The Clinical Characteristic Differences between Thrombosis-related Edema and Lymphedema Following Radiotherapy or Chemoradiotherapy for Patients with Cervical Cancer

Pei-Liang WANG¹, Yong-Bo CHENG² and Gulina KUERBAN³*

Cervical cancer/Radiotherapy/Chemoradiotherapy/Thrombosis-related edema/Lymphedema.

Thrombosis-related edema and lymphedema are two principal types of lower extremity edema results from radiotherapy alone or chemoradiotherapy for patients with cervical cancer. To characterize differences between them, a retrospective study was performed. We collected data including age, race, body weight, FIGO stage, histology type, platelet count, haemoglobin, time of definitely diagnosis, therapeutic regimen, edema type and which leg edema firstly occurred in. Of 40 patients who were eligible for this study, 32 were diagnosed as thrombosis-related edema and 8 diagnosed as lymphedema. The differences in patient age (p = 0.004), proportion of race (p = 0.021), the latent time (p = 0.002) and the mean platelet count (p = 0.019) were statistically significant. Among 32 patients with thrombosis-related edema, 34.4% were in stage II and 53.1% in stage III, 78.1% were squamous cell carcinoma. Among 8 patients with lymphedema, 87.5% were in stage II and 62.5% were squamous cell carcinoma. The differences were not statistically significant for weight (p = 0.94), histology type (p = 0.648), edema site (p = 0.236), haemoglobin (p = 0.088) between the two grouping patients. Although the small patient cohort is a limitation, the results suggest that the patients with thrombosis-related edema may have higher proportion, lower age, shorter latent edema time and more platelet count than those with lymphedema. Also, thrombosis-related edema was likely inclined to Uigur and lymphedema to Han race. We did not find statistical differences in weight, edema site, histology type and haemoglobin between patients with thrombosis-related edema and lymphedema.

INTRODUCTION

Lower extremity edema is one of the frequent side effects of radiotherapy or chemoradiotherapy for patients with cervical cancer.¹⁻³ It is well known that there are two principal types of lower extremity edema, i.e., thrombosis-related edema and lymphedema.³,⁴ Numerous studies have evaluated them especially focusing on prevalence and risk factors,²,⁴,⁵ but these researches have explored separately, only for thrombosis-related edema or only for lymphedema. Few reports have described differences between them in a same grouping patients with less variability in therapeutic regimens. Therefore, in this study, we compared differences between clinical characteristics of thrombosis-related edema and lymphedema in patients with cervical cancer receiving relatively similar treatments at our department. It is hoped that such analysis may be helpful in prophylaxis, early diagnosis and treatment of lower extremity edema following radiotherapy or chemoradiotherapy for patients with cervical cancer.

PATIENTS AND METHODS

Patients

Approved by university and hospital ethical committees, we performed a retrospective review of the medical records of 1621 patients (1053 Uigur and 568 Hans) after treatment for cervical cancer at The Affiliated Tumor Hospital of Xinjiang Medical University from January 2002 to December 2007. 40 women were identified to be eligible for this study from 49 patients developed lower extremity edema in the 1621 patients. They were diagnosed definitely as invasive cervical cancer by histopathology, FIGO stage IB-IVA, treat-
ed with radiotherapy alone or chemoradiotherapy. Women whose lower extremity edema due to other causes such as phlebitis and initially treated with surgery were excluded. The diagnosis of 32 patients with thrombosis-related edema was based on clinical symptoms, signs and examination by color Doppler ultrasound in combination with phlebography. The diagnosis of 8 patients with lymphedema was based on clinical presentation, lymphoscintigraphy, and the exclusion of thrombosis using color Doppler ultrasound in combination with phlebography. Before enrollment, every diagnosis was confirmed again by doctor in charge of the patient.

Radiotherapy and chemoradiotherapy

Patients received external beam radiation therapy and intracavitary brachytherapy, with or without chemotherapy. Linear accelerators were used to treat opposed anterior and posterior fields. The superior border was at iliac crest level, the lower border was at inferior margin of pubic symphysis, the two lateral borders were in sides of interior one third of femoral heads. The prescribed radiation dose to the clinical target was at a daily fraction of 2 Gy, 5 days per week, dose of tumor 30 Gy. Continuous four-field radiation dose was at a daily fraction of 1.8 Gy, 4 days per week, dose of tumor 25 Gy; midline shielding with a 4-cm-wide rectangular block was used to decrease the dose to the rectum and bladder. Point A based intracavitary brachytherapy was administered with afterloading applicator with high-dose-rate Iridium-192 source once a week, dose of tumor 40 Gy.

During the external beam radiation therapy and intracavitary brachytherapy treatment, concurrent cisplatin-based chemotherapy were administered to 29 patients. Cisplatin was used alone or in combination with 5–FU, bleomycin, vincristine or ifosfamide.

All patients were not transfused with packed platelet and not treated with erythropoietin.

Data collection

Data were collected from enrolled patients, including age, race, body weight, FIGO stage, histology type, platelet count and haemoglobin before treatment, time of definitely diagnosis of lower extremity edema after completion of radiotherapy or chemoradiotherapy, edema type and which leg edema firstly occurred in. Information sheets were completed according to medical records.

Statistic analysis

Two independent sample t-test was used to compare the two means. The proportion comparison between Uigur and Han race was assessed with the corrected Chi-Square test, same for comparison of site of edema firstly occurred in. Mann-Whitney test was used to assess differences in the latent time for two types of lower extremity edema and haemoglobin of corresponding two group patients. One sample t test was performed to compare platelet count and haemoglobin to their normal reference values. All tests were carried out at the 5% level of significance, using the SPSS 10.0 statistical software package.

RESULTS

Principal types of lower extremity edema

According to the above-mentioned eligibility, there were 40 patients were enrolled in this study. Of 40 patients, 32 were diagnosed as thrombosis-related edema and 8 diagnosed as lymphedema. The proportion of thrombosis-related edema was higher than that of lymphedema (80% vs. 20%).

Details of the proportions of types of lower extremity edema were listed in Table 1.

General characteristics of patients

Table 1 showed the basic medical data for the eligible patients. The patients with lymphedema had higher age than those with thrombosis-related edema (mean 60.1 vs. mean 49.4 years, \( t = 3.097, p = 0.004 \)). Weight were similar between two groups, totally 38 patients except 2 with immobility status causing a lack of information (\( t = 0.075, p = 0.940 \)). There was significant difference in proportion of lymphedema or thrombosis-related edema between Uigur and Han race (\( \chi^2 \) value 5.309, \( p = 0.021 \)). Lymphedema was inclined to Han, in contrast, thrombosis-related edema to Uigur. Of 32 patients with thrombosis-related edema, 34.4% were in FIGO stage II and 53.1% in FIGO stage III. Of 8 patients with lymphedema, 87.5% were in FIGO stage II. Among thrombosis-related edema and lymphedema group patients, the majority of cervical cancer were found to be squamous cell carcinoma (78.1% and 62.5%, \( \chi^2 \) value 0.208, \( p = 0.648 \)), there were only 7 and 3 adenocarcinoma respectively. With respect to left or right leg, the two types of lower extremity edema had no site specific (\( \chi^2 \) value 1.406, \( p = 0.236 \)).

The latent time of lower extremity edema was from completion of radiotherapy or chemoradiotherapy to time of confirmed diagnosis. 59.4% of latent time of thrombosis-related edema were in six months, 87.5% in twelve months. The latent time of lymphedema were 2 to 3 years except one patient 2 month. On average, the former was shorter than the

<table>
<thead>
<tr>
<th>Types of treatment</th>
<th>Thrombosis-related edema</th>
<th>Lymphedema</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>8 (20%)</td>
<td>3 (7.5%)</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>24 (60%)</td>
<td>5 (12.5%)</td>
<td>29 (72.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (80%)</td>
<td>8 (20%)</td>
<td>40 (100%)</td>
</tr>
</tbody>
</table>

Table 1. The proportions of two types of lower extremity edema following radiotherapy and chemoradiotherapy for cervical cancer, n (%).
latter. The difference between them was statistically significant \((u = 38, p = 0.002)\).

**Platelet count and haemoglobin level**

The mean platelet count in thrombosis-related edema group was \(332 \times 10^9/L\) (range 84–741 \(\times 10^9/L\)) and lymphedema group was \(185.5 \times 10^9/L\) (range 113–265 \(\times 10^9/L\)). There was a significant difference between them \((t = 2.442, p = 0.019)\). The range of normal value of platelet was 100–300 \(\times 10^9/L\). As shown in Fig. 1, increases of \(>300 \times 10^9/L\) were observed in 53% patients with thrombosis-related edema, regarded \(300 \times 10^9/L\) as test value, one sample t test analysis had no significant difference \((t = 1.196, p = 0.241)\). The platelet count of patients with lymphedema were all in normal range.

The mean haemoglobin in thrombosis-related edema group was 95.3 g/L (range 31–143 g/L) and in lymphedema group was 116.5 g/L (range 85–149 g/L). There was no statistic difference between them \((u = 77.5, p = 0.088)\). The range of normal value of haemoglobin was 110–150 g/L. Taken the lower limit 110 g/L as test value, a significant difference was detected between the values of patients with

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**Table 2.** General characteristics of patients (totally 40 patients).

<table>
<thead>
<tr>
<th>Variable and stratification</th>
<th>Thrombosis-related edema (32)</th>
<th>Lymphedema (8)</th>
<th>(p) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 51 (30–65)</td>
<td>Median 60 (42–68)</td>
<td>0.004</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>Mean 66.5 (44–115)</td>
<td>Mean 66.45 (49–80)</td>
<td>0.940</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uigur</td>
<td>21</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>11</td>
<td>7</td>
<td>0.021</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Histology type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>25</td>
<td>5</td>
<td>0.648</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Leg edema firstly occurred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left leg</td>
<td>18</td>
<td>2</td>
<td>0.236</td>
</tr>
<tr>
<td>Right leg</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Latent time (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Median 4 (range 0.4–12)</td>
<td>Median 24 (range 24–24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>Median 5.25 (range 0.03–72)</td>
<td>Median 24 (range 2–36)</td>
<td>0.019</td>
</tr>
<tr>
<td>Platelet ((\times 10^9/L))</td>
<td>332</td>
<td>185.5</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin ((g/L))</td>
<td>95.3</td>
<td>116.6</td>
<td>0.088</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Platelet count of patients with thrombosis-related lower extremity edema following radiotherapy or chemoradiotherapy.

**Fig. 2.** Haemoglobin of patients with thrombosis-related lower extremity edema following radiotherapy or chemoradiotherapy.
thrombosis-related edema and the test value ($t = 2.646, p = 0.013$), as shown in Fig. 2. Majority of haemoglobin of patients with lymphedema were in normal range.

**DISCUSSION**

In this retrospective study, we compared differences in clinical characteristics between thrombosis-related edema and lymphedema after radiotherapy alone or chemoradiotherapy for patients with cervical cancer, totally 40 patients in the same department of radiotherapy for gynecologic oncology. There were clear differences in proportion, latent time between the two types of edema and in age, racial proportion and platelet count between two group patients.

Numerous studies have evaluated incidence of thrombosis or lymphedema of lower extremity in patients after cervical cancer treatment, the former ranging from 8.5%–16.7%5–8 and the latter ranging from 2%–21%.2,9,10 However, it is difficult to make comparison between these incidences because of varying treatment. Eliminated the confounding factor, our study showed the proportion of patients with thrombosis-related edema was markedly higher than that of patients with lymphedema (80% vs. 20%). This significant difference was probably relevant to risk factors. It is well known that thrombosis-related edema occurs most directly with malignancy, chemotherapeutic agents, radiation, hormonal therapy, immobility status, alteration in platelet aggregation, elevated plasma von Willebrand factor, hypercholesterolemia, hypomagnesaemia, and so on.11–16 As opposite to this, principal lymphedema contributors were radiotherapy, individualized risk such as obesity.2,17–19 Although clinical significance of part of above risk factors is not an absolute certainty, on the whole, risk factors induced thrombosis-related edema are more than those induced lymphedema. Interaction among them are complicated and still unclear at present. Combined with clinical observations on types of lower extremity edema, it is considered by us that thrombosis-related edema is easier to occur than lymphedema.

This study showed a significantly longer latent time of lymphedema when compared to that of thrombosis-related edema. The difference is considered to be associated with the mechanisms that initiate lymphedema or thrombosis-related edema. Lymphedema is the result of the accumulation of protein-rich fluid in the soft tissues secondary to inadequate lymphatic drainage. The alterations of lymphatic drainage come from pathological changes such as radionecrosis and granulation of small lymphatic vessels, lymph nodes, and soft-tissue around vessels.6,20,21 Furthermore, it is necessary for a bit more normal tissue damage around the target of radiation, which expands the area of fibrosis. Such course has developed a long time after radiotherapy, which results in the longer latent time of lymphedema. As opposite to mechanism of lymphedema, thrombosis-related edema are due to thrombosis, based on framework of Virchow’s triad, the alterations in its components (blood composition, the vessel wall, and blood flow) following cervical cancer treatment are more rapid than that of fibrosis, despite some endothelial lesions persisting for many years after the anticancer treatment.6,22 Therefore, the former have a longer latent time compared to that of the latter.

The study comparing platelet count between patients with thrombosis-related edema and lymphedema showed a significant difference. This phenomenon may result from pathogenetic mechanism: the former is related to platelet and the latter not so. Previous investigations have found a coagulation disorders in some patients with tumor, including thrombocytopathy,15 which contributes to thrombosis and not to fibrosis. 53% of patients with thrombosis-related edema have higher platelet count, but regarded 300 × 10^9/L as test value, one sample $t$ test analysis had no significant difference. The limited number of patients probably caused this.

During the course of investigation, we found no one patient simultaneously suffering from lymphedema and thrombosis-related edema according to above-mentioned diagnostic criteria. Chemotherapy and radiotherapy are main risk factors of thrombosis and lymphedema.9,13,23 In theory, the two types of lower extremity edema may appear in the same patient receiving the above-mentioned treatments. However, this phenomenon has not been observed among 40 patients in our study or patients reported in previous studies. Probably there coexist the two types of lower extremity edema that not diagnosed by us. Probably there never coexist the two types of lower extremity edema in a same patient. In any case this issue is worthy of further study. Additionally, the result of thrombosis-related edema is inclined to Uigur and lymphedema to Han are needed to be confirmed and we will continue to do so in the future.

In conclusion, in this single institutional retrospective study limited by a small patient cohort, there may be significant differences in pathogenetic characteristics between thrombosis-related edema and lymphedema, the two principal types of lower extremity edema following radiotherapy alone or chemoradiotherapy for cervical cancer. The patients with thrombosis-related edema may have higher proportion, lower age, shorter latent edema time and more platelet count than those with lymphedema. With respect to race, thrombosis-related edema was likely inclined to Uigur and lymphedema to Han. We did not find a statistical difference in weight, edema site, histology type and haemoglobin between patients with thrombosis-related edema and lymphedema. Large cohorts of patients are needed to do the necessary multivariate analysis to elucidate the exact differences in clinical characteristics between above two types of lower extremity edema.

**REFERENCES**


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