

# Discussion on the Necessity of Bilateral Inguinal Lymphatic Area Irradiation for Cervical Cancer with Invasion of the Lower One Third of Vagina

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## Research

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## Abstract

## Background

The rate of inguinal lymph node metastasis is relatively low in cervical cancer patients. According to the NCCN (National Comprehensive Cancer Network) guidelines for cervical cancer, patients with cervical cancer invading the lower 1/3 of the vagina require bilateral inguinal lymphatic area preventive irradiation. But do they need preventive inguinal area irradiation?

## Methods

A total of 184 patients with cervical cancer accompanied by the lower 1/3 of the vagina invasion were selected as the study subjects. In this study, a trial and control method was used to select 180 patients without inguinal lymph node metastasis. The patients were divided into preventive radiotherapy group (109 cases) and non-preventive radiotherapy group (71 cases). During and after treatment, the occurrence of inguinal skin damage, lower extremity edema and femoral head necrosis was observed.

## Results

Thirteen cases (7.07%) of 184 patients were found with inguinal lymph node enlargement by imaging examination, and only 4 cases (2.17%) were further confirmed by pathology. In prophylaxis irradiation group, there were 26 (23.85%) cases of side injury. In the follow-up of two groups after treatment there was no recurrence in the inguinal lymph nodes.

## Conclusion

The inguinal lymph node metastasis rate in patients with cervical cancer invading the lower third of the vagina is 2.17%. In order to avoid such a low incidence, we carry out preventive irradiation, which will cause 23.85% of local secondary injuries. And even if we do not perform preventive inguinal lymph node irradiation, there is no difference in the recurrence rate of inguinal lymph nodes between the two groups. Preventive inguinal lymph node irradiation isn't necessary for these patients.

## Background

Lymphatic metastasis is the main metastatic mode of cervical cancer [1]. The rate of inguinal lymph node metastasis is relatively low. The lymphatic drainage of the lower 1/3 of the vagina is similar to that of the vulvar carcinoma, which is drained to the inguinal lymph nodes through the inguinal pathway [2]. Inguinal lymph node metastasis mainly occurs in vulvar cancer and vaginal cancer patients with invasion of the lower third of the vagina. Patients with cervical cancer invading the lower 1/3 of the vagina, according to the NCCN (National Comprehensive Cancer Network) guidelines for cervical cancer, require bilateral inguinal lymphatic area preventive irradiation [3]. This principle of treatment is based on the radiotherapy regimen for vaginal cancer patients with invasion of the lower third of the vagina. It has been reported that the incidence of inguinal lymph node metastasis of stage III of vulvar cancer is only 10%–26% [4], indicating that most patients with early vulvar cancer did not have inguinal lymph node metastasis. Then, cervical cancer patients with invasion of the lower third of the vagina have a lower incidence of inguinal lymph node metastasis than vulvar cancer. At present, sentinel lymph node (SLN) biopsy is used in vulvar cancer to avoid systematic lymph node dissection, reduce the injury and postoperative complications of surgery to patients, and improve the quality of life of patients. The inguinal lymph node metastasis rate of cervical cancer is 8%. Similarly, in order to reduce the treatment side-effects of cervical cancer patients with invasion of the lower third of the vagina, this study proposed that due to the different sites of cervical cancer and vaginal cancer foci, which lead to different metastasis modes, preventive radiation in the inguinal lymphatic region should not be carried out according to the principle of the treatment of vagina cancer patients with invasion of the lower third of the vagina. For vaginal cancer with invasion of the lower third of the vagina, the inguinal lymph nodes are regional lymph nodes, and the pelvic lymph nodes are distant lymph nodes. Pelvic lymph nodes in cervical cancer are regional lymph nodes, while inguinal lymph nodes are distant lymph nodes. This may be related to the different origin of the center of primary foci. The center of the vaginal cancer lesion is located in the vagina, and the local lesions are deeply infiltrated, which easily invades the local lymphatic vessels and causes the lesion to spread. While the focal center of cervical cancer was located in the cervix and far away from the lower 1/3 of the vagina, leading to a small possibility of local lymphatic vessel invasion. Moreover, we found that with the treatment of cervical cancer, cervical lesions shrink and the range of vaginal invasion significantly shrinks, presenting a "centripetal" rule. This phenomenon also supports that most of the vaginal lesions in cervical cancer patients are not deeply infiltrated. Studies have reported that the inguinal lymph node metastasis rate of vaginal cancer is 22% [5], and the inguinal lymph node metastasis rate of cervical cancer is 8% [6], indicating that the inguinal lymph node metastasis rate of cervical cancer is significantly lower than that of vaginal cancer. However, there is no report on the incidence of inguinal lymph node metastasis in patients with cervical cancer invading the lower third of the vagina. The main purpose of this study is to explore the incidence of inguinal lymph node metastasis in patients with cervical cancer in the lower 1/3 of the vagina invaded, and to explore the necessity of bilateral inguinal lymph node preventive irradiation in these patients.

## Materials And Methods

### Patients

A total of 184 patients with cervical cancer accompanied by the lower 1/3 of the vagina invasion who visited Harbin Medical University Cancer Hospital from January 2014 to December 2019 were selected as the study subjects. Inclusion criteria: pathologically confirmed cervical cancer; patients in the lower third of

the vagina invaded; fully exercised the right to know, have normal communication and cognitive skills; undergo radiotherapy. Computed tomography CT, magnetic resonance imaging MRI, positron emission tomography PET, PET-CT, and ultrasound US were used in all patients to detect lymph node enlargement in the inguinal region. The enlarged inguinal lymph nodes were then pathologically examined by ultrasound guided fine needle aspiration (USgFNAC), and the pathological sections were reviewed by two senior pathologists. In this study, a trial-and-control method was used to select 180 patients without inguinal lymph node metastasis. The patients were divided into preventive radiotherapy group (109 cases) and non-preventive radiotherapy group (71 cases) according to whether the inguinal lymph node was irradiated or not. The age, pathological type, invasion of vaginal wall and pelvic lymph node metastasis of the two groups were shown in Table 1. The differences were not statistically significant ( $P > 0.05$ ) and were comparable.

Approval from the Medical Ethics Committee of Harbin Medical University Cancer Hospital was obtained for the purpose of research.

## Treatment

We designed and optimized image-guided intensity modulated radiation therapy (IGRT) to treat the pelvic cavity and the inguinal area with Varian Eclipse Planning System. Patients in both groups were required to cover 95% of the isodose curve with PTV, no PTV dose cold spot, no hot spot of the femoral head dose, and the hot spot dose did not exceed 105% of the prescribed dose. The prescribed dose in the inguinal region was 2.0Gy/ F×25F, a total of 50Gy.

## Data analysis and statistical methods

During and after treatment, the occurrence of inguinal skin damage, lower extremity edema and femoral head necrosis was observed. Local recurrence of inguinal lymph nodes from discharge to December 2020 was followed up for 12 to 84 months. SAS 9.4 software was used for statistical analysis. Measurement data were expressed as mean±standard deviation, and comparison between groups was performed by T test. Frequency (percentage) was used for enumeration data, and comparison between groups was made by chi-square test. The test level  $\alpha = 0.05$  and  $p < 0.05$  indicated that the difference was statistically significant.

## Results

### Determination of vaginal wall invasion and inguinal lymph node metastasis rate

Vaginal invasion of 184 cases of cervical cancer patients with invasion of the lower third of the vagina is shown in Table 2. There are a total of 13 types of vaginal invasion. The case of the front vaginal wall invaded is 133 (72.28%), and the back vaginal wall invaded is 19 cases (10.33%). Both the anterior-posterior vaginal wall and the four vaginal wall invaded are seven cases (3.8%). Thirteen cases (7.07%) were found with inguinal lymph node enlargement by imaging examination, and only 4 cases (2.17%) were further confirmed by pathology, as shown in Figure 1. The detailed information of 4 patients with inguinal lymph node metastasis is shown in Table 3. In the follow-up of two groups after treatment there was no recurrence in the inguinal lymph nodes.

### Comparison of the incidence of local side injury between the two groups

In the group without inguinal region prophylaxis irradiation, only three patients had skin reactions in inguinal region, such as congestion and redness, dry desquamation, and wet peeling. In the inguinal area prophylaxis irradiation group, there were 26 cases of side injury, among which three cases both had local skin damage and lower limb edema. The incidence of side injury was significantly different between the two groups ( $p < 0.05$ ). See Table 4.

## Discussion

Lymphatic metastasis is the main spreading method of cervical cancer [7]. Cervical cancer lymphatic metastasis is divided into two groups: the level one group mainly includes paracervical lymph nodes, parauterine lymph nodes, obturator lymph nodes, internal iliac lymph nodes, external iliac lymph nodes, and presacral lymph nodes; level two groups mainly include common iliac lymph nodes, inguinal lymph nodes, and main arterial lymph nodes. Patients with definite inguinal lymph node metastasis and patients with invasion of the lower third of the vagina should receive inguinal region irradiation according to NCCN guidelines. Irradiation in the inguinal region may cause skin damage, even rupture, local contracture, edema of the lower extremities and necrosis of the femoral head, which may bring certain physical and mental harm to the patients. Radiotherapy is needed for patients with inguinal lymph node metastasis, but does cervical cancer patient with invaded lower third of the vagina without lymph node metastasis need preventive inguinal area irradiation?

At present, imaging examination methods are often used to assess the metastasis of lymph nodes. Common imaging examinations include computer tomography CT [8–9], magnetic resonance imaging MRI [10–11], positron emission tomography PET<sup>12</sup>, PET-CT [13–15], and ultrasound US [16] for inguinal lymph node examination, but the accuracy is not high. Ultimately, ultrasound-guided fine needle aspiration (USgFNAC) is required for pathological examination [9,16,17]. Stecklein et al. found that 33 (8%) of the 407 patients with stage III-IV vulvar cancer had inguinal lymph node enlargement through imaging examination, but only eight (2%) of the cases were actually tumor metastasis after biopsy. All the 33 patients underwent radiotherapy and chemotherapy. Three years later, there were 4 cases of lymph node recurrence in the inguinal region, including three cases of simultaneous vulvar region recurrence. Therefore, lymph node recurrence in the inguinal region may be related to vulvar region recurrence [18]. Henriksen's study found that the inguinal lymph node metastasis rate of cervical cancer was 8%, but the clinical estimate was more than 25% wrong when compared with autopsy results, and the lymph nodes with inflammation and sclerosis were mistaken for malignant metastasis [6]. In this study, 13 cases (7.07%) of 184 patients with cervical cancer were found to have inguinal lymph node enlargement, while only four cases (2.17%) were pathologically confirmed to have inguinal lymph node metastasis, indicating a significant difference between imaging and pathological diagnosis. Our study found that two of the four patients with inguinal lymph node metastasis were cervical cancer stage IV patients, with multiple metastases in the whole body including supraclavicular lymph nodes. Inguinal lymph node metastasis may be associated with strong invasion and metastasis ability of cancer cells and the late stage of the disease. At present, there is no clear evidence that cervical cancer patients with invasion of the lower third of the vagina are prone to inguinal lymph node metastasis, especially those confirmed by pathology.

We compared the local secondary injury and local recurrence rate of the groin in 180 patients with cervical cancer accompanied by the lower 1/3 vaginal invasion. We found that there was no recurrence in the inguinal lymph nodes in the non-preventive irradiation group, except for the local side damage less than the preventive irradiation group. Some studies have found that the rate of inguinal lymph node metastasis in patients with cervical cancer recurrence accounts for 9.8%. Even if the inguinal lymph node recurrence occurs, the prognosis after active treatment of enlarged lymph nodes is better [19]. In the follow-up of cervical cancer patients after treatment by Fagundes et al. for 10 years, 199 cases of 312 patients with stage III ~ IVA developed recurrence and metastasis, among which 8 cases (4%) had inguinal lymph node metastasis. It can be seen that the rate of inguinal lymph node recurrence and metastasis after treatment of advanced cervical cancer is not high [20].

## Conclusion

In summary, the inguinal lymph node metastasis rate in patients with cervical cancer invading the lower third of the vagina is 2.17%, which is very low. In order to avoid such a low incidence, we carry out preventive irradiation of the groin area, which will cause 23.85% of local secondary injuries of varying severity. And even if we do not perform preventive inguinal lymph node irradiation, there is no difference in the recurrence rate of inguinal lymph nodes between the two groups. Based on this, we raised the question of whether preventive inguinal lymph node irradiation is necessary for patients with cervical cancer invading the lower 1/3 of the vagina. In our study, we also found that the vaginal wall of two patients with inguinal lymph node metastasis was deeply invaded and reached the vaginal opening. Therefore, preventive radiotherapy may be required for those patients with deep vaginal wall invasion. This requires big data analysis of multiple centers and more cases.

## Abbreviations

NCCN: National Comprehensive Cancer Network; SLN: sentinel lymph node; CT: Computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound; USgFNAC: ultrasound guided fine needle aspiration; IGRT: image-guided intensity modulated radiation therapy; PTV: planning target volume;

## Declarations

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### Authors' contributions

Conception and design: Haiyan Cheng, Lina Wang, Kejin Huang.

Data collection and verification of the raw data: Lina Wang, Kejin Huang, Qi Li

Powell Data analysis and interpretation: Lina Wang, Le Wang, Lina Gu, Yuxia Wang

Writing the manuscript and the decision to submit for publication: Lina Wang, Kejin Huang, Le Wang, Lina Gu, Yuxia Wang, Qi Li, Haiyan Cheng

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Ethics approval and consent to participate

Approval from the Medical Ethics Committee of Harbin Medical University Cancer Hospital was obtained for the purpose of research.

### Consent for publication

The manuscript is approved by all authors for publication.

### Competing interests

The authors declare that they have no competing interests.

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## Tables

| Table 1 Clinical data characteristics of the two groups of patients  |                               |                                  |
|--|-------------------------------|----------------------------------|
|  | Preventive radiotherapy group | No preventive radiotherapy group |
| Total  | 109                           | 71                               |
| Age,years  | 54.93±8.01                    | 56.91±11.67                      |
| Lesion length,cm   | 5.45±1.39                     | 5.42±1.50                        |
| Vaginal invasion,N(%)  |                               |                                  |
| anterior wall  | 94(86%)                       | 57(80%)                          |
| posterior wall   | 22(20%)                       | 15(21%)                          |
| left lateral wall  | 13(12%)                       | 3(4%)                            |
| right lateral wall   | 16(15%)                       | 2(3%)                            |
| Pelvic lymph node metastasis,N(%)  | 39(36%)                       | 28(39%)                          |
| Pathological classification,N  |                               |                                  |
| quamous cell carcinoma   | 106                           | 68                               |
| Adenocarcinoma   | 2                             | 1                                |
| Undifferentiated carcinoma   | 1                             | 2                                |
| The differences of clinical data characteristics of the two groups were not statistically significant (P>0.05) . |                               |                                  |

| Table 2 List of vaginal invasion in 184 cases patients with cervical cancer |            |           |           |            |             |  |
|---|------------|-----------|-----------|------------|-------------|--|
| No  | Front wall | Back wall | Left wall | Right wall | Total(%)    |  |
| 1   | 1          | 0         | 0         | 0          | 133(72.28%) |  |
| 2   | 0          | 1         | 0         | 0          | 19(10.33%)  |  |
| 3   | 1          | 1         | 0         | 0          | 7(3.8%)     |  |
| 4   | 1          | 1         | 1         | 1          | 7(3.8%)     |  |
| 5   | 0          | 0         | 1         | 0          | 4           |  |
| 6   | 0          | 1         | 0         | 1          | 3           |  |
| 7   | 0          | 0         | 0         | 1          | 3           |  |
| 8   | 1          | 0         | 0         | 1          | 3           |  |
| 9   | 0          | 1         | 1         | 0          | 1           |  |
| 10  | 0          | 1         | 1         | 1          | 1           |  |
| 11  | 1          | 0         | 1         | 1          | 1           |  |
| 12  | 1          | 0         | 1         | 0          | 1           |  |
| 13  | 1          | 1         | 1         | 0          | 1           |  |
| Note: 1-Yes, 0-No   |            |           |           |            |             |  |

| No | Age | Stage | TNM    | Tumor long diameter (cm) | Pathologic type         | Vaginal wall invasion |           |           |            | Pelvic and abdominal lymph node metastasis  | Inguinal lymph node metastasis | SCC (ng/ml) | skin injur. |
|----|-----|-------|--------|--------------------------|-------------------------|-----------------------|-----------|-----------|------------|---|--------------------------------|-------------|-------------|
|    |     |       |        |                          |                         | Front wall            | Back wall | Left wall | Right wall |   |                                |             |             |
| 1  | 75  | IIIA  | T3N2M1 | 5                        | Squamous cell carcinoma | 1                     | 0         | 0         | 0          | Bilateral pelvic lymph nodes, abdominal paradominal lymph node                                  | Bilateral                      | 52.3        | 0           |
| 2  | 53  | IVB   | T3N2M1 | 9                        | Squamous cell carcinoma | 1                     | 0         | 0         | 0          | Bilateral pelvic lymph nodes, abdominal paradominal lymph node, left supraclavicular lymph node | Right                          | 14.5        | 1           |
| 3  | 59  | IVB   | T3N2M1 | 6                        | Squamous cell carcinoma | 1                     | 0         | 0         | 0          | Bilateral pelvic lymph nodes, abdominal paradominal lymph node, left supraclavicular lymph node | Bilateral                      | 12.8        | 0           |
| 4  | 81  | IIIB  | T3N0M1 | 4                        | Squamous cell carcinoma | 0                     | 1         | 0         | 0          | 0   | Right                          | 46.8        | 0           |

|       | N   | Radiation injury         |                |         |             | $\chi^2$ | P      |
|-------|-----|--------------------------|----------------|---------|-------------|----------|--------|
|       |     | Lower extremity edema, N | Skin damage, N | Both, N | Total, N(%) |          |        |
| No RT | 71  | 0                        | 3              | 0       | 3 (4.22%)   | 12.361   | 0.0004 |
| RT    | 109 | 5                        | 18             | 3       | 26 (23.85%) |          |        |

RT=radiotherapy No RT=no radiotherapy. Both: Lower extremity edema and Skin damage

## Figures

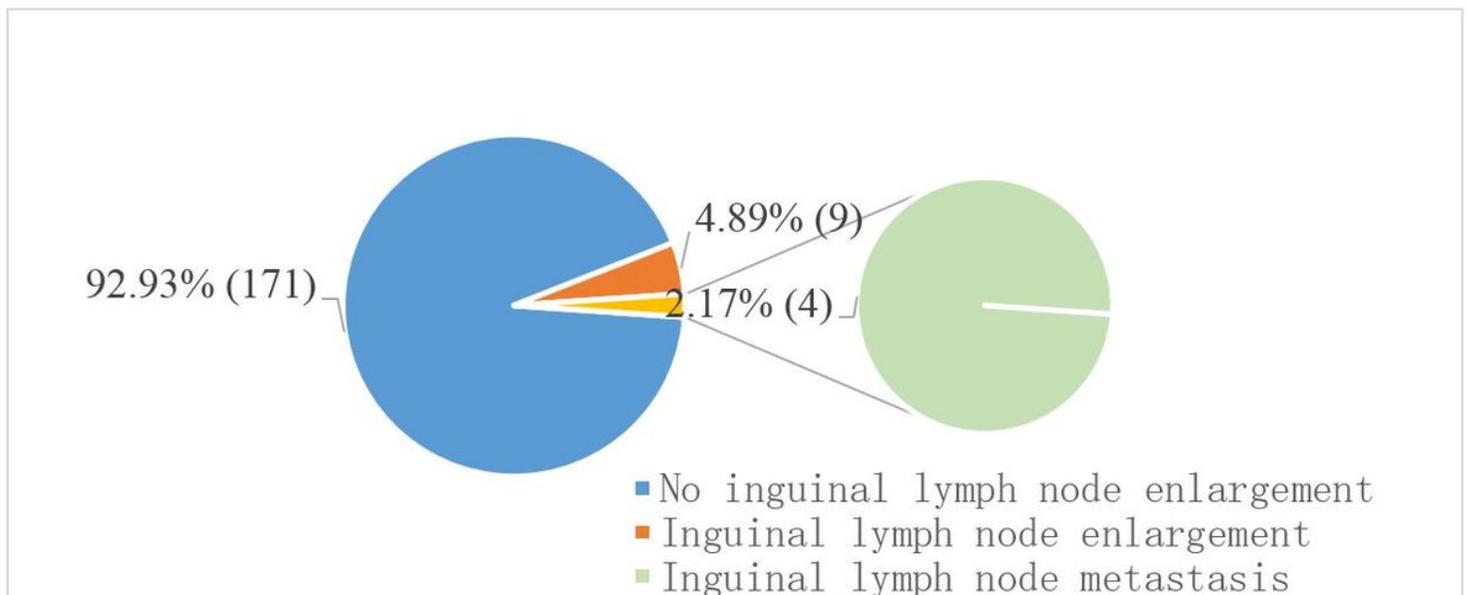
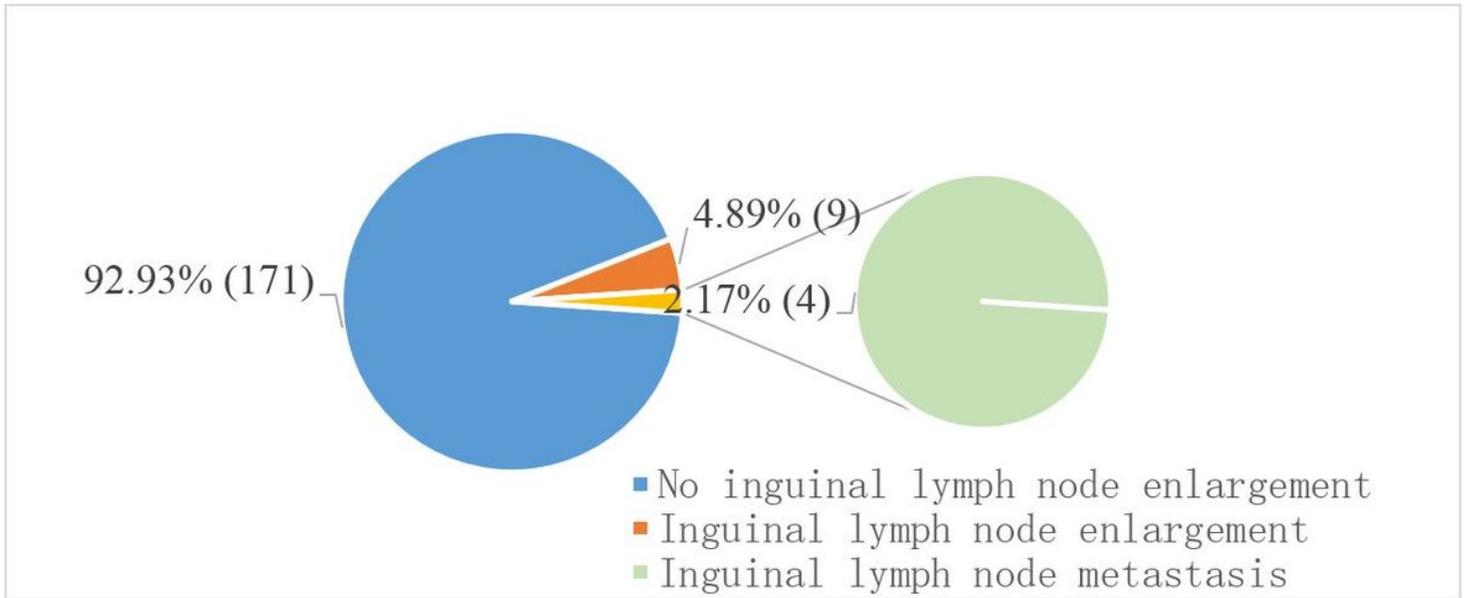


Figure 1

13 cases (7.07%) were found with inguinal lymph node enlargement by imaging examination, and only 4 cases (2.17%) were further confirmed by pathology.



**Figure 1**  
13 cases (7.07%) were found with inguinal lymph node enlargement by imaging examination, and only 4 cases (2.17%) were further confirmed by pathology.