Analysis of Lymph Node Metastasis and Risk Factors in 975 Patients with FIGO 2009 Stage IA-IVA Cervical Cancer

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Abstract

Objective

To summarize the lymph node metastasis (LNM) rate of patients with stage IIA-IIA cervical cancer, and further analyze its distribution characteristics and related risk factors.

Methods

According to FIGO 2009, the clinical data of 975 patients with stage IIA-IIA cervical cancer treated in our hospital from January 2010 to December 2018 were retrospectively analyzed. The incidence and distribution of LNM were analyzed, and the influencing factors of cervical cancer LNM were analyzed by univariate and multivariate Logistic regression.

Results

In this study, the LNM rate was 14.8%(144/975), and a total of 20288 lymph nodes were removed, among which 359 lymph nodes had metastasis. According to the statistics of the number and frequency of metastatic lymph nodes in different regions, the metastatic rate was the highest in the parauterine/obturator regions. Univariate analysis showed that pregnancy > 3 times, tumor size > 4cm, gross type, FIGO stage, pathological type, positive lymphovascular space invasion (LVSI), deep cervical stromal invasion (outer 1/2 invasion), parametrial involvement and uterine corpus invasion (UCI) were all correlated with LNM ($P < 0.05$). Multivariate analysis showed tumor lesion >4cm (OR=2.253, 95%CI: 1.486-3.416, $P < 0.001$), positive LVSI (OR=5.353, 95%CI: 3.303-8.676, $P < 0.001$), deep cervical stromal invasion (OR=3.461, 95%CI: 2.106-5.688, $P < 0.001$) and deep UCI (myometrial invasion $\geq 50\%$) (OR=3.529, 95%CI: 1.321-9.427, $P = 0.012$) were independent risk factors for LNM.

Conclusion C

erivical cancer patients are more likely to have LNM if the tumor size > 4cm, positive LVSI, deep cervical stromal invasion and deep UCI. In clinical treatment, attention should be paid to the evaluation of LNM.

Introduction

Cervical cancer is the fourth most common cancer in women in the world [1, 2]. Lymph node metastasis (LNM) is the main way of cervical cancer metastasis, and also is an important factor affecting the prognosis of patients [3, 4]. The International Federation of Gynecology and Obstetrics (FIGO) 2018 new staging of cervical cancer have included LNM. Once LNM occurs, staging is IIIC [5]. The revised FIGO stage reflects the importance of LNM [6], and can better assess the risk of cervical cancer patients [7].

For early-stage cervical cancer, the main purpose of lymph node resection is to determine whether there is positive lymph node, and to provide a basis for postoperative supplementary therapy. In China, sentinel lymph node biopsy is not widely used, and most early-stage cervical cancer has undergone systematic lymph node resection, which leads to many cervical cancer patients without LNM to receive unnecessary surgery. Especially for early-stage low-

risk patients (tumor size < 2cm, no LVSI, depth of invasion < 10mm, no LNM indicated by imaging examination) [8], which leads to increased surgical risk and complications.

So which patients are more likely to have LNM? There are many studies about LNM of cervical cancer [9–14], but few studies on large samples. Since our hospital is a large obstetrics and gynecology hospital in China, many cervical cancer patients were admitted to our hospital. In this study, 975 patients with FIGO 2009 early-stage cervical cancer in our hospital were analyzed for LNM, so as to enhance the attention of preoperative evaluation of LNM and provide evidence for clinical treatment.

Material And Methods

Patients

The clinical data of cervical cancer patients admitted to Beijing Obstetrics and Gynecology Hospital affiliated to Capital Medical University/Beijing Maternal and Child Health Care Hospital from January 2010 to December 2018 were collected. Inclusion criteria were: (1) pathological diagnosis of cervical cancer, including squamous carcinoma, adenocarcinoma and adenosquamous carcinoma; (2) FIGO 2009 stage IA–IIA; (3) radical hysterectomy combined with pelvic lymphadenectomy and/or para-aortic lymphadenectomy; (4) complete clinical data. Exclusion criteria were: (1) cervical cancer of pregnancy; (2) cancer of the cervical stump; (3) special and rare types of cervical cancer; (4) presence of a cancer other than cervical cancer; (5) others do not meet inclusion criteria.

A total of 975 patients were included, ranging in age from 21 to 73 years, with an average age of (45.95±9.20) years; FIGO stage: IA 64 cases, IB 706 cases, IIA 205 cases; Histological types: 697 cases of squamous carcinoma, 136 cases of adenocarcinoma, 142 cases of adenosquamous carcinoma; Para-aortic lymph nodes were resected in 58 cases without metastasis.

The patients were divided into the positive group (the metastasis group, n = 144) and the negative group (the non-metastasis group, n = 831) based on the postoperative pathology examination.

Clinical data collection

Bilateral pelvic lymph nodes were divided into five regions: common iliac, external iliac, internal iliac, parauterine/obturator and deep inguinal (suprafemoral) lymph nodes. The number of metastatic lymph nodes in each region was counted and the proportion was calculated. Due to the different total number of lymph nodes in each region, the distribution was again calculated according to the frequency of occurrence of metastatic lymph nodes in each region. Then age, body mass index (BMI), menopausal status, number of pregnancies and births, prior surgical history, tumor size, FIGO stage, gross type (exophytic or endophytic tumor), histological type, differentiation, stromal invasion depth, lymphovascular space invasion (LVSI), uterine corpus invasion (UCI), parametrial involvement (PMI) and vaginal margin were analyzed to explore risk factors of cervical LNM. The difference in the clinical presentation of tumors is called the gross type. Tumors were classified according to the dominant morphology for clinical presentation. Ulcerative tumors and tumors with barrel-shaped morphology were referred to as endophytic tumors. Fungating tumors with or without small superficial ulcerations were referred to as exophytic tumors.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 software package (IBM Corp., Armonk, NY, USA). The data were expressed as median and range or mean with standard deviation where appropriate, and compared using the Mann -Whitney U test. The rates of LNM in the defined fields were shown as percentages. The risk factors for LNM were identified by univariate and multivariate logistic regression analysis. The level of significance was set at 0.05 in all tests.

Results

LNM and distribution characteristics

The incidence of LNM in this group was 14.8% (144/975). A total of 20288 lymph nodes were removed, ranging from 11 to 49 lymph nodes per case, with a median of 19 lymph nodes per case. The positive group was compared with the negative group, and the difference was not statistically significant (P=0.216). There were 359 metastatic lymph nodes, ranging from 1 to 14 per case, and the median number of metastatic lymph nodes was 2 per case.

According to the number of metastatic lymph nodes, the parauterine/obturator region accounted for the most (39.3%, 141/359), followed by external iliac (33.1%, 119/359), internal iliac (13.7%, 49/359), deep inguinal (7.2%, 26/359) and common iliac (6.7%, 24/359).

According to the number of LNM locations, the number of metastases in the parauterine/obturator region was also the largest (36.9%, 81/220), followed by external iliac (33.6%, 74/220), internal iliac (13.6%, 30/220), deep inguinal (9.1%, 20/220) and common iliac (6.8%, 15/220). The results of the two statistical methods are consistent. (Table 1)

Table1 The distribution of lymph node metastasis in the patients

Anatomical region	Lymph node metastasis	
	According to the number	According to occurrences
Total	359100%	220100%
common iliac	24(6.7)	15(6.8)
external iliac	119(33.1)	74(33.6)
internal iliac	49(13.7)	30(13.6)
parauterine/obturator	141(39.3)	81(36.9)
deep inguinal	26(7.2)	20(9.1)

Univariate analysis of the clinical pathological parameters

The potential clinicopathologic risk factors associated with lymphatic metastasis were investigated and analyzed. Univariate analysis showed that gravidity > 3 times, tumor size > 4cm, gross type, FIGO stage, pathological type, positive LVSI, deep cervical stromal invasion (outer 1/2 invasion), PMI and UCI were all influential factors for LNM. However, there were no statistically significant differences in age, BMI, menopause, parity times, previous surgical history, tissue differentiation and vaginal margin between the two groups. (Table 2)

Table2 Univariate analysis of risk factors for lymph node metastasis

Risk factors		Lymph node metastasis		χ^2	R
		negative(n=831)	positive(n=144)		
Age (years)	≤45	417(85.5)	71(14.5)	0.038	0.846
	≥45	414(85.0)	73(15.0)		
BMI (kg/m ²)	≤25	522(85.0)	92(15.0)	0.061	0.806
	≥25	309(85.6)	52(14.4)		
Menopausal	Premenopause	587(85.1)	103(14.9)	0.047	0.828
	Postmenopause	244(85.6)	41(14.4)		
Gravidity	≤3	558(83.5)	110(16.5)	4.858	0.028
	≥3	273(88.9)	34(11.1)		
Parity	≤2	731(85.1)	128(14.9)	0.100	0.752
	≥2	100(86.2)	16(13.8)		
Surgical history	No	430(86.7)	66(13.3)	1.716	0.190
	Yes	401(83.7)	78(16.3)		
Tumor size	≤4cm	636(88.2)	85(11.8)	19.525	P 0.001
	≥4cm	195(76.8)	59(23.2)		
Gross type	Exophytic	491(88.5)	64(11.5)	25.642	P 0.001
	Endophytic	272(77.9)	77(22.1)		
	Unknown	68(95.8)	3(4.2)		
Stage(FIGO2009)	IA	61(95.3)	3(4.7)	11.883	0.003
	IB	608(86.1)	98(13.9)		
	IIA	162(79.0)	43(21.0)		
Histologic grading	G1	27(100)	0(0)	5.346	0.069
	G2	625(85.3)	108(14.7)		
	G3	179(83.3)	36(16.7)		
Pathologic type	Squamous cell carcinomas	602(86.4)	95(13.6)	11.725	0.003
	Adenocarcinoma	121(89.0)	15(11.0)		
	adenosquamous carcinoma	108(76.1)	34(23.9)		
LVSI	Negative	511(95.3)	25(4.7)	96.567	P 0.001
	Positive	320(72.9)	119(27.1)		
Stromal invasion	Inner 1/2	487(95.3)	24(4.7)	86.543	P 0.001
	Outer 1/2	344(74.1)	120(25.9)		

Vaginal margin	Negative	821(85.3)	141(14.7)	0.208	0.648
	Positive	10(76.9)	3(23.1)		
PMI	Absent	812(86.2)	130(13.8)	18.540	□ 0.001
	Present	19(57.6)	14(42.4)		
UCI	No	765(87.3)	111(12.7)	30.933	□ 0.001
	Endometrial invasion	13(86.7)	2(13.3)		
	Myometrial invasion<50%	43(68.3)	20(31.7)		
	Myometrial invasion≥50%	10(47.6)	11(52.4)		

BMI = body mass index, LVSI = lymphovascular space involvement, PMI = parametrial invasion, UCI = uterine corpus invasion.

Multivariate logistic regression analysis of patients with LNM

To further confirm the identified risk factors, the multivariate logistic regression analysis were performed. LNM was only associated with tumor size ≥ 4cm, positive LVSI, cervical staomal outer 1/2 invasion, and deep UCI (myometrial invasion ≥50%). (Table 3)

Table3 Multivariate analysis of risk factors for lymph node metastasis

Variables	Comparison	OR	95%CI	P
Tumor size	≥4cm vs. ≤4cm	2.253	1.486-3.416	□0.001
LVSI	Positive vs. Negative	5.353	3.303-8.676	□0.001
Stromal invasion	Outer 1/2 vs. Inner 1/2	3.461	2.106-5.688	□0.001
UCI	Endometrial invasion vs. No	0.554	0.111-2.767	0.471
	Myometrial invasion<50% vs. No	1.821	0.976-3.398	0.060
	Myometrial invasion≥50% vs. No	3.529	1.321-9.427	0.012

CI = confidence interval, LVSI = lymphovascular space involvement, UCI = uterine corpus invasion.

Discussion

Main findings

Our data showed that the incidence of LNM in 975 cervical cancer patients was 14.8%, and the metastasis rates were 4.7% in stage IA, 13.9% in stage IB, and 21.0% in stage IIA. Although clinical stage is not an independent risk factor for LNM, it can be seen that the rate of LNM increases with the increase of clinical stage, and this result is consistent with previous reports [15, 16]. We further analyzed the partitions of metastatic lymph nodes, and the conclusions were consistent according to the number and frequency of metastatic lymph nodes. The results showed that the parauterine/obturator regions were the most easily affected anatomical partitions. Similar reports also remind us to pay attention to LNM excision of the parauterine and obturator regions[16, 17].

It can be seen that among the four independent risk factors, "positive LVSI" is the factor with the highest OR value (table 3), and similar reports have been reported in the past [18, 19]. Therefore, we should pay special attention to preoperative pathological with "LVSI positive", even if imaging examination did not suggest metastasis. Then we further analyzed the relationship between preoperative pathology and LNM, and found that among all patients (975), 416 cases were positive LVSI as indicated by preoperative pathology, while 107 cases were confirmed for LNM by postoperative pathology, accounting for 74.3% (107/144) of all LNM patients. In addition, it can be seen that 3 patients with stage IA had LNM (table 2). After careful review of clinical data, preoperative biopsy pathology showed positive LVSI in all 3 patients. It is suggested that attention should be paid to the "positive LVSI" result of preoperative biopsy, and systematic lymphadenectomy is required even in stage IA [20].

Deep inguinal lymph node resection is an independent risk factor for lymphedema of lower extremity [21]. The removal of deep inguinal lymph nodes has been controversial for a long time. In our study, there was a certain rate of deep inguinal LNM, and a total of 20 patients had deep inguinal LNM, among which 18 patients (18/20) were positive LVSI. Therefore, for people with independent risk factors, especially positive LVSI, systematic resection of lymph nodes, including deep inguinal lymph nodes, should be recommended.

In the past, we did not pay enough attention to UCI, and believe that it did not affect staging. In this study, 99 patients had UCI, and the LNM rate of patients with endometrial, myometrial invasion<50% and myometrial invasion $\geq$ 50% was 13.3%, 31.7% and 52.4% respectively. Among them, only uterine deep myometrial invasion was an independent risk factor affecting LNM. Therefore, we remind that great attention must be paid to UCI of cervical cancer, especially to the "depth of UCI". It is recommended to strengthen preoperative examination and evaluation for these patients, and complete lymph node resection may also be needed. In addition, studies have shown that LNM is also an independent risk factor for UCI[22], and uterine deep myometrial invasion is an independent risk factor for poor prognosis of cervical cancer patients[23, 24]. The presence of UCI should be considered as a poor prognostic factor in the diagnosis and treatment protocol, and systematic chemotherapy or prophylactic irradiation of the para-aortic lymph node region may be considered as an option due to its increased risk of para-aortic LNM [25].

In conclusion, it is recommended to strengthen the evaluation of LNM if there are risk factors such as tumor size>4cm, positive LVSI, deep cervical stromal invasion or deep UCI. Currently, imaging examinations, such as magnetic resonance imaging (MRI) or computed tomography (CT), are commonly used to assess LNM. But relevant articles show that diffusion weighted-MRI (DW-MRI) has the highest sensitivity and positron emission tomography-CT (PET-CT) has the highest specificity [15, 26–28]. Therefore, the intensity of preoperative imaging examination should be strengthened and attention should be paid to the treatment when the above risk factors occur, and it is suggested to consider systematic complete lymph node resection.

Limitations

Although some studies support that LNM is related to tissue differentiation [29], this study did not find this result. In addition, Li et al. [30] pointed out that endogenous type was an independent risk factor for PMI. Our study analyzed the relationship between LNM and gross type, and the results showed that the difference was statistically significant in univariate analysis, but it was not an independent risk factor. The reason may be related to the large span of FIGO stage in this study and the vague gross type of some early patients. Since this study is a single-center and retrospective study, it needs a multi-center, large-sample and prospective study to provide a more valuable reference for clinical practice.

Significance

In recent years, there have been many studies on sentinel lymph node[31-33], and relevant articles have pointed out that sentinel lymph node mapping has a good detection rate for early-stage cervical cancer tumors [34,35], but in early-stage cervical cancer, overall detection rate of sentinel lymph node mapping is elevated while bilateral detection rate is lower[36].

Therefore, according to the principle of individualized treatment, for early-stage cervical cancer without lymph node enlargement and metastasis in imaging examination, can it be classified as low-risk or high-risk according to the risk of LNM? Meanwhile, for early-stage cervical cancer, can systematic lymph node dissection be performed only in high-risk patients? Sentinel lymph node mapping in low-risk patients? In conclusion, for early-stage cervical cancer, attention should be paid to the evaluation of LNM, and it is urgent to form evaluation criteria and optimize evaluation methods as soon as possible.

Declarations

Author contributions LC is first author, LC designed the study and wrote the paper. WK supervised and revised the paper. JL, CH and TL conducted the analyse. LC, BJ and DS collected the data. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical approval The study used previously collected/existing clinical data and medical records; therefore, the need for informed consent was waived. The study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent revisions.

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