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Distribution patterns of lymph node metastasis in early stage invasive cervical cancer

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Abstract

The spatial distribution of lymph node (LN) metastasis was analyzed to provide data for an evidence-based approach to radiotherapy field design, particularly for guiding intensity-modulated radiation therapy. A total of 1886 postoperative patients were retrospectively reviewed. Pelvic LNs were classified as common iliac nodes, external iliac nodes, internal iliac nodes/obturator nodes, and deep inguinal nodes. The distribution of LN metastasis in these subgroups was calculated, and the distribution patterns of LN metastasis according to the pathologic types were investigated.

We identified 392 eligible patients with LN metastasis. The frequency and number of external iliac node metastasis were higher in the left side in both single subgroup ($P < .01$) and cosubgroup ($P = .04$) analyses, whereas few differences were found in other subgroups. Among patients with squamous cell carcinoma, left external iliac node metastasis was observed in 102 (15.13%) patients, whereas right metastasis was observed in 65 (9.64%) patients, and the difference was significant ($P < .01$).

The present results indicated uneven distribution of LN metastasis in the different subgroups, which could help surgeon focus on the dissection of the left subgroups, and help oncologists define margins, refine target volumes for radiation, and improve the accuracy of postoperative radiotherapy especially in patients with squamous cell carcinoma.

Abbreviations: FIGO = Federation International of Gynecology and Obstetrics, ICC = invasive cervical cancer, IMRT = intensity-modulated radiation therapy, LN = lymph node, LNM = lymph node metastasis, SCC = squamous cell carcinoma.

Keywords: cervical cancer, external iliac nodes, lymph node, metastasis, target volume

1. Introduction

Invasive cervical cancer (ICC) is the third most common malignancy and the fourth leading cause of cancer-related death in women worldwide.[1] Radical hysterectomy with or without para-aortic lymphadenectomy or radiotherapy are the standard treatments for early-stage disease.[2]

Although lymph node metastasis (LNM) is a negative prognostic factor, the current FIGO staging system for ICC does not consider lymph node status. LNM is associated with a decrease in the 5-year overall survival rate from 85% to 53%.[3,4] LNM, parametrial invasion, and/or positive margins are associated with a high risk of recurrence in ICC, and postoperative adjuvant treatments are urgently needed to improve survival rates.[5]

For both primary and postoperative patients, standard pelvic radiation fields include the external and internal iliac, obturator, and presacral lymph nodal basins. Patients with involvement of the upper common iliac or paraaortic lymph nodes require treatment of the para-aortic nodal region.[6] Hence, precise delineation of the lymph node region at risk is critical for successful radiotherapy.

The aim of this study was to outline the spatial distribution of LNM to provide data for an evidence-based approach to radiotherapy field design, particularly for guiding intensity-modulated radiation therapy (IMRT).

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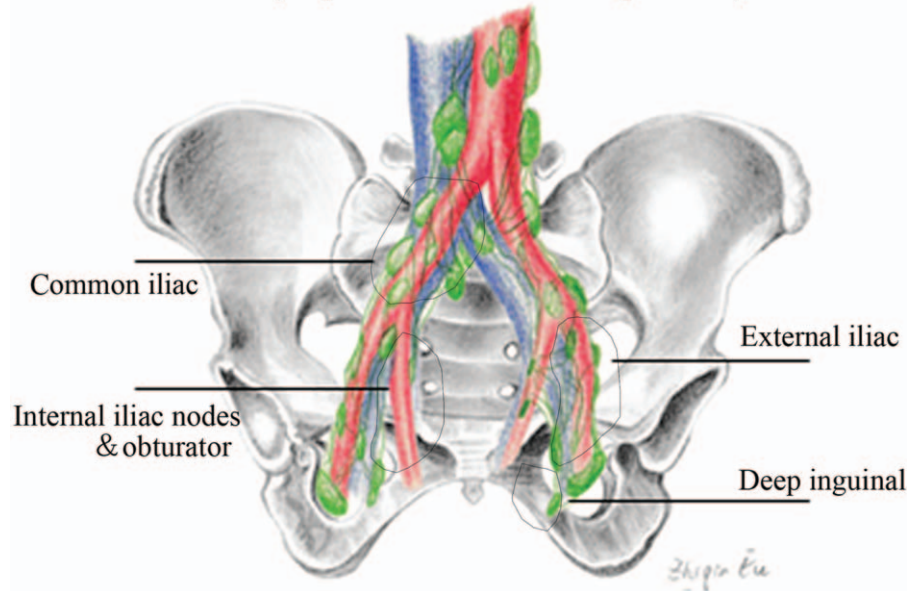
2. Material and methods

Study participants were patients diagnosed with Federation International of Gynecology and Obstetrics (FIGO) stage I–IIA2 ICC treated by radical hysterectomy and pelvic and/or para-aortic lymphadenectomy at Zhejiang Cancer Hospital, Zhejiang Province, China between August 2008 and June 2014. The pathological data were extracted from the institution's electronic databases after informed consent was obtained from all patients. The Medical Ethics Committee of Zhejiang Cancer Hospital approved the study.

Nodal groups were defined as follows: pelvic and para-aortic lymph nodes. The pelvic lymph nodes were classified as common iliac nodes, external iliac nodes, internal iliac nodes/obturator nodes, and deep inguinal nodes (Fig. 1). Para-aortic lymph nodes

Figure 1. Pelvic lymph node metastasis pathway. The pelvic lymph nodes were classified as common iliac nodes, external iliac nodes, internal iliac nodes and obturator nodes, and deep inguinal nodes.

were defined as all LNs adjacent to the aorta or inferior vena cava. Common iliac nodes were defined as all LNs adjacent to the common iliac vessels from the aortic bifurcation to the division of common iliac artery into the external and internal iliac branches. External iliac nodes surrounded the external iliac vessels until they pass through the inguinal ligament. Internal iliac nodes were next to the internal iliac vessels and their branches and tributaries. Obturator nodes were within the triangle between the external and internal iliac vessels.[7] Deep inguinal nodes were located in the femoral canal medial to the femoral vein.

2.1. Statistical analysis

Statistical analyses were performed using the SPSS 16.0 software package (IBM, Armonk, NY). Summary statistics are presented as frequencies and percentages. The Student t test was used to

analyze the significance between groups. $P<.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In total, 1886 patients were retrospectively reviewed; LNM was identified in 392 eligible patients (20.78%), excluding 2 patients who did not belong to any subgroup of pelvic lymph nodes and 12 patients with single presacral or paracinal LNM. The median age of patients was 46 years (range, 26–71 years); 337 patients had squamous cell carcinoma (SCC) and 33 patients had adenocarcinoma. There were 200 patients with FIGO stage I and 192 patients with stage II ICC.

The numbers and frequencies of LNM in each subgroup are summarized in Table 1. Two hundred eighty-six patients

Table 1

Numbers and frequencies of lymph node metastasis in each subgroup.

Subgroups	No. of LNM		Subgroups	Frequencies of LNM	
Para-aortic lymph node	96		Para-aortic lymph node	31	
Common iliac nodes − R	95		Common iliac nodes - R	59	
Common iliac nodes - L	108		Common iliac nodes - L	54	
External iliac nodes - R	140		External iliac nodes − R	77	
External iliac nodes - L	187		External iliac nodes - L	118	
Internal iliac&Obturator nodes - R	295		Internal iliac&Obturator nodes - R	203	
Internal iliac&Obturator nodes - L	306		Internal iliac&Obturator nodes - L	193	
Deep inguinal nodes - R	27		Deep inguinal nodes - R	24	
Deep inguinal nodes - L	47		Deep inguinal nodes - L	32	
Left PLNs	648	53.78%		286	51.26%
Right PLNs	557	$P=.145$		271	$P=.27$

Two hundred eighty-six patients suffered left pelvic LNM, and had a total number of 648 involved nodes. No differences in the number or frequency of LNMs between the right and left pelvic nodes. Thirty-one patients suffered para-aortic LNM, with 96 involved nodes.
L = left; LNM = lymph node metastasis; PLNs = pelvic lymph nodes; R = right.
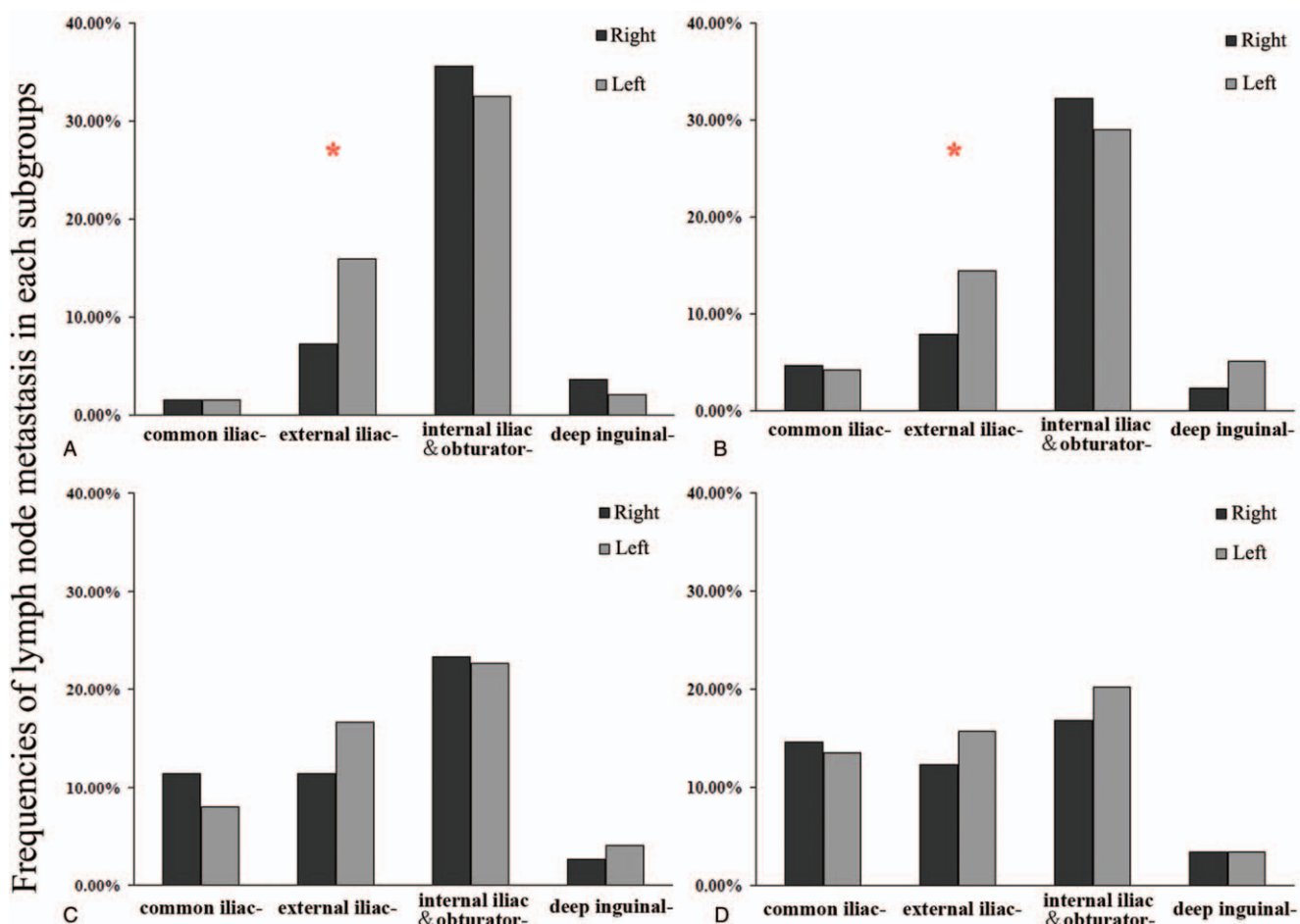
Figure 2. Frequencies of lymph node metastasis in each subgroup. (A) Single lymph node metastasis subgroup. (B) Co-lymph node metastasis subgroup. (C) Tri-lymph node metastasis subgroup. (D) Tetra- or more lymph node metastasis subgroup. $^{*}P < .05$.

(51.26%) suffered left pelvic LNM, and had a total number of 648 (53.78%) involved nodes. However, there were no differences in the number or frequency of LNMs between the right and left pelvic nodes. Meanwhile, 31 patients suffered para-aortic LNM, with 96 involved nodes.

3.2. Distribution of lymph node metastasis

The distribution patterns of LNM were investigated by dividing patients into groups as follows: single-, co-, tri-, and tetra- or more LNMs. In the single subgroup, left external iliac node metastasis (31 patients, 15.98%) was more frequent than right node metastasis (14 patients, 7.22%) ($P < .01$). The numbers were 3 (left) and 3 (right) for common iliac nodes ($P > .05$), 63 (left) and 69 (right) for internal iliac nodes and obturator nodes ($P > .05$), and 4 (left) and 7 (right) for deep inguinal node metastasis ($P > .05$). The co-subgroups showed differences between the left and right external iliac node metastasis ($P = 0.02$), whereas there were no differences between the other co-subgroups or between the tri- and tetra- or more subgroups (Fig. 2). As shown in Fig. 3, only the external iliac node subgroups showed significant differences between the left and right numbers of involved nodes in the single subgroup ($P < .01$) and co-subgroup ($P = .04$), whereas few differences were found in other subgroups.

We further investigated the distribution patterns of LNM according to the pathologic types. Of 337 patients with SCC, 102 (15.13%) had left external iliac node metastasis and 65 (9.64%) had right node metastasis, and the difference in frequency was statistically significant ($P < .01$); however, there were no differences between the other subgroups (47 vs 51 for common iliac nodes; 164 vs 172 for internal iliac nodes and obturator nodes; and 29 vs 17 for deep inguinal nodes; $P > .05$). Meanwhile, no differences were observed in patients with adenocarcinoma in each subgroup (Fig. 4).

4. Discussion

ICC remains a global concern, with 85% of cases occurring in developing countries. Because of insufficient resources, inefficient heath systems, and a limited number of trained health care providers, cervical cancer prevention and control are difficult to achieve in these countries.[8]

LNM is an important pathway through which ICC can spread. Pelvic and/or para-aortic LNM is common, with an incidence rate of 0% to 4.8% for stage IA, 0% to 17% for stage IB, 12% to 27% for stage IIA, and 25% to 29% for stage IIB cervical cancer.[9–11] Concurrent chemotherapy is the recommended treatment for ICC patients with LNM.[3] Because of inadequate data on the spatial distribution of lymph nodes, target volume
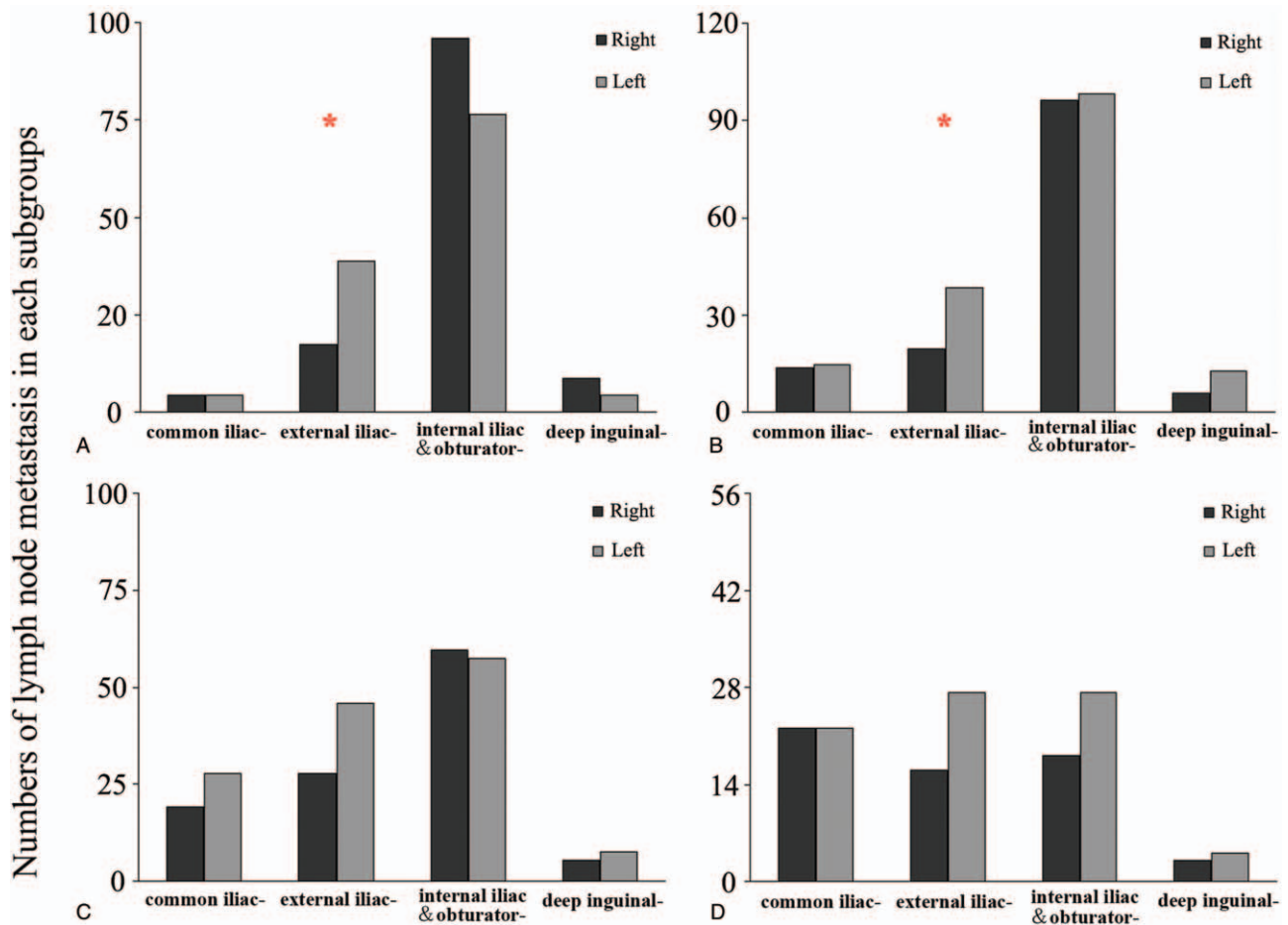
Figure 3. Numbers of lymph node metastases in each subgroup. (A) Single lymph node metastasis subgroup. (B) Co-lymph node metastasis subgroup. (C) Tri-lymph node metastasis subgroup. (D) Tetra- or more lymph node metastasis subgroup. $^{*}P < .05$.

design is often defined primarily on the basis of the distribution of normal lymphatics or according to vascular and bony landmarks, regardless of the potentially uneven distribution of LNM. Hence, a better understanding of LNM distribution patterns may help

oncologist define subgroup margins, as well as improve the delivery of precision radiotherapy. Especially in the era of IMRT, which has the potential to increase the dose to the target and reduce the dose to normal tissues, accurate delineation is pivotal
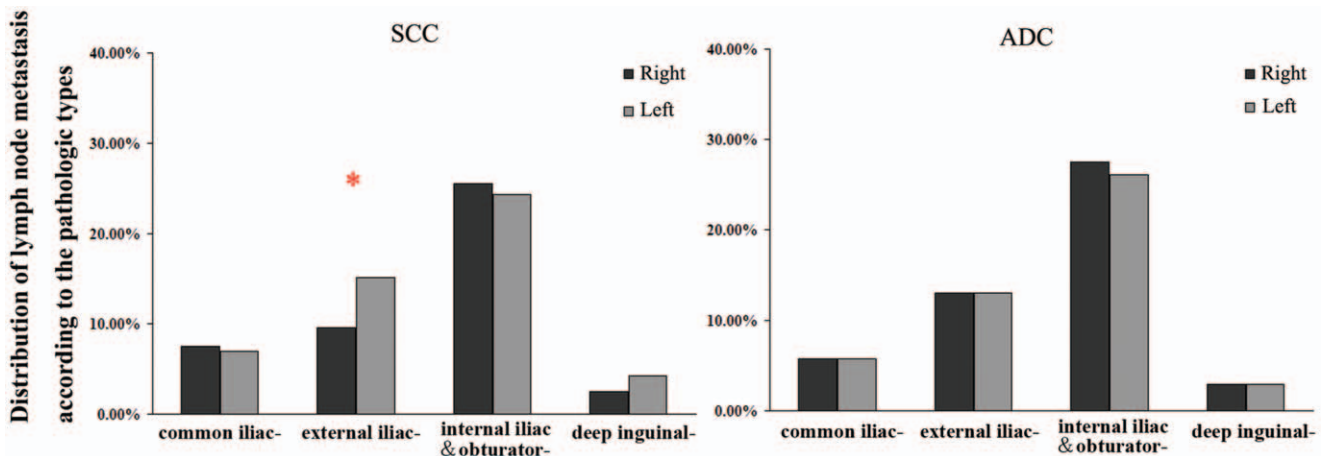
Figure 4. Distribution patterns of LNM according to pathologic types. Patients with squamous cell carcinoma were more likely to have left external iliac node metastasis. $^{*}P < .05$.

for IMRT to ensure that the target is not under- or overtreated. To the best of our knowledge, few studies have focused on investigating the distribution patterns of pelvic LNM in postoperative ICC patients at a subgroup level.

The present results of subgroup analysis showed an obvious uneven distribution of lymph node involvement within each subgroup. LNM was more common on the left side both in frequency and in total numbers. A novel finding of the present study was the higher frequency and number of LNM in the left external iliac node subgroup than the right one in the single subgroups. However, few differences were observed in other subgroups. A similar finding was obtained in co-subgroup analysis. These findings suggest that previously defined margins around the left external iliac nodes do not accurately delineate the nodal region at risk, and the contour should be broadened to cover this specific region. The phenomenon remains unclear. Takiar et al[12] reported an asymmetric distribution of para-aortic lymph node involvement in cervical cancer. These authors identified an increased risk of involvement of the para-aortic lymph nodes to the left of the aorta or the aortocaval nodes relative to the nodes to the right of the vena cava; the majority (96%) of the lymph nodes identified were immediately aortocaval or in the left para-aortic region, whereas only 3 (4%) of the lymph nodes identified were in the paracaval region, to the right of the inferior vena cava.[12] A similar phenomenon was reported in a study of para-aortic node distribution in Stage II seminoma patients.[13] These similarities in nodal distribution may indicate an uneven route of pelvic LNM, which is consistent with the fact that gynecologic inflammation is more common on the left side. This could be attributed to differences in blood supply, pelvic pressure, and/or lymphatic circulation between the 2 sides.

We analyzed the relationship between the distribution patterns of LNM and pathologic types, and the results suggested that patients with SCC were more likely to have left external iliac node metastasis, demonstrating that the asymmetric distribution may be relevant to SCC. This pattern should be considered in patients with SCC who undergo surgery and/or postoperative radiotherapy.

The main strength of the present study is that all participants were recruited from a single institution, ensuring uniform treatment guidelines, surgical expertise, and quality control of pathology. The present study provides useful information that may improve the accuracy of target volume delineation, which could help radiation oncologists refine target volumes with special consideration for the left external iliac node margins. This could ensure the accuracy of postoperative radiotherapy for patients with ICC, especially those who undergo IMRT.[14]

In summary, the present results indicated that involved nodes are distributed unevenly within subgroups. This could help surgeon focus on the dissection of the left subgroups, and help oncologist define subgroup margins, refine target volumes, and improve the accuracy of postoperative radiotherapy, especially in SCC patients.

Author contributions

YC and PZ are responsible for the original concept of the study. CF is responsible for data collecting and processing. KZ and QD were responsible for data cleaning and analysis. YC drafted the manuscript, which was revised by PZ. All authors approved the final manuscript.

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