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Original Research

A survey of lymph node involvement under preoperative medical imaging in cervical cancer patients

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Abstract

Objective: To investigate the characteristics and distribution patterns of clinically metastatic nodes assessed by Computed Tomography (CT) in preoperative cervical cancer patients; to address the importance of obturator and/or inguinal lymph nodes as sentinel lymph nodes. **Methods**: A total of 217 patients with cervical carcinoma treated by lymph node dissection (LND) between 2009 and 2014 were included. All preoperative CT/MRI (Magnetic Resonance Imaging) imaging data of these patients were reviewed. The relationship of patient characteristics age, tumor stages, and corresponding lymph node metastasis status were analyzed. We put emphasis on the distribution pattern of positive lymph nodes from pre-operative imaging and compared the different frequencies of each regional and non-regional lymph node group respectively. The data of the 5-year survival rate from follow-up was taken into consideration too. SPSS 24.0 (IBM Corp., Chicago, IL, USA) was used for statistical analysis. **Results**: The overall lymph node metastasis (LNM) rate was 92.6% in 217 cases. When regional nodes were involved, obturator groups were concerned in 154 (76.6%). The inguinal group was involved in 146 (72.6%) in the area of non-regional lymph node. The 5-year survival rates of return visits were 92.6% and 82.1% in stage IB and IIA, respectively. Age distribution was not associated with the International Federation of Gynecology and Obstetrics (FIGO) stage as well as the incidence and patterns of nodal metastasis. **Conclusions**: obturator and inguinal groups play a decisive role in the metastases process of cervical cancer, and can be regarded as a candidate for sentinel lymph nodes.

Keywords: Cervical cancer; Lymph node metastasis; Sentinel lymph node

1. Introduction

The major way of tumor cellular migration in female reproductive cancer is widely considered as the lymphatic vessels [1–4], and sentinel lymph node (SLN) is the first involved lymph node of a cancerous organ [5]. However, on account of the complexity of pelvic lymphatic pathways and imprecise localization of SLNs, its application is still challenging in cervical cancer [5,6]. A correctly understanding of the distribution and invasive rules of the tumor in the process of cervical cancer can help us understand the incidence and patterns of lymph nodes metastasis (LNM) of the pelvic cavity [7].

The current treatments of women with early-stage cervical cancer are radical hysterectomy with/without bilateral and sometimes even systematic pelvic lymphadenectomy [8]. Recently, SLN biopsy has been introduced as a less invasive alternative to elective lymph node dissection (LND) for assessment of nodal metastasis, which has gained rapid acceptance. SLN mapping has been widely used in the diagnosis and treatment of breast cancer and other gynecological tumors [9–13]. However, due to the lack of available reference for lymph node drainage in pelvic cavity, adapting its use in pelvic malignant remains challenging. Moreover, if imaging examination can be used to diagnose pelvic LNM before surgery, excessive LND may not be required [14]. Thus, we conducted a retrospective study to preliminarily investigate the distribution pattern of LNM in cervical cancer and to identify the clinical value of the obturator and inguinal LN as SLNs by preoperative imaging.

2. Patients and methods

2.1 Patients

We retrospectively reviewed clinical data of 217 cases be diagnosed with cervical cancer and performed CT/MRI (Computed Tomography/Magnetic Resonance Imaging) scan in the Department of Obstetrics and Gynecology at West China Second University Hospital Affiliated to Sichuan University from 2009 to 2014. All included pa-

tients with cervical cancer (stage IA–IIIA) were treated with LND and discharged. Patients who could not give informed consent or did not perform contrast-enhanced CT scans were excluded. We recorded the patient's survival status after five years by checking the patient's last medical history or telephone follow-up. If a patient had died, the date of death was recorded.

2.2 Imaging data

All patients received a contrast-enhanced CT scan in the supine position with a Big-Bore CT (Philips, Brilliance6). Images were acquired from upper bound of T11 to the lower edge of ischial tuberosity, and the layer thickness was 5 mm, the matrix was set 512 × 512. Lymph nodes with the shortest axis >1 cm was defined as positive by CT/MRI examination in this study. Imaging results of all cases were estimated by at least two experienced radiologists, respectively.

2.3 Statistical analysis

We used descriptive statistical methods to describe the clinical characteristics of patients, and categorical data were presented in numbers and percentages. LNM patterns and patient characteristics were compared using chi-squared tests. All statistical analyses were performed by SPSS 24.0 (IBM Corp., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

3. Results

We identified a total of 217 cervical cancer patients with median age of 44 years (range: 17–68). In terms of age, 45.2% were aged 40–49 years, 26.7% were aged 30–39 years, 18.9% were aged 50–59 years, 5.1% were more than 60 years old and 4.1% were less than 30 years old. According to the staging criteria of FIGO, among all the patients, including 14 patients of stage IA, 123 patients of stage IB, 71 patients of stage IIA, 8 patients of stage IIB and one patient of stage IIIA, 201 (92.6%) patients have been observed as positive lymph nodes metastases (N1). We divided patients into five groups (grouped by 10 years of age) and analyzed the difference between patients' characteristics and LNM status (Table 1). Fisher's exact test was used for all comparisons between groups. No significant difference between the lymph nodes metastases with age were found ($p = 0.546$, Pearson chi-square 2.010), nor with FIGO stage ($p = 1.000$, Pearson chi-square 0.832). The details were listed in Table 1.

We compared the distribution of all FIGO stages in each age group (Table 2). However, not statistically significant between the FIGO stage and age were observed (all p values > 0.05).

We preliminarily analyze distribution of LNM presented in Fig. 1. The results showed that LNM of cervical cancer mostly occurs in the obturator region of the pelvic cavity (76.6%, 154/201). However, it is not confined to the pelvic cavity, and was detected in the distal lymph nodes, especially in the inguinal site at a high detection rate of 72.6% (146/201).

Table 1. Patient characteristics and analysis between patients with and without positive lymph node.

Characteristic		Value (%)	Lymph node status		X^2	p-value
			N1	N0		
AGE, YEAR						
Median (range)		44 (17–68)				
TOTAL		217	201 (92.6)	16 (7.4)	2.010	0.546
	<30	9 (4.1)	8	1		
	30–39	58 (26.7)	56	2		
	40–49	98 (45.2)	89	9		
	50–59	41 (18.9)	38	3		
	≥60	11 (5.1)	10	1		
FIGO stage (%)					0.832	1
	IA	14 (6.5)	13	1		
	IB	123 (56.7)	113	10		
	IIA	71 (32.7)	66	5		
	IIB	8 (3.7)	8	0		
	IIIA	1 (0.4)	1	0		

NOTE: N1, cervical cancer patients with positive lymph node(s); N0, cervical cancer patients without positive lymph node(s).

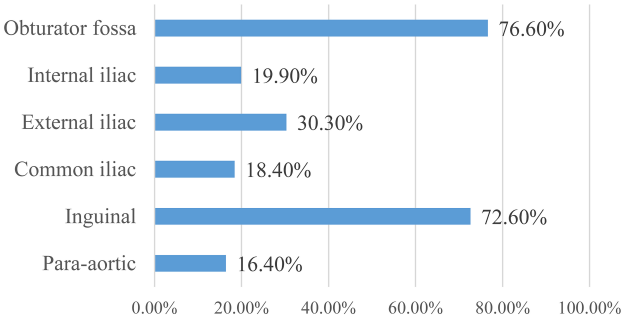

Fig. 1. Distribution of LNM.

According to the TNM system, nodal metastases stages can be classified by regional or non-regional localization primarily. Thus, we compared the different frequency of LNM sites at different stages to identify the distribution patterns of nodal metastases. The Table 3 indicated that the most common site was the obturator region (77%, stage I; 77%, stage II) in the group with regional LNM, and external iliac region was the second highest (30.2%, stage I; 31.1%, stage II). In the group with non-regional LNM, the highest rate of LNM was inguinal LN (70.6%, stage I; 75.7%, stage II).

To identify the route of early-stage cervical cancer LNM, we analyzed the detection rate and frequency of LNM sites at IB and IIA stages (Table 4). 27 patients

Table 2. Distribution of FIGO stage in each age group.

FIGO stage	Year Group					Total (N = 217)	Pearson Chi-square	*p*-value
	<30	30–39	40–49	50–59	≥60			
IA	1	4	8	0	1	14	3.194	0.337
IB	6	32	58	22	5	123	3.067	0.555
IIA	2	18	28	18	5	71	1.880	0.869
IIB	0	3	4	1	0	8	1.406	1.000
IIIA	0	1	0	0	0	1		

Table 3. The regional vs non-regional lymphatic metastasis.

Localization	Regional			Non-Regional		
FIGO stage N (%)	Obturator fossa	Internal iliac	External iliac	Common iliac	Inguinal	Para-aortic
TOTAL (n = 201)	154 (76.6)	40 (19.9)	61 (30.3)	37 (18.4)	146 (72.6)	33 (16.4)
I (n = 126)	97 (77)	27 (21.4)	38 (30.2)	20 (15.9)	89 (70.6)	23 (18.3)
IA (n = 13)	9 (69.2)	1 (7.7)	5 (38.5)	1 (7.7)	7 (53.8)	2 (15.4)
IB (n = 113)	88 (77.9)	26 (23)	33 (29.2)	19 (16.8)	82 (72.6)	21 (18.6)
II (n = 74)	57 (77)	13 (17.6)	23 (31.1)	16 (21.6)	56 (75.7)	9 (12.2)
IIA (n = 66)	52 (78.8)	12 (18.2)	21 (31.8)	15 (22.7)	51 (77.3)	8 (12.1)
IIB (n = 8)	5 (62.5)	1 (12.5)	2 (25)	1 (12.5)	5 (62.5)	1 (12.5)
IIIA (n = 1)	0	0	0	1	1	1

had only regional lymph node metastases (metastasis rate 15.1%). There were 22 patients with non-regional LNM alone (metastasis rate 12.3%) and 130 patients with both regional and non-regional metastases (metastasis rate 72.6%), including 81 patients with stage IB (71.7%, 81/113) and 49 patients with stage IIA (74.2%, 49/66). 70 cases (39.1%, 70/179) had both obturator lymph node and inguinal LNM.

A total of 92 patients were enrolled by examination of last medical history or telephone follow-up. The 3-year and 5-year survival rate are listed in Table 5. In the return visit, there were 54 patients in stage IB and 28 patients in stage IIA. The 3-year and 5-year survival rate of patients were 96.2% and 92.6% in stage IB, respectively. The 3-year survival rate was 100% and the 5-year survival rate was 82.1% for patients in stage IIA.

According to survival outcomes, patients were divided into two groups. Multivariate analysis was performed on the LNM factor associated with survival outcomes in patients, such as obturator LNM, internal and external iliac LNM, common iliac LNM, inguinal LNM, and so on. It can be seen from Table 6. It is a pity that there was no correlation between LNM sites and survival outcomes (all p values > 0.05).

Table 4. The detection rate of lymph node metastasis site between IB and IIA.

Location	Total	FIGO stage, n (n %)	
		IB	IIA
	179	113	66
Regional LN, only	27 (15.1)	19 (16.8)	8 (12.1)
①	6 (3.3)	3 (2.7)	3 (4.5)
②③	8 (4.5)	6 (5.3)	2 (3)
①②③	9 (5)	8 (7.1)	1 (1.5)
Others	4	2	2
Non-regional LN, only	22 (12.3)	13 (11.5)	9 (13.6)
⑤	15 (8.4)	9 (8)	6 (9.1)
others	7	4	3
Regional & Non-regional	130 (72.6)	81 (71.7)	49 (74.2)
①⑤	70 (39.1)	46 (40.7)	24 (36.4)
①③⑤	9 (5)	4	5
①④⑤	5 (2.8)	2	3
①⑤⑥	5 (2.8)	4	1
③⑤	5 (2.8)	3	2
①②③④⑥	5 (2.8)	2	3
Others	31 (17.3)	20 (17.7)	11 (16.7)

NOTE: ① Obturator fossa, ② Internal iliac, ③ External iliac, ④ Common iliac, ⑤ Inguinal, ⑥ Para-aortic.

4. Discussion

The status of the lymph nodes is an important prognostic factor in cervical tumor patients and often utilized to plan the extent of lymph node dissection and adjuvant therapy [15]. Intensity-modulated radiotherapy and introduction of the sentinel lymph node concept in oncological surgery have dramatically changed the management guide-

Table 5. Survival Rate in the return visit.

FIGO stage	Follow up (N = 92)	Survival	Death	3-year survival rate (%)	5-year survival rate (%)
IA	7	7	0	100	100
IB	54	49	5	96.2	92.6
IIA	28	23	5	100	82.1
IIB	2	1	1	50	50
IIIA	1		1	0	0

Table 6. Multivariate analysis of LNM factors associated with survival outcomes.

Region	B	S. E	Wald	df	*p*-value	OR	95% CI for OR
Obturator fossa	–0.714	0.805	0.788	1	0.375	0.489	0.101–2.370
Internal iliac	–0.474	1.206	0.155	1	0.694	0.622	0.059–6.617
External iliac	1.482	1.166	1.616	1	0.204	4.404	0.448–43.289
Common iliac	–1.455	0.830	3.073	1	0.080	0.233	0.046–1.187
Inguinal	–1.092	0.708	2.376	1	0.123	0.336	0.084–1.345
Para-aortic	0.281	0.911	0.095	1	0.758	1.324	0.222–7.893

lines of numerous cancers nowadays [16]. Furthermore, both surgery and radiotherapy tend to precise aim on the tumor itself and the involved lymph node sites. Therefore, the clear identification of affected lymph nodes is required and significant, which can avoid over-treatment and reduce complications. Clinical data also indicated the highest frequency of metastatic lymph nodes in the obturator and external iliac regions [4,17]. Ouldamer *et al*. [18] summarized and analyzed 27 papers, including 1301 patients with early cervical cancer, and found that the most common sentinel lymph nodes were obturator, internal iliac and external iliac lymph nodes, accounting for 83.7%, while common iliac (6.6%), para-aortic (2%) and inguinal region (0.07%) were relatively rare. Although Michel G, *et al*. [19] has reported a low overall frequency of lymph node involvement (26%) with 18% in obturator and 11% in external iliac from 421 patients. Kasuya G *et al*. [20] showed the highest rate in obturator (91%) and external iliac (27%) among 273 enlarged nodes. In our study, we analyzed the types of lymphatic metastasis using preoperative imaging results and clinical investigation data of 217 cervical cancer patients who underwent lymphadenectomy, the results showed metastasis rate of obturator lymph nodes is the highest and the next is inguinal nodes (Table 3). This may prompt that obturator and inguinal lymph nodes can be assessed as potential SLB.

Henriksen divided the major lymph nodes into two groups according to the distribution of lymph nodes in cervical cancer: the primary group, which includes the paracervical, ureteral, obturator, hypogastric, and external iliac nodes, and the secondary group which includes the common iliac, aortic. sacral, and inguinal nodes. In most occasions, one or more nodes of the primary group are usually involved before reaching the level of the secondary group [21]. In order to clarify lymphatic metastasis pattern in cervical cancer, we further analyzed the incidence of different lymph node groups in early stages (IB–IIA). In the group with only regional lymph node metastases, obturator lymph nodes accompanied by internal and external iliac lymph node metastases showed a higher rate than isolated obturator lymph node metastases. The proportion of concomitant LNM was higher in the stage IB, compared with the stage IIA (Table 4). Anatomist Plentl A has described the most important route of cervical LNM is along the lateral parametrium to obturator, external iliac, internal iliac and common iliac lymph nodes [18,22]. In the group of regional accompanied by non-regional lymph node metastases, obturator LNM accompanied by inguinal LNM accounted for the highest proportion, and the metastasis rate of inguinal and common iliac lymph nodes is gradually increasing with the progress of the clinical stage. It is suggested that besides of the regional obturator, internal and external iliac LNM, non-regional lymph nodes as inguinal should also be considered during lymph node dissection. In addition, because of the abundant and complicated lymphatic network in female pelvis cavity [23], we also found other different types of metastasis pattern shown in Table 4. In the Regional & Non-regional group, except for 70 cases with both obturator and inguinal LNM, there were 5 cases (2.8%) with the common iliac LNM without passing through the internal and external iliac LN, and even existed skip metastasis to Para-aortic LN (5 cases, 2.8%). These results indicated the complexity of pelvic lymphatic pathway and more research is needed [24].

In previous studies, inguinal LNM was an ambiguous pattern, while in our study, inguinal nodes showed a high incidence and an increasing rate in early stages. McMahon *et al*. [4] described that the lower nodes of lateral chain of external iliac group receives the efferent vessels from the inguinal nodes, and medial chain of external iliac node corresponds to the obturator nodes, all the lymphatics drain into successive groups of nodes; then which form several ascending chains and finally terminate in the inferior part of the lateral aortic chain on the corresponding side. Therefore, we hypothesized that cervical cancer tumors may metastasis by joining this drainage pattern, this may explain the high incidence of inguinal nodes accompanied by obturator nodes. Interestingly, when inguinal or obturator LNs were negative, para-aortic LNs scan were rare, this also help to prove the significance of them as sentinel nodes.

Lymph node status is a crucial factor affecting the prognosis of cervical tumor patients. To clarify the relationship between lymph node metastasis sites and patient survival outcome, we performed a multivariate analysis on the lymph node status of the follow-up patients. While the analysis results showed there was no correlation between LNM sites and survival outcome. Kwon *et al*. [25] described patient survival rate was significantly reduced as the number of positive pelvic lymph node groups increased or common iliac/paraaortic nodes were involved. Another retrospective study indicated site-specific LNM all had significant effect on survival outcomes as well [26]. However, these differ from the finding presented here. We suspect the reason might that the number of patients in each stage was not evenly distributed.

Several limitations of our study are listed below. Firstly, the number of cases was small with a large time span and rates of loss to follow-up were high. Secondly, although the inclusion and exclusion criteria were strictly observed, bias might still exist. Accordingly, future prospective randomized studies with large number of cases are needed to address these limitations.

5. Conclusions

We have analyzed patterns of LNM in a cohort of patients with early-staged cervical cancer. Our research showed the highest detection rate of obturator lymph nodes, and especially a high incidence of inguinal nodes and inguinal nodes with obturator nodes, and pre-treatment imaging may be beneficial for a more reasonable surgical plan. Furthermore, in early stages, incidence of inguinal nodes increased with tumor progress. Thus, we concluded that the obturator and inguinal nodes may be appropriate for inclusion in SLN evaluating the therapeutic role of lymphadenectomy of uterine cervical tumor.

Abbreviations

LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; SLN, sentinel lymph node; FIGO, The International Federation of Gynecology and Obstetrics.

Author contributions

Both HX and TY are involved in the study analysis and interpretation of data design, data analysis, write-up. JMH and HY Zeng are involved in the acquisition of data, and LJL and HY Zhou are involved in the conception and design of the idea. All have read and approved the final copy of this manuscript for submission.

Ethics approval and consent to participate

This retrospective study was approved by the ethics committee of the West China Second University Hospital of Sichuan University (25/06/2009). The study was conducted in accordance with the Declaration of Helsinki. We only collected the clinical data of female patients with cervical cancer, and did not interfere with the treatment plan of patients, which would not bring physiological risk to patients. Researchers can protect the information provided by patients, and will not disclose personal privacy. Informed consent was obtained from all patients.

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Conflict of interest

The authors declare no conflict of interest.

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