator or obturator fossa and 38 cases (43.68%) with the existence of multiple lymph node metastasis, among which 33 cases were with the lymphatic drainage along the way: the obturator or the obturator fossae→internal iliac→external iliac→common iliac lymph node metastasis; 1 case with all lymph nodes metastasis except for the left deep inguinal; 1 case with the lymph node metastases to both common iliac directly; and 2 cases from obturator fossa to deep inguinal lymph node. Chi-square test shows that Lymph node involvement was significantly associated with survival time, as is shown in **Figure 1**.

Table 2 shows the findings from univariate analysis that the FIGO stage (P=0.026), SCC-Ag before treatment (P<0.001), histological type (P=0.006), preoperative radiotherapy (P=0.044), invasive depth of vaginal portion of the cervix (P=0.006) and cervical canal (P<0.001) were significant predictors of positive lymph nodes. Univariate analysis failed to demon-

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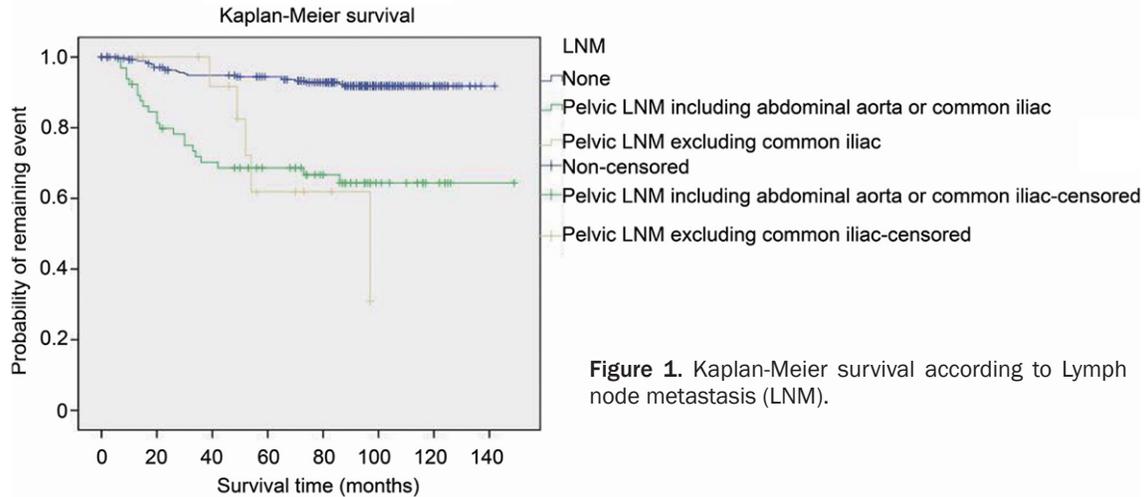


Figure 1. Kaplan-Meier survival according to Lymph node metastasis (LNM).

Table 2. The risk factors of pelvic lymph node metastasis of cervical carcinoma in univariable and in multivariate logistical analysis

Location	Left side	Right side	Total (cases, %)
Common iliac	9	10	19 (10.16%)
Internal iliac	12	13	25 (13.37%)
External iliac	14	16	30 (16.04%)
obturator	24	29	53 (28.34%)
Obturator fossae	21	34	55 (29.41%)
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Total	82	105	187 (100%)

strate that tumor size, differentiation, preoperative chemotherapy were significant predictors of positive pelvic lymph nodes. In a multivariate analysis with use of backward logistic regression analysis, FIGO ($P=0.043$), SCC-Ag ($P=0.04$), penetration $\geq 50\%$ of thickness of cervical canal ($P=0.003$) were significantly associated with prediction of positive pelvic lymph nodes.

Figure 1 shows that lymph node metastasis was more significantly associated with 5-year survival time compared with node-negative patients ($67\pm 5\%$ vs. $94\pm 1\%$, $P<0.001$); patients with lymph node metastasis including abdominal aorta or common iliac lymph node had poorer prognosis compared with metastasis excluding common iliac lymph node metastasis ($61\pm 16\%$ vs. $69\pm 6\%$, $P<0.001$).

Figure 2 shows the findings from receiver-operating characteristics (ROC) curves in 319 patients

(The data of 46 patients are unknown). Patients with positive LN had significantly higher levels of SCC-Ag before treatment than patients with negative LN (5.53 ± 8.38 $\mu\text{g/L}$ vs. 2.59 ± 4.89 $\mu\text{g/L}$, $P<0.001$). In this study, the “best” cutoff of SCC-Ag was 2.85 ng/mL, Chi-square test analysis showed that there was higher lymph node involvement when $\text{SCC-Ag}>2.85$ $\mu\text{g/L}$ (42.3% vs. 17.5% $P<0.001$). And the SCC-Ag values of 2.85 $\mu\text{g/L}$, 4 $\mu\text{g/L}$ and 8.6 $\mu\text{g/L}$ corresponded to a specificity of 81.5%, 86.83% and 92.18%, a sensitivity of 47.4%, 36.83% and 19.74% for judging the lymph node involvement respectively.

Discussion

Cervical cancer is the third most common female-related cancer worldwide [4]. Lymph node status is the most important prognostic factor and major determinant of treatment in patients with early cervical cancer [5]. The purpose of this study was to evaluate the distribution pattern of lymph node metastasis (LNM) and to identify preoperative and surgical pathologic factors, which may help to predict positive lymph nodes in patients.

Among 365 patients, 87 (23.84%) were found with positive pelvic lymph nodes. The obturator and obturator fossa was most frequently involved, with a rate of 57.75%, followed by external iliac (16.04%), and internal iliac lymph nodes (13.37%). Previous studies have demonstrated that the obturator node group is the most common site of pelvic nodal metastasis [6]. Zhang et al [7] divided the pelvic lymph

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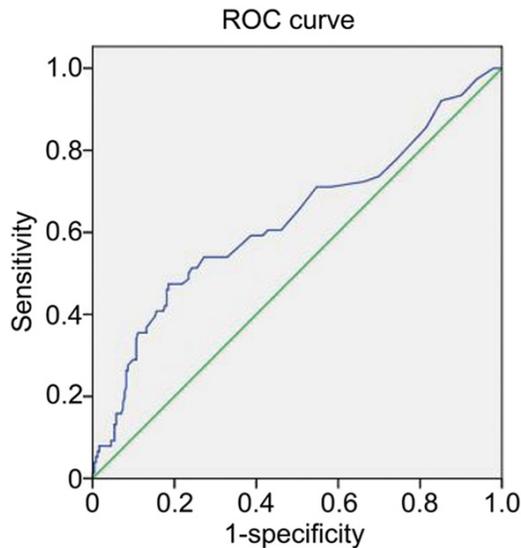


Figure 2. Receiver-operating characteristic (ROC) curves for SCC-Ag comparing data obtained from patients with negative or positive LN in the total population. The area under the curve is 0.630 (standard error 0.040), p -value =0.001. The “best” cutoff point corresponds to a SCC-Ag level of 2.85 ng/mL (LR=2.56).

nodes into three levels: The level-I lymph nodes consist of parametrial and obturator lymph nodes; Internal and external iliac lymph nodes can be considered as level-II lymph nodes, and the common iliac and inguinal lymph nodes as level-III nodes. Similarly, we observed the three levels above in those patients of multiple lymph node metastasis. We concluded 49 cases (56.32%) of one-site lymph node metastasis, and 8 cases (43.68%) of multiple lymph node metastasis.

According to the literature [8, 9], the incidence of pelvic lymph node metastasis in stage Ib cervical cancer ranged from 11.5% to 21.7% in patients who have had a surgical resection. For stage IIa and IIb cervical cancers, the incidence ranged from 10% to 26.7% and 28.6% to 43.4%, respectively. We found that positive pelvic lymph nodes were 17.57% for 148 stage Ia2-Ib1 patients, 24.39% for 41 stage Ib2 patients, and 28.97% for 176 stage IIa-IIb. As in **Table 2** and **Figure 1**, FIGO stage was a significant predictor of positive lymph nodes, which was in coincidence with the recent lit [10].

To predict the risk factors of lymph node metastasis, the preoperative factors contribute to determine the preferred primary treatment

modality for patients. Lukaszuk K et al [11] reported that lymph node metastasis was related to the volume of primary lesion, depth of cervical and vaginal invasion, and with invasion of the corpus. Other studies showed that lymph node metastasis is also related to various histopathological factors, including tumor size [12], deep cervical stromal invasion [13], parametrial involvement [14] and LVS [15]. In this study, we provided the invasive depth of vaginal portion of the cervix or cervical canal information in pathological results routinely. In multivariate analysis, we found that FIGO SCC-Ag, penetration of cervical canal were significantly associated with predicting of positive pelvic lymph nodes.

Approximately 80% of this series of cervical cancer cases were SCC carcinomas. And serum SCC-Ag is one of the most common tumor markers for clinical monitoring of SCC cervical cancer. This finding might be partly explained by previous reports [16]. By means of univariate analysis and multivariate analysis in our study, SCC-Ag was significantly associated with nodal metastasis. However the overall clinical performance of the marker to predict LN involvement was poor. The presence of SCC-Ag values of 2.85 μ g/L, 4 μ g/L and 8.6 μ g/L corresponded to a specificity of 81.5%, 86.83% and 92.18%, a sensitivity of 47.4%, 36.83% and 19.74% for judging the lymph node involvement respectively. It was clear that there was higher lymph node involvement when SCC-Ag >2.85 μ g/L ($P < 0.001$). Van de Lande et al [17] demonstrated that SCC-Ag (>1.65 ng/mL) can predict LN metastases more accurately in stage Ib1 than in stage Ib2+IIa. Because of smaller tumors in stage Ib1, an elevated marker is more likely to reflect the presence of LN metastases in it than in higher stages. In conclusion, the value of “best” cutoff of SCC-Ag needs further study.

Although a wide variety of independent prognostic indicators in cervical cancer had been discussed previously, results have been inconclusive. Currently, more consistent opinion is that the lymph node is an important prognostic factor. D. Denschlag et al [18] reported that the 5-year overall survival rates for all cervical cancer with lymph node involvement was 64%, which was similar to our study results (67%), Long Huang et al [19] reported that there were significant differences in the 5-year overall sur-

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vival rates of patients with pelvic lymph node metastasis (excluding common iliac lymph node metastasis) and common iliac lymph node metastasis (67.5% vs. 46.1%, $P=0.029$). In this study, the 5-year overall survival rates in lymph node (including abdominal aorta or common iliac lymph node metastasis) group had poorer prognosis compared with patients with pelvic lymph node (excluding common iliac lymph node metastasis) group (61% vs. 69% $P<0.001$).

In conclusion, for patients with cervical carcinoma treated with RHND, 23.84% of them were encountered with positive pelvic lymph nodes. Lymph node metastasis is an important prognostic factor for survival. By means of univariate and multivariate analyses, we have demonstrated that FIGO, SCC-Ag, invasive depth of cervical canal emerged to be the most significant predictors of positive lymph nodes. The "best" cutoff of SCC-Ag was 2.85 ng/mL and its real value needs further study.

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Disclosure of conflict of interest

None.

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