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ORIGINAL RESEARCH

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Unveiling the lymph node drainage route in stage IB1 to IIA2 cervical cancer: insights from a retrospective cohort study

Shuiling Zu[1,†], Haixing Feng[2,†], Jianqing Zheng[3,*], Fangjie He[1,4,*]

[1]Department of Gynecology, Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University, 350000 Fuzhou, Fujian, China
[2]Guangdong Key Laboratory for Biomedical Measurements and Ultrasound Imaging, School of Biomedical Engineering, School of Medicine, Shenzhen University, 518060 Shenzhen, Guangdong, China
[3]Department of Radiation Oncology, The Second Affiliated Hospital of Fujian Medical University, 362000 Quanzhou, Fujian, China
[4]Department of Obstetrics and Gynecology, The First People's Hospital of Foshan, 528000 Foshan, Guangdong, China

***Correspondence**
hfj5362@fsyyy.com
(Fangjie He);
shmilyhbf@fjmu.edu.cn
(Jianqing Zheng)

† These authors contributed equally.

Abstract

This study aimed to identify the drainage route and the first station of lymph node metastasis (LNM) in patients with stage IB1 to IIA2 cervical cancer. The clinicopathological data of stage IB1 to IIA2 cervical cancer patients who underwent radical surgery between 2018 and 2022 were retrospectively retrieved and assessed. Hematoxylin and eosin-stained cervical cancer specimens, including cervix and lymph node tissues, were collected and reviewed independently by two pathologists blinded to the patients' clinical information. Of the 429 investigated patients, the mean number of lymph nodes removed per patient was 30, and the number of lymph nodes removed between the left and right pelvis was comparable. Additionally, of the 121 (28.2%) patients with LNM, the number of LNM between the left and right pelvis was comparable, and 64 (52.9%) patients had one area of LNM. The internal iliac lymph node was the primary area of LNM, followed by the obturator and external iliac lymph nodes. These three areas accounted for approximately 80% of all LNM cases. We also observed that in cases with LNM in any of these three areas, the second station of drainage area was fixed in more than 50% of patients. The most common first stations of LNM in stage IB1–IIA2 cervical cancer patients were found to be the internal iliac, obturator and external iliac lymph nodes in sequence, and complete removal of these lymph nodes is crucial for those without satisfactory or even failed sentinel lymph node mapping.

Keywords

Cervical cancer; Sentinel lymph node; Drainage route; Mapping; Lymph node metastasis

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide [1]. Although class C radical hysterectomy and system pelvic lymphadenectomy are the primary surgical treatment strategies for patients with stage IB1–IIA2 cervical cancer [2], they are often associated with severe comorbidities, such as lymphedema, lymphocysts and lymphatic fistula [3, 4]. To minimize the risk of intraoperative adverse events and postoperative lymphatic complications while retaining the clinical information on lymph node status, restricting the surgery to sentinel lymph nodes (SLN) has been increasingly implemented in clinical practice.

SLN mapping is already established as one of the standard staging procedures in melanoma and breast cancer [5]. However, its significance in cervical cancer remains undetermined because of the complex anatomy of the uterus and surrounding tissuesThe upper paracervical lymphatic pathway, which follows the course of the uterine artery and passes through the upper paracervical lymphovascular tissue (UPLT), is a key route for drainage of the uterus. This pathway frequently runs in close proximity to the lymphatic vessels of the external iliac/interiliac and obturator regions, forming a complex network that plays a crucial role in the spread of cancer cells and the dissemination of metastases [6, 7]. Hence, anatomically, paracervical lymph nodes represent the SLN of cervical cancer. However, conflicting findings from previous SLN mapping studies suggested that the internal iliac, external iliac and obturator lymph nodes may also serve as SLN for cervical cancer [8, 9]. This lack of consensus on the optimal SLN location can have adverse consequences on the diagnostic accuracy of SLN and the survival outcomes of cervical cancer patients [10]. Thus, achieving a more definitive understanding of the anatomical and functional characteristics of the SLN network in cervical cancer is critical for optimizing diagnostic and therapeutic strategies in this disease.

To fill this gap in literature, this present study aimed to determine the first station of lymph node metastasis (LNM) and delineate the drainage route of lymph nodes in patients with stage IB1–IIA2 cervical cancer.

2. Methods

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2.1 Study design and cohort

The clinical and pathological data of patients who underwent surgical treatment for cervical cancer between 01 July 2018, and 30 November 2022, at our institution were retrieved and reviewed. Patients who met the following criteria were included: (1) clinically staged as IB1 to IIA2 cervical cancer according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system [11, 12]; (2) underwent type C2 (Querleu and Morrow surgical classification system) radical hysterectomy and bilateral pelvic lymphadenectomy with or without paraaortic lymphadenectomy; and (3) did not receive neoadjuvant therapy. The study exclusion criteria were: (1) current pregnancy; (2) presence of cervical stump carcinoma; or (3) cancer other than cervical cancer. In total, 429 patients were eligible.

2.2 Pathology review

Hematoxylin and eosin-stained cervical cancer specimens, including cervix and lymph nodes, were collected, fixed with formalin, embedded in paraffin, sectioned to a thickness of 4 μm, stained with hematoxylin and eosin, and reviewed independently by two pathologists blinded to the clinical information of the patients. Of note, the lymph node status reviewed by the two pathologists was consistent with those in the original pathological reports.

2.3 Surgical procedures

All patients underwent pelvic with or without paraaortic lymphadenectomy. The primary surgical procedures were performed as follows: (1) the retroperitoneum was opened to expose the psoas major, the bifurcation of the iliac vessels and the ureter; (2) we identified and freed the internal iliac vessels and exposed the obturator region and obturator nerve; (3) then, the space between the psoas major and external iliac vessels were opened; (4) the pelvic lymph nodes, including common iliac nodes, external iliac nodes, internal iliac, obturator nodes and deep inguinal lymph nodes, were removed [13, 14]. Although the paracervical lymph nodes were not routinely assessed and freed perioperatively as postoperative specimens, they were identified and retrieved by pathologists. Additionally, patients with a tumor size >4.0 cm underwent paraaortic lymphadenectomy, and few received presacral lymphadenectomy.

Further, all patients underwent type C2 radical hysterectomy, which was performed according to the resection sequence of the round ligament, adnexal pedicle, sacral ligament, cardinal ligament, and bladder cervicovaginal ligament.

2.4 Postoperative adjuvant therapy

Patients were treated with postoperative adjuvant radiotherapy with or without chemotherapy. Of note, the treatment decision-making was based on a risk-stratified method using the Sedlis criteria [15], including the presence of three intermediate-risk factors (lymphovascular space invasion (LVSI), stromal invasion depth and tumor diameter) or any high-risk factors (positive resection margin, parametrial involvement (PMI) and LNM), and might have also been influenced by patient and physician preferences.

2.5 Statistical analysis

Rates are used to express the percentage of the presented data. The Student's *t*-test was used to compare continuous variables between two groups. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 26.0; IBM Inc., Chicago, IL, USA). A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

The clinical and pathological characteristics of the investigated cervical cancer patients are summarized in Table 1. Of the 429 patients, the mean number of lymph nodes removed per patient was 30, and the number of lymph nodes removed was comparable between the left and right pelvis for the total, common iliac, internal iliac, external iliac, obturator, deep inguinal and paracervical lymph nodes (Table 2).

Additionally, 121 (28.2%) patients were found to have LNM, and their number of LNM was comparable between the left and right pelvis for the total, common iliac, internal iliac, external iliac, obturator, deep inguinal and paracervical lymph nodes (Table 3).

3.2 First station of LNM

Of the 121 patients with LNM, 47 (38.8%) had one LNM, 26 (21.5%) had two LNM, 17 (14.0%) had three LNM, and 31 (25.6%) had more than three LNM. In addition, according to the different lymph node areas, 64 (52.9%) patients had one area of LNM, while the others had two or more areas of LNM based on postoperative pathological findings. The internal iliac lymph node was the primary area of LNM, followed by the obturator and external iliac lymph node areas. These three areas accounted for about 80% of the total LNM (Table 4). The distribution of LNM in each stage is shown in Table 5, from which we can observe that most patients were staged as IB2 and IB3 cervical cancer, and the internal iliac, obturator and external iliac lymph nodes were the primary areas of LNM.

In regard to the paracervical lymph nodes, they were resected in twelve patients, of whom 7 (58.3%) were found to have metastasis, including 2 patients with only one area of metastasis and 5 patients with two or more areas of metastasis.

3.3 Second station of LNM

Of the 121 patients with LNM, 27 (22.3%) patients had two areas of LNM, of whom the internal iliac at the obturator area (22.2%) had the highest proportion of LNM, followed by the internal iliac at the external iliac area (18.5%) and the obturator at the external iliac area (14.8%). These three areas accounted for approximately 55.5% of the total LNM (Table 6).

4. Discussion

This study demonstrated that the first station of LNM is not fixed in patients with stage IB1–IIA2 cervical cancer. The most common first station of LNM was sequentially identified as the internal iliac, obturator and external iliac lymph nodes,

TABLE 1. The clinical and pathological characteristics of patients with stage IB1 to IIA2 cervical cancer.

Characteristic	Number (%)
Age, mean (SD), years	51.4 (10.3)
Stage	
IB1	122 (28.4)
IB2	147 (34.3)
IB3	117 (27.3)
IIA1	23 (5.4)
IIA2	20 (4.7)
Tumor diameter, mean (SD), cm	3.5 (1.8)
≤2	130 (30.3)
2.1–4	161 (37.5)
>4	138 (32.2)
Histological type, n (%)	
Squamous cell carcinoma	346 (80.7)
Adenocarcinoma	59 (13.8)
Adenosquamous carcinoma	9 (2.1)
Others	15 (3.5)
Grade, n (%)	
G1	8 (1.9)
G2	344 (80.2)
G3	77 (17.9)
Stromal invasion depth	
≤1/2	175 (40.8)
>1/2	254 (59.2)
LVSI	
No	264 (61.5)
Yes	165 (38.5)
PMI	
No	424 (98.8)
Yes	5 (1.2)
RMI	
No	418 (97.4)
Yes	11 (2.6)
LNM	
No	308 (71.8)
Yes	121 (28.2)

LVSI, lymphovascular space invasion; PMI, parametrial involvement; RMI, resection margin involvement; LNM, lymph node metastasis; SD, standard deviation.

TABLE 2. The comparison of left and right pelvic lymph nodes removed.

Characteristic	Left pelvis	Right pelvis	*p*
Number (%)	429 (100.0)	429 (100.0)	
Lymph nodes removed, mean (SD)			
Total iliac nodes	13.3 (6.1)	13.5 (5.9)	0.616
Common iliac nodes	2.6 (2.3)	2.4 (2.0)	0.217
External iliac nodes	2.8 (2.2)	3.0 (2.2)	0.377
Internal iliac nodes	2.7 (2.1)	2.6 (2.1)	0.569
Obturator nodes	3.1 (2.7)	3.2 (2.6)	0.383
Deep inguinal nodes	2.1 (1.8)	2.2 (2.0)	0.228
Paracervical nodes	0.01 (0.2)	0.03 (0.3)	0.215

SD, standard deviation. Paracervical lymph nodes were not routinely searched and freed from postoperative specimen, and it was found and indicated by pathologist.

TABLE 3. The comparison of left and right pelvic LNM.

Characteristic	Left pelvis	Right pelvis	*p*
Number (%)	121 (100.0)	121 (100.0)	
LNM, mean (SD)			
Total iliac nodes	1.7 (2.3)	1.3 (2.2)	0.169
Common iliac nodes	0.3 (1.1)	0.1 (0.4)	0.097
External iliac nodes	0.4 (0.8)	0.3 (0.8)	0.286
Internal iliac nodes	0.4 (0.8)	0.4 (0.8)	0.624
Obturator nodes	0.5 (1.1)	0.4 (0.8)	0.355
Deep inguinal nodes	0.1 (0.4)	0.2 (0.7)	0.488
Paracervical nodes	0.02 (0.2)	0.02 (0.1)	1.000

LNM, lymph node metastasis; SD, standard deviation.

TABLE 4. Distribution of only one area with LNM.

Characteristic	Number (%)
In total	64 (100.0)
Paraaortic nodes	1 (1.6)
Presacral nodes	0 (0.0)
Common iliac nodes	4 (6.3)
External iliac nodes	8 (12.5)
Internal iliac nodes	26 (40.6)
Obturator nodes	17 (26.6)
Deep inguinal nodes	6 (9.4)
Paracervical nodes	2 (3.1)

LNM, lymph node metastasis. For Paracervical nodes, twelve patients were found to have paracervical lymph nodes section, and 7 (58.3%) patients were found to have metastasis, including 2 patients with only one area of metastasis and 5 patients with two or more areas of metastasis.

TABLE 5. Distribution of only one area with LNM in each stage.

Characteristic	IB1	IB2	IB3	IIA1	IIA2
Number (%)	5 (100.0)	20 (100.0)	27 (100.0)	6 (100.0)	6 (100.0)
Paraaortic nodes	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Presacral nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Common iliac nodes	0 (0.0)	1 (5.0)	2 (7.4)	0 (0.0)	1 (16.7)
External iliac nodes	1 (20.0)	2 (10.0)	4 (14.8)	1 (16.7)	0 (0.0)
Internal iliac nodes	1 (20.0)	9 (45.0)	10 (37.0)	3 (50.0)	3 (50.0)
Obturator nodes	1 (20.0)	6 (30.0)	6 (22.2)	2 (33.3)	2 (33.3)
Deep inguinal nodes	1 (20.0)	1 (5.0)	4 (14.8)	0 (0.0)	0 (0.0)
Paracervical nodes	0 (0.0)	1 (5.0)	1 (3.7)	0 (0.0)	0 (0.0)

LNM, lymph node metastasis. Paracervical lymph nodes were not routinely free from postoperative specimen, and it was found and indicated by pathologist.

TABLE 6. Patients with two area of LNM.

Characteristic	Number (%)
In total	27 (100.0)
Internal iliac and obturator nodes	6 (22.2)
Internal and external iliac nodes	5 (18.5)
Internal and common iliac nodes	2 (7.4)
Internal iliac and paraaoric nodes	2 (7.4)
Internal iliac and deep inguinal nodes	2 (7.4)
obturator and external iliac nodes	4 (14.8)
obturator and paracervical nodes	2 (7.4)
obturator and deep inguinal nodes	1 (3.7)
External and common iliac nodes	1 (3.7)
External iliac and obturator nodes	1 (3.7)
Common iliac and paraaoric nodes	1 (3.7)

LNM, lymph node metastasis. Paracervical lymph nodes were not routinely free from postoperative specimen, and it was found and indicated by pathologist.

accounting for about 80% of all LNM in these patients. Furthermore, when the LNM occurred in any of these three areas, the second station of drainage area was fixed at this location in more than 50% of patients. Hence, complete resection of the internal iliac, external iliac and obturator lymph nodes is crucial for cervical cancer patients without satisfactory or even failed SLN mapping.

Currently, SLN is recommended as an alternative method to estimate lymph node status and guide adjuvant chemoradiotherapy [16]. The use of blue dye, radionuclide and fluorescent tracer are the primary methods for detecting SLNs. Meta-analyses of pooled data from SLN mapping studies revealed that SLN detection rates ranged between 89% and 92%, and sensitivity ranged between 89% and 90% [17, 18]. Therefore, SLN biopsy may be useful for decreasing the need for pelvic lymph node section in patients with stage IA2–IIA2 cervical cancer. However, these previous studies also revealed that the position of SLN is not fixed to a group of lymph nodes. Furthermore, one previous study reported that tracer type, metastatic nodes, body mass index and surgical year might also affect the identification of SLN location. Thus, surgical efforts, techniques and experience are important factors for accurately determining SLN location [19, 20]. This present research revealed that the internal iliac, obturator and external iliac lymph nodes represented the primary site of lymph node metastasis (LNM), accounting for about 80% of cases in patients with cervical cancer. Thus, resection of these lymph nodes might be necessary for patients who exhibit unsatisfactory or suspicious results during SLN mapping. Moreover, we demonstrated that these areas were also the second station of LNM in more than 50% of the patients. Notably, our study employed a pathology-confirmed approach to SLN mapping, providing more reliable results than intraoperative tracer-based methods.

For patients with tumor size <2 cm, the use of tracer mapping for intraoperative identification of SLN was reported to be particularly effective [21, 22]. However, in this present study, the first station of LNM did not show a significant association with tumor size. Thus, further analyses using larger cohorts of patients are needed to clarify these differences.

In this current study, the paracervical lymph nodes were not routinely retrieved from the postoperative specimens by surgeons but were found and retrieved by the pathologists. Of 12 patients with paracervical lymph node resection, 7 (58.3%) patients had metastatic paracervical lymph nodes. This high proportion may indicate that paracervical lymph nodes could be the first station of lymph node drainage. A previous study revealed that of 52.4% of patients with at least one paracervical lymph node, 3.9% had paracervical SLN metastasis [23], which differs from our study findings and might be due to the limited information on paracervical lymph nodes. Hence, the current study could not accurately assess the status of paracervical lymph nodes.

This study had some limitations that should be highlighted. First, due to the retrospective nature of the study, the presence of selection bias should be considered. Second, although the results revealed that the most common first station of LNM was the internal iliac, obturator and external iliac lymph nodes in sequence, we did not assess the paracervical lymph node in this study. Third, the association of clinicopathological factors and the first station of LNM was not determined due to the limited number of cases. Hence, more research is needed to further clarify the lymphatic drainage pathway in cervical cancer.

5. Conclusions

In conclusion, the most common first station of LNM, in sequence, was the internal iliac, obturator and external iliac lymph nodes in patients with IB1–IIA2 cervical cancer. Hence, complete resections of these lymph nodes might be warranted for cervical cancer patients without satisfactory or even failed SLN mapping.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, Fangjie He, upon reasonable request.

AUTHOR CONTRIBUTIONS

FJH—conceived and designed the study. JQZ—participated in the conception and performed the data collection and analysis. SLZ—participated in the design and draft of the manuscript. HXF—performed the data collection and analysis. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Institutional Review Board of the First People's Hospital of Foshan (L2022-27). The requirement of informed consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki. Patient identity could not be identified in the publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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