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ORIGINAL RESEARCH

Can Ultrasound Evaluation of Lymph Node Size and Necrosis Rate Predict Chemotherapy Response in Cervical Tuberculous Lymphadenitis?

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Purpose: To explore the relationship between the initial size and the necrotic rate of lymph nodes evaluated by ultrasound in patients with cervical tuberculous lymphadenitis (CTL) and therapeutic response.

Methods: Overall, 55 patients were included in this study. Conventional ultrasound and contrast-enhanced ultrasound examination were performed before anti-tuberculosis chemotherapy. Based on the different therapeutic outcomes, they were divided into responder groups (n = 39) and non-responder groups (n = 16). The relationship between the initial size (maximum area, length diameter, short diameter), rate of necrosis, and therapeutic response were compared and analyzed between two groups.

Results: There was a significant difference in maximum area, short diameter and rate of necrosis of lymph nodes between the responder groups and the non-responder groups ($P < 0.05$). The receiver-operating-characteristic (ROC) curve analysis was used to differentiate the two groups, it showed that the area under the curve was 0.746 for maximum area and 0.721 for short diameter, respectively. The cut-off value for the lymph node maximum area and short diameter based on ROC curve analysis was determined as 3.94cm^2 (sensitivity 76.9%, specificity 68.7%) and 1.15cm (sensitivity 59.0%, specificity 93.7%), respectively. A negative correlation was observed between maximum area, short diameter, and therapeutic response.

Conclusion: The initial maximum area and short diameter of lymph nodes were found to have a negative correlation with chemotherapy response in patients with CTL. The treatment outcomes are typically unsatisfactory for lymph nodes exhibiting an initial necrosis rate of 50% or higher. These findings may be helpful for evaluating therapeutic response.

Plain Language Summary: In this study, we evaluated the relationship between the initial size and the necrotic rate by ultrasound with cervical tuberculous lymphadenitis (CTL) and therapeutic response. We found that the initial maximum area and short diameter of lymph nodes have a negative correlation with chemotherapy response in patients with CTL. The treatment outcomes are typically unsatisfactory for lymph nodes exhibiting an initial necrosis rate of 50% or higher. These findings may be helpful for evaluating therapeutic response in the early stages.

Keywords: ultrasound, tuberculous lymphadenitis, cervical, anti-tuberculosis chemotherapy, response

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by the *Mycobacterium tuberculosis* (MTB) complex, which ranks among the top ten leading causes of death worldwide.[1–3] Extra-pulmonary TB (EPTB) is a significant component of the TB epidemic, and although the global incidence rate of TB shows a downward trend, the number of EPTB cases decreases slowly.[4]

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Cervical tuberculous lymphadenitis (CTL) is the most common form of EPTB, for which systemic anti-TB chemotherapy is the primary treatment option. This typically involves oral medication for a minimum duration of six months.[5–8] The Infectious Disease Society of America (IDSA) guideline recommends surgical excision only in exceptional circumstances such as drug-resistant organisms or paradoxical upgrading reactions.[9,10] However, ineffective long-term medication may result in liver and kidney damage, as well as mental stress for the patient. Therefore, predicting the effectiveness of chemotherapy for CTL at an early stage could help guide clinical adjustments to treatment plans.

For patients with CTL, bacteriological evaluation of the response to treatment is often limited by the difficulty in obtaining follow-up specimens. Response often judged on the basis of clinical and image findings.[11] However, there are limited data on the relationship between ultrasound image and treatment outcome. Conventional ultrasound (US) can visually display the size and morphology of lymph nodes, while contrast-enhanced ultrasound (CEUS) significantly improves identification ability regarding necrotic areas. The combination of these two techniques has shown promising clinical value in evaluating CTL.[12,13] The aim of this study was to assess the initial maximum area, length diameter, short diameter, and necrosis rate of lymph nodes before chemotherapy, to determine whether these ultrasound evaluation indicators can predict prognosis in CTL.

Materials and Methods

Patients

All patients or their guardians signed an informed consent form agreeing to the use of their relevant data in this study. The study protocol was approved by the Human Research Ethics Committee of Hangzhou Red Cross Hospital (2022-YS-151). This study complies with the Declaration of Helsinki. From February 2020 to December 2022, a total of 55 patients were retrospectively enrolled, and these patients were confirmed as CTL finally. The images for each patient were obtained in DICOM format from the PACS database, and patient information was collected from the hospital records.

The inclusion criteria were as follows: (1) positive acid-fast bacilli (AFB) smear, MTB culture, or molecular biology testing (Gene X-pert and next-generation sequencing); (2) initial and uninterrupted anti-TB chemotherapy for at least 6 months; (3) complete imaging data, including conventional US and contrast-enhanced ultrasound (CEUS) examinations before treatment, and conventional US examinations after 6 months of treatment; (4) age above 18 years with no allergy to US contrast agents.

The exclusion criteria were as follows: (1) recurrent CTL; (2) loss of follow-up during anti-TB treatment, irregular medication, or inability to complete the entire course of treatment due to various reasons, or incomplete medical records; (3) HIV positive; (4) drug resistance developed during the treatment process; and (5) a sinus was formed at the initial treatment.

All cases received standard anti-TB chemotherapy: 2HRZE/4HRE, which means the HRZE regimen was used for 2 months in the intensive phase and 4 months in the continuing phase. Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E) were utilized. Therapeutic response at the end of 6 months was defined as follows: (1) responder group-patients with no or only small residual palpable lymph nodes and no symptoms; (2) non-responder group-appearance of new symptoms, persistence of new lymph nodes, and/or insufficient changes in lymph nodes.[14]

Conventional US and CEUS Examination

We utilized the Philips iU-Elite US diagnostic instrument (Washington, USA) equipped with L12-5 (Frequency range: 5–12 MHz) and L9-3 (Frequency range: 3–9 MHz) probes, as well as the Mindray Resona 7S (Shenzhen, China) equipped with L14-5 (Frequency range: 5–14 MHz) and L9-3U (Frequency range: 3–9 MHz) probes.

In the conventional US method, patients were positioned supine or laterally, and each area was examined following the corresponding anatomical regions' protocol. The largest suspicious lymph node was selected as the target for observation, and its length diameter and short diameter were measured in the longitudinal section. The maximum area was delineated along the outer edge of the lymph nodes with continuous measurement technique.

CEUS examination low mechanical index (0.06) pulse reverse harmonic imaging and the sulfur hexafluoride microbubble ultrasonic contrast agent SonoVue (Bracco SpA, Milan, Italy) were used for patient examination. The

images were stored in the instrument hard-disk for subsequent analysis. Select the image with the largest area of no enhancement (maximum necrotic area) when lymph node enhancement reaches its peak. The estimated necrosis rate is categorized as <50% or ≥50% based on the extent of necrotic area, which accounts for 50% of the total lymph node area.

Statistical Analysis

The data were analyzed by SPSS 25.0 statistical software (IBM). Count data were expressed as percentages (%) and compared using the Chi-square test. Measurement data, which followed a normal distribution, were presented as mean ± SD and compared using the *t*-test. Non-normally distributed data were expressed as median [interquartile range (IQR)], and the two groups were compared using the Mann–Whitney *U*-test. The correlation with therapeutic response was analyzed using Spearman analysis. Receiver-operating-characteristic (ROC) curve analysis was performed to differentiate between the two groups. A significant difference was defined as $P < 0.05$.

Results

Patient

Among the 55 CTL patients, 39 (70.91%) were in the responder group, including 12 males and 27 females, with an age range of 19–77 years. The median age was 30.00 (4; IQR, 26–49) years. There were 16 cases (29.09%) in the non-responder group, including 5 males and 11 females, with an age range of 22–63 years. The median age was 33.00 (4; IQR, 23.75–42) years. There was no statistically significant difference in age and gender between the two groups ($P > 0.05$). The demographic characteristics of the patients are presented in Table 1.

Analysis of Lymph Node Size and the Rate of Necrosis

There was a significant difference in maximum area (2.38 [4; IQR, 1.44–3.76] cm² vs 4.80 [4; IQR, 2.56–8.77] cm²), short diameter (1.20 [4; IQR, 1.00–1.60] cm vs 1.55 [4; IQR, 1.23–2.00] cm) and rate of necrosis between the responder groups and the non-responder groups ($P < 0.05$). There was no significant difference in the length diameter between the two groups (2.40 [4; IQR, 2.30–4.20] cm vs 3.39±1.08 cm) ($P > 0.05$). Table 1 presents these findings. Figure 1 displays US images of a non-responder patient.

In ROC curve analysis (Figure 2), the maximum area and short diameter of the CTL were compared between responder groups and non-responder groups, the AUC was 0.746 and 0.721 ($P = 0.004$ and $P = 0.011$, respectively). Based on the ROC curve analysis, the cut-off value for the maximum area and short diameter of lymph node was determined to be at a size of 3.94 cm^2 (sensitivity 76.9%, specificity 68.7%) and 1.15 cm (sensitivity 59.0%, specificity 93.7%). The data are presented in Table 2.

Table 1 General Characteristics of 55 Patients with Cervical Tuberculous Lymphadenitis

Characteristic	Responder (n=39)	Non-Responder (n=16)	χ^2 or Z value	P value
Age (y)	30.00 (26–49)	33.00 (23.75–42)	−0.474	0.636
Sex (%)			0.001	0.972
Males	12 (30.77%)	5 (31.25%)		
Females	27 (69.23%)	11 (68.75%)		
A_1 (cm^2)	2.38 (1.44–3.76)	4.80 (2.56–8.77)	−2.845	0.004
L (cm)	2.40 (2.30–4.20)	3.39±1.08	−1.939	0.053
S (cm)	1.20 (1.00–1.60)	1.55 (1.23–2.00)	−2.571	0.010
A (%)			6.782	0.025
<50%	20 (51.28%)	4 (25.00%)		
≥50%	14 (35.90%)	12 (75.00%)		
No necrosis	5 (12.82%)	0 (0.00%)		

Abbreviations: A_1, maximum area; L, maximum length diameter; S, maximum short diameter; A, necrotic rate.

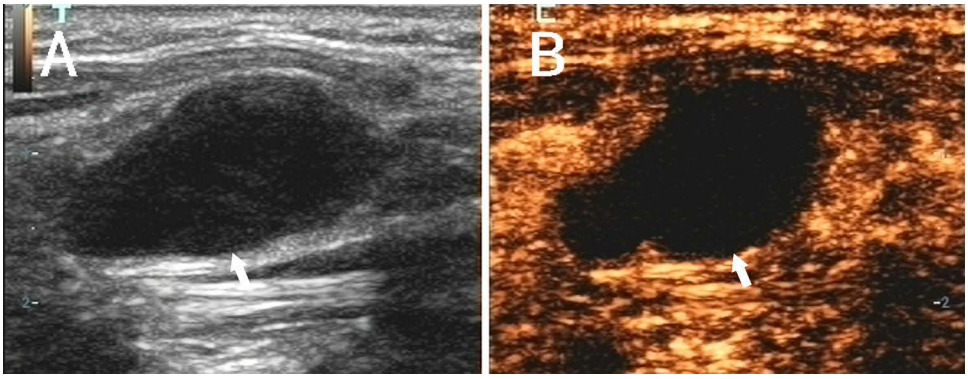

Figure 1 The ultrasound image of a non-responder cervical tuberculous lymphadenitis patient (45-year-old man). (**A**) Conventional ultrasound showed lymph node (indicated by arrows), the maximum length diameter was 2.4 cm, and short diameter was 1.2 cm. (**B**) Contrast-enhanced ultrasound showed that the area without enhancement was lymph node necrosis (arrows), the necrotic rate ≥ 50%.

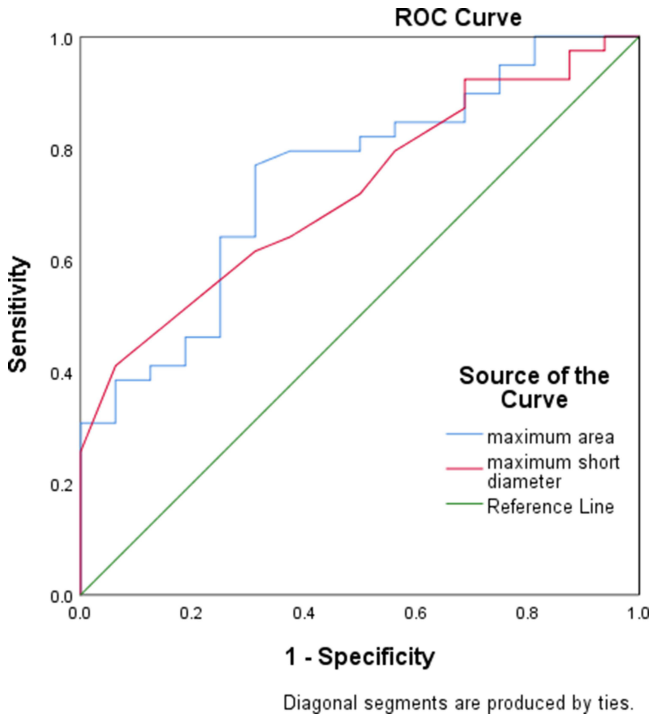

Figure 2 Receiver-operating-characteristic curve for the maximum area and short diameter of cervical tuberculous lymphadenitis in the analysis of response to anti-tuberculous chemotherapy. The AUC was 0.746 and 0.721, respectively.

Correlation Analysis

A negative correlation was observed between the maximum area, short diameter, and therapeutic response with correlation coefficients r = −0.423, $P = 0.001$, r = −0.350, $P = 0.009$, respectively, as shown in Figure 3.

Table 2 ROC Analysis of the Relationship Between the Maximum Area, Short Diameter and Therapeutic Response

Characteristic	AUC	SE	P value	95% CI	Cut-off value	Sensitivity	Specificity
A_I	0.746	0.071	0.004	0.607–0.885	3.94	76.9	68.7
S	0.721	0.070	0.011	0.585–0.858	1.15	59.0	93.7

Abbreviations: A_I, maximum area; S, maximum short diameter; AUC, area under the curve; SE, standard error; 95% CI, 95% confidence interval.

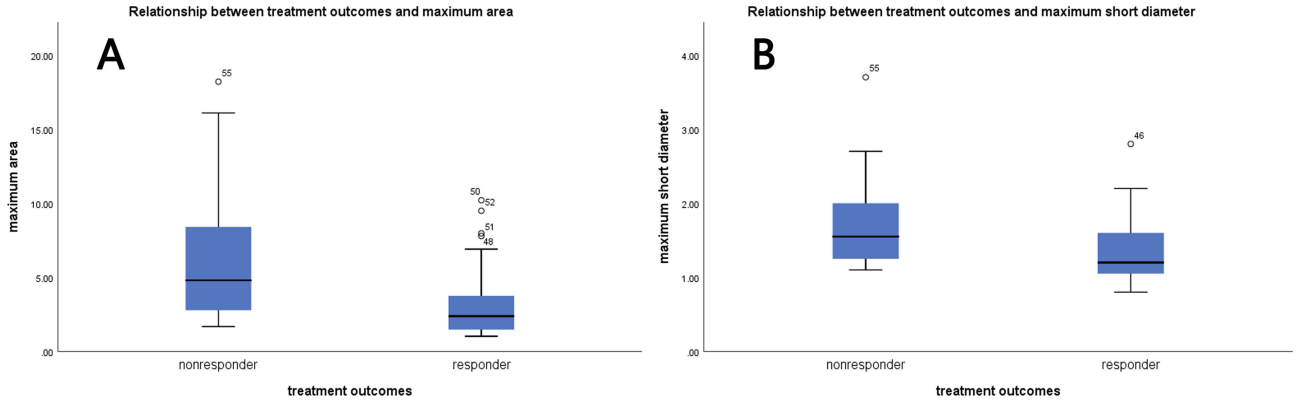

Figure 3 Box plot shows relationship between therapeutic outcomes, initial maximum area and short diameter of cervical tuberculous lymphadenitis. (**A**) There was a statistically significant difference between the maximum area and therapeutic response [responder group vs non-responder group, 2.38 (1.44–3.76) cm^2 vs 4.80 (2.56–8.77) cm^2, $P = 0.004$]. (**B**) There was a statistically significant difference between the short diameter and therapeutic response [responder group vs non-responder group, 1.20 (1.00–1.60) cm vs 1.55 (1.23–2.00) cm, $P = 0.010$]. The upper edge of the box is the 75th percentile of the data set; lower hinge represents the 25th percentile. The line in the box represents the median, circles and small stars are outliers.

Discussion

According to the Global Tuberculosis Report 2023 published by the World Health Organization (WHO), TB remains a significant global public health challenge.[3] Currently, anti-TB chemotherapy is considered as the primary treatment for CTL, with the standard "6-month regimen" still being used for drug-sensitive tuberculosis treatment.[3] Multiple studies have demonstrated that systemic anti-TB chemotherapy effectively treats CTL, and a six-month treatment may be sufficient for drug-susceptible organisms. There is no significant difference in treatment effectiveness between 6 and 9 months of therapy.[7,15–17] Furthermore, not all residual lymph nodes after 6 months of concurrent anti-TB treatment indicate recurrence or treatment failure.[18] Therefore, this study selected 6 months after chemotherapy to evaluate the therapeutic response of CTL.

A significant challenge for TB control efforts has been the monitoring of TB therapy and determination of TB treatment success.[19] Early and accurate evaluation of CTL prognosis is beneficial for adjusting treatment plans.[20] The commonly used smear microscopy or culture is not available to monitor patients with CTL.[11] Although a range of risk factors have been shown to be associated with poor TB patient treatment outcomes, including demographic variables, history of TB treatment, disease severity, and clinical signs and symptoms,[19] few have been applied to CTL. Importantly, more research is needed to assess the utility of different markers in predicting response to treatment outcomes in patients with CTL. In case of studies on tuberculous lymphadenitis, Lee et al[11] concluded that residual lymph nodes at the end of treatment have usually been used for assessing treatment outcomes. Yu et al[14] evaluated the value of multimodal ultrasonography in assessing therapeutic response of CTL to anti-TB drugs, the result showed no statistically significant difference in the maximum length diameter between the responder groups and non-responder groups before treatment, but did not involve the maximum initial area, short diameter and necrotic area ratio of lymph nodes.

The US imaging of lymph nodes is widely accessible and frequently used, making it the preferred examination modality for diagnosing CTL.[21] In this study, the correlation between the initial lymph node size and the prognosis of anti-TB chemotherapy in patients with CTL was evaluated by US examination. Our study found that the specificity of lymph node short diameter with a cut-off value of 1.15 cm in predicting non-response to anti-TB chemotherapy was as high as 93.7%, and the AUC was 0.721, indicating that it had a certain value in predicting the therapeutic response of CTL based on lymph node short diameter levels. The causes may be highly toxic MTB or weakened human immune system leads to destructive growth of MTB in infected lymph nodes, resulting in rapid caseating necrosis and liquefactive necrosis. This increases pressure within the lymph nodes and changes their shape to round or quasi-round. Therefore, if the initial short diameter of the lymph nodes is large, the pressure in the lesions is high, indicating a high risk of treatment failure. In addition, there was no significant difference in the length of lymph nodes between the two groups in this study, which was consistent with the research of Yu[14] and Je et al.[22] However, the results of multivariate analysis by Chahed et al[23] showed that the length of lymph nodes ≥3 cm was an independent risk factor for poor treatment effect, contradicting the results of this study.

Predictive value of maximum lymph node area for response to anti-TB treatment has been rarely reported. In this study, we found a negative correlation between the maximum area and therapeutic response. The cut-off value of 3.94 cm^2 predicted a sensitivity, specificity, and AUC of no response to chemotherapy at 76.9%, 68.7%, and 0.743, respectively. Some scholars calculated the lymph node volume based on CT to predict the treatment response, with a sensitivity of 88.2%, a specificity of 74.3%, and an AUC of 0.845.[15] Although lymph node volume-based prediction may be more effective, its clinical application is limited by the cumbersome acquisition of lymph node volume and time-consuming computer processing. In contrast, the lymph node area can be directly delineated and displayed on the ultrasound instrument, which is simple, time-saving and labor-saving, and more convenient for primary hospitals without good conditions to evaluate the prognosis of treatment. Furthermore, Zhao et al[24] applied ultrasound in the prediction of CTL rupture found, the lymph node volume in the ruptured group was significantly larger than that in the unruptured group, with high risk of treatment failure, which may be related to internal pressure of the lymph node and infection severity. These findings are consistent with our study.

The formation of necrosis is related to the progression of the disease, and its increase could be considered as a factor contributing to poor drug therapeutic response.[14] Joo et al[15] found that 32.7% of TCL cases requiring additional surgical treatment were associated with a high necrotic rate. In this study, 75.00% of non-responsive groups had a high necrosis rate, and there was a statistically significant difference in necrosis rates between the two groups. This suggests that the initial high necrosis rate in CTL patients indicates that the current drug treatment plan may not prevent disease progression and could potentially lead to treatment failure.

This study possesses certain limitations. First, the relatively limited sample size of this study and analysis conducted at a single institution. Therefore, studies with large sample sizes and multiple institutions. Second, the study employed a 6-month follow-up period, neglecting long-term follow-up for all cases, which resulted in cases with slow progression being overlooked. Consequently, there is a degree of error in the follow-up results of the patients. Third, the necrosis within CTL may manifest as microfocal lesions, posing challenges for visualization using conventional US and CEUS. The analysis of CTL ultrasound images and prognosis is a long-term and complex undertaking, necessitating further comprehensive and detailed investigation in the future.

Conclusions

In conclusion, the necrotic rate of CTL was not associated with therapeutic response. The assessment of maximum lymph node area and short diameter by ultrasound may predict the treatment prognosis of CTL at an early stage, which is beneficial for adjusting the treatment plan and reducing the burden on public health.

Data Sharing Statement

Data will be made available on reasonable request.

Ethics Approval and Consent to Participate

All patients gave written informed consent and the study was approved by the Human Research Ethics Committee of Hangzhou Red Cross Hospital. This study complies with the Declaration of Helsinki.

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Disclosure

The authors declared that there was no potential interest and commercial conflict in this study.

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