Histogram Analysis of Computed Tomography Images to Differentiate Lacrimal Lymphoma and Lacrimal Inflammatory Pseudotumor

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Research Article

Keywords: Lacrimal lymphoma, Lacrimal inflammatory pseudotumor, Computed tomography, Histogram

Posted Date: April 12th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2777206/v1

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Abstract

Background To investigate the value of the histogram analysis to identify between lacrimal lymphoma(LL) and lacrimal inflammatory pseudotumor(LIP).

Methods CT images of 30 patients with LL and 43 patients with LIP were analyzed for imaging features and histogram parameters. Tumor morphology and histogram parameters of LL and LIP were compared. Receiver operating characteristic (ROC) analysis of area under the curve (AUC), sensitivity, and specificity were used to measure the differential diagnostic efficacy of these parameters.

Results Compared those in LIP group lesions in LL group were more bilateral and had clearer boundary (P=.036 and .000, respectively), while no significant difference of other CT features was found between groups(all P>.05). The variance of the LIP group were greater than that of the LL group, with statistically significant differences (P=.000). The mean, skewness, kurtosis, 1th, 10th, and 50th percentiles of the LL group were greater than those of the LIP group, with statistically significant differences (all P<.05). Acceptable discrimination was detected between LL and LIP with mean, variance, skewness, kurtosis, 1th, 10th, and 50th percentiles alone (AUC =0.789, 0.825, 0.716, 0.762, 0.624, 0.719, and 0.666 respectively). The combination of these histogram parameters yielded excellent discrimination between LL and LIP(AUC = 0.961), with sensitivity and specificity values greater than 0.800.

Conclusions Histogram analysis of CT images is feasible for differentiating LL from LIP. It can be used as a supplementary tool for differentiating the lacrimal tumors.

Background

Lacrimal gland tumors (LGTs) are uncommon with an estimated incidence of < 1/1000000 per year. LGTs represent 3–18% of all orbital tumors commonly[1–3]. There are four main groups of lacrimal gland lesions: inflammatory, lymphoid, primary epithelial tumors, and metastatic tumor[4]. Traditionally, it has been reported that approximately 50% of LGTs originated from epithelial elements and 50% are of non-epithelial origin. Among the non-epithelial tumors, 50% are lymphoid tumors and 50% are inflammatory lesions[5]. Lacrimal lymphoma(LL) and Lacrimal inflammatory pseudotumor(LIP) are the most common diseases of the non-epithelial tumors. Although the clinical manifestations of LL and LIP are generally similar, the treatment programme and recovery outcome are quite different.

There have been many studies about differential diagnosis of the LGTs by imaging examinations such as ultrasonography (US), computed tomography (CT), and magnetic resonance (MR)[6–9]. Advances in techniques have improved their usefulness as tools for morphological diagnosis and differential diagnosis. Ultrasound is widely used in the diagnosis of ocular diseases due to the advantages of convenient, safe, non-invasive and cheap. But the low clarity, resolution, and penetration limit its clinical application. MR with high soft tissue resolution plays an increasingly important role in the diagnosis of lacrimal gland disease, especially distinguish between the orbital and palpebral lobes of lacrimal gland. Nevertheless, its disadvantages include limited availability for patients with metal prostheses or certain
pacemakers, high cost and long waiting times. CT, an accessible, affordable and high-resolution examination equipment, can be used to help clinicians evaluate tumors to confirm the presence of LGTs, assess the extent of tumor, and detect erosive changes of orbital wall, to facilitate the determination of benign or malignant nature of the tumor for appropriate treatment. But interpretation of CT findings is mainly dependent on subjective, naked-eye judgment and the clinical experience, the differential diagnosis of LGTs is still an insurmountable problem. Gray-scale histogram analysis of the CT images can extract a variety of image information that cannot be distinguished by the naked eye. It can also reflects the microstructures of LGTs and the distribution of internal biology indicators. Due to the advantages of the CT gray-scale histogram, it has been used in the differential diagnosis of different types of tumors and tumor grade[10–12].

In this study, we predicted that the histogram parameters of CT images would differ between LL and LIP. Therefore, the objective of this study was to compare these parameters of CT gray-scale histogram of LL and LIP, and hope to propose a new method to distinguish between LL and LIP further.

**Methods**

**Patient Selection**

Written informed consent was waived owing to the noninterventional and retrospective nature of this study. The need for informed consent was waived by the ethics committee of the First Affiliated Hospital of the Medical College, because of the retrospective nature of the study. All the methods were performed in accordance with relevant guidelines and regulations.

In this retrospective analysis, 124 consecutive patients with LGTs treated in the First Affiliated Hospital of the Medical College of Shihezi University from January 2009 to December 2021 were initially included. We excluded 26 patients because of controversial or epithelial-originated pathological diagnosis, leaving 98 patients who were diagnosed with LL or LIP, which were conformed by surgical pathology, as shown in Figures 2 and 3. Next, 19 patients with no orbital CT examination were excluded, resulting in 79 patients. Finally, 6 patients were excluded because of unclear or incomplete CT images. In total, 73 patients were included in the study (Figure 1). There were 30 patients (17 males and 13 females) in LL group and 43 patients (26 males and 17 female) in LIP group.

**CT examination**

A Philips Brilliance 16 row CT scan (Discovery CT750 HD, GE Medical Systems, Waukesha, WI, USA) was used for all orbital CT scanning. Scanning parameters: 200mAs, 120KV, matrix 512, the reconstruction layer thickness of 1mm. Routine orbital CTs were performed.

**Image acquisition and analysis**

The general characteristics of lacrimal gland masses were independently analyzed by a physician well-experienced in CT diagnosis and a chief physician in ophthalmology. Both examiners were blinded to the
pathological diagnoses of the tumors. The following CT image features of tumor morphology in the 95 lesions were analyzed: 1. Whether the tumor is bilateral. 2. Whether the boundary is clear. 3. Whether the shape is regular. 4. Whether the tumor is wrapping around the eye.

After downloading the images through the picture archiving and communication systems (PACS) workstation, the both physician used Mazda4.6 software (http://www.eletel.p.lodz.pl/mzada/) to complete the histogram analysis. As it was challenging to distinguish between the orbital and palpebral lobes of the lacrimal gland, the entirety of the gland was treated as a single structure, with the image in which the gland was largest being selected for analysis.

For the analysis of histograms, region of interest (ROI) was drawn with red along the edge of the LGTs and a consensus was reached on the most appropriate ROI for LGTs by 2 fore-mentioned physicians. Histograms were automatically generated by used Mazda for each ROI and the characteristic parameters were derived, as shown in Figures 2 and 3.

**Statistical Analysis**

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. The chi-square test was employed to compare the differences of count data. All continuous variables were reported as mean±standard deviation (SD), which tested for normality and analyzed using analysis of variance (ANOVA). Parameters with normal distribution and homogeneity of variances were analyzed by used independent-samples T test. For parameters that did not satisfy normal distribution and uneven variance, two independent-samples non-parametric Test was adopted for data analysis.

The ROC curves with different statistically significant parameters were drawn, with the sensitivity as the ordinate and 1-specificity as the abscissa. The area under the curve(AUC) was calculated, and their diagnostic efficacy was analyzed. Cutoff values were established by calculating the maximal Youden index (Youden index=sensitivity+specificity-1). P values less than 0.05 were considered statistically significant.

**Results**

Compared those in LIP group, lesions in LL group were more bilateral and had clearer boundary (P = .036 and .000, respectively), while no significant difference of other CT features was found between groups (all P > .05). As shown in Table 1.
Table 1
Tumor morphology of LL and LIP

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tumor classification</th>
<th>$\chi^2$ value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LL</td>
<td>LIP</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>4.389</td>
<td></td>
<td>.036*</td>
</tr>
<tr>
<td>Yes</td>
<td>5(16.7)</td>
<td>17(39.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25(83.3)</td>
<td>26(60.5)</td>
<td></td>
</tr>
<tr>
<td>Boundary</td>
<td>34.596</td>
<td></td>
<td>.000*</td>
</tr>
<tr>
<td>Clear</td>
<td>30(85.7)</td>
<td>14(23.3)</td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>5(14.3)</td>
<td>46(76.7)</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>0.051</td>
<td></td>
<td>.822</td>
</tr>
<tr>
<td>Regular</td>
<td>19(54.3)</td>
<td>34(56.7)</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>16(45.7)</td>
<td>26(43.3)</td>
<td></td>
</tr>
<tr>
<td>Wrap around the eye</td>
<td>0.013</td>
<td></td>
<td>.910</td>
</tr>
<tr>
<td>Yes</td>
<td>20(57.1)</td>
<td>35(58.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15(42.9)</td>
<td>25(41.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference. $P < 0.05$.

The average variance values of LL and LIP were $360.691 \pm 123.425$ and $585.216 \pm 202.377$. The variance of the LIP group was greater than that of the LL group, with statistically significant differences ($P = .000$). The mean values of LL and LIP were $114.542 \pm 8.021$ and $105.065 \pm 8.682$. The average skewness values of LL and LIP were $0.823 \pm 0.894$ and $0.213 \pm 0.710$. The average kurtosis values of LL and LIP were $2.230 \pm 3.152$ and $0.321 \pm 1.307$. The average 1st percentiles values of LL and LIP were $70.040 \pm 18.189$ and $61.444 \pm 16.430$. The average 10th percentiles values of LL and LIP were $89.040 \pm 12.545$ and $78.221 \pm 14.155$. The average 50th percentiles values of LL and LIP were $113.240 \pm 9.189$ and $107.311 \pm 9.793$. The mean, skewness, kurtosis, 1th, 10th, and 50th percentiles of the LL group were greater than those of the LIP group, with statistically significant differences (all $P < 0.05$). As shown in Table 2.

LL, lacrimal lymphoma; LIP, lacrimal inflammatory pseudotumor;
Table 2
Histogram parameters of LL and LIP

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LL</th>
<th>LIP</th>
<th>t/z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>114.542 ± 8.021</td>
<td>105.065 ± 8.682</td>
<td>5.530</td>
<td>.000*</td>
</tr>
<tr>
<td>Variance</td>
<td>360.691 ± 123.425</td>
<td>585.216 ± 202.377</td>
<td>-5.449</td>
<td>.000*</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.823 ± 0.894</td>
<td>0.213 ± 0.710</td>
<td>-3.615</td>
<td>.000*</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>2.230 ± 3.152</td>
<td>0.321 ± 1.307</td>
<td>-4.401</td>
<td>.000*</td>
</tr>
<tr>
<td>Perc1th</td>
<td>70.040 ± 18.189</td>
<td>61.444 ± 16.430</td>
<td>2.407</td>
<td>.018*</td>
</tr>
<tr>
<td>Perc10th</td>
<td>89.040 ± 12.545</td>
<td>78.221 ± 14.155</td>
<td>-3.669</td>
<td>.000*</td>
</tr>
<tr>
<td>Perc50th</td>
<td>113.240 ± 9.189</td>
<td>107.311 ± 9.793</td>
<td>3.044</td>
<td>.003*</td>
</tr>
<tr>
<td>Perc90th</td>
<td>136.740 ± 12.088</td>
<td>134.889 ± 13.202</td>
<td>0.713</td>
<td>.477</td>
</tr>
<tr>
<td>Perc99th</td>
<td>169.380 ± 28.056</td>
<td>164.267 ± 30.854</td>
<td>-1.103</td>
<td>.270</td>
</tr>
</tbody>
</table>

LL, lacrimal lymphoma; LIP, lacrimal inflammatory pseudotumor;

*Statistically significant difference. \( P < 0.05 \).

Acceptable discrimination was detected between LL and LIP with mean, variance, skewness, kurtosis, 1th, 10th, and 50th percentiles alone (AUC = 0.789, 0.825, 0.716, 0.762, 0.624, 0.719, and 0.666 respectively). The combination of these histogram parameters yielded excellent discrimination between LL and LIP (AUC = 0.961), with sensitivity and specificity values greater than 0.800. As shown in Table 3.

Table 3
ROC analysis of solitary and multiple parameters to diagnose LL and LIP

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden index</th>
<th>Optimal cutoff value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.789</td>
<td>0.820</td>
<td>0.711</td>
<td>0.531</td>
<td>108.415</td>
</tr>
<tr>
<td>Variance</td>
<td>0.825</td>
<td>0.756</td>
<td>0.820</td>
<td>0.576</td>
<td>440.2</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.716</td>
<td>0.720</td>
<td>0.689</td>
<td>0.409</td>
<td>0.328</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.762</td>
<td>0.689</td>
<td>0.740</td>
<td>0.429</td>
<td>0.54</td>
</tr>
<tr>
<td>Perc1th</td>
<td>0.624</td>
<td>0.360</td>
<td>0.911</td>
<td>0.271</td>
<td>81</td>
</tr>
<tr>
<td>Perc10th</td>
<td>0.719</td>
<td>0.600</td>
<td>0.756</td>
<td>0.356</td>
<td>88.5</td>
</tr>
<tr>
<td>Perc50th</td>
<td>0.666</td>
<td>0.820</td>
<td>0.444</td>
<td>0.264</td>
<td>107</td>
</tr>
<tr>
<td>Multiparameter</td>
<td>0.961</td>
<td>0.889</td>
<td>0.960</td>
<td>0.849</td>
<td>0.588</td>
</tr>
</tbody>
</table>

AUC, area under the curve; LL, lacrimal lymphoma; LIP, lacrimal inflammatory pseudotumor;
Masses of the lacrimal gland are relatively uncommon, with an incidence of approximately 1.3 per 1 million people per year\cite{13,14}. A palpebral mass in the lateral upper eyelid, inferonasal globe displacement, proptosis, ptosis, diplopia, extraocular motility deficits, and vision loss are all possible signs and symptoms of lacrimal gland enlargement. So far, based on clinical history, clinical signs and symptoms, epidemiological factors, and imaging findings, distinguishing among the various causes of lacrimal gland enlargement can be difficult\cite{15}. Lacrimal lymphoma (LL) and lacrimal inflammatory pseudotumor (LIP) are common causes of lacrimal gland enlargement. The clinical presentation, including history and physical examination, and radiographic imaging findings of them are greatly similar, the clinical treatment options and recovery are quite different, so it is important to differentiate LL from LIP.

LL most commonly occurs among older adults, with a female predominance. Generally, it’s B-cell non-Hodgkin lymphoma, and Mucosa Associated Lymphoid Tissue (MALT) lymphoma is the most frequent histology sub-type\cite{16}. The basic pathological changes of LL is the damage of the lacrimal gland parenchyma and the diffuse full of lymphocytes\cite{17}. The principal treatment strategy for LL is surgical resection combined with radiotherapy, with a potential benefit achieved from adjuvant chemotherapy\cite{18}. LL involving the lacrimal gland tend to progress slowly, and the response to treatment is relatively good; however, the effect of recovery is quite diverse because of the difference of tissue type, clinical stage and individual constitution. LIP is a kind of non-specific type of orbital inflammatory pseudotumor, occurring among adults\cite{19}. The basic pathological changes of LIP include inflammatory cell infiltration, fibrosclerosis, and cell degeneration\cite{20,21}. The choice of treatment methods are closely related to the pathological tissues classification. The current treatment options include corticosteroid therapy, surgical resection, and radiology therapy. Also, the effect of recovery is quite diverse because of the difference of tissue type.

The gray-scale histogram analysis of CT images is a kind of image quantitative analysis technology. By calculating the characteristic parameters of ROI in the images, it evaluates the distribution of ROI gray-scale intensity, provides more and more comprehensive quantitative informations, and has the advantages of simple operation, quantitative objective, and strong repeatability. To date, multiple studies available in the literature have reported that histogram analysis performs well in distinguishing between benign and malignant tumors, evaluating response to treatment, as well as predicting prognosis\cite{22–24}. In this study, the histogram parameters of LL and LIP were analyzed to explore the feasibility and the value of CT images gray-scale histogram in identifying between LL and LIP.

Compared those in LIP group, lesions in LL group were more bilateral and had clearer boundary (P = .036 and .000, respectively), while no significant difference of other CT features was found between groups (all P > .05), which was consistent with the preview results\cite{25}. LL has low malignant degree, not growing into the surrounding tissues commonly, and showing clear boundary on imaging mostly. The tissue within LIP is loose, and chronic inflammation of tissue causes multiple inflammatory mediators to reach
the surrounding tissue space through the vessel wall with high permeability, resulting foggy boundary on imaging.

In the present study, we found that the average variance value of LL and LIP were $360.691 \pm 123.425$ and $585.216 \pm 202.377$. The variance of the LIP group were greater than those of the LL group, with statistically significant differences ($P = .000$), which was consistent with the results reported\[26\]. Wang also discovered that the variance of the LIP group were greater than those of the LL group in texture analysis based on MR contrast-enhanced T1WI(MR CE-T1WI)\[27\]. Although the gray-scale histogram parameters originated from different radiographic imaging, the results of these two studies still remain comparable. Also, previews studies indicated that the differences of these histogram parameters reflected the differences of the microstructures between the two kinds of tumors, and the greater the variance, the stronger the heterogeneity of the tumor\[28\]. So, it was reasonable to speculate that LIP was more heterogeneous compared to LL. The LIP, as the term indicates, are diverse and have a complex tissue structure, with basic structures including collagen bers, glandular epithelium, acinars tissues, inflammatory cell, vascular vessels, and inflammatory mediators, whereas LL contains solely lymphocytes with round nuclei replacing normal lacrimal gland tissue, just like the Figs. 2 and 3. The great histopathological differences of LL and LIP may be one reason of our results. Of course, the existence of other reasons was not excluded.

We found that the mean, skewness, kurtosis, 1th, 10th, and 50th percentiles of the LL group were greater than those of the LIP group, with statistically significant differences (all $P<.05$). However, 90th and 99th percentiles of the LL group were greater than those of the LIP group, with no statistically significant differences ($P = .417$ and $P = .270$). The mean value can reflect the central trend and the average level of the data. We speculated that the average gray value of LL was significantly higher than that of LIP, owing to the texture of the tumour to some extent. The high cellularity components of LL are relatively hard, whereas LIP contains mostly cystic areas, including acinars tissues, vascular vessels, and inflammatory mediators, whose hardness is relatively low. This finding was confirmed by our results. But the relationship between the histopathological tissue and the parameters of gray-scale histogram of LGTs is not clear.

We found that the skewness values of LL was higher than that of LIP, which was justly consistent with the results reported by Wang et al. Skewness was a scale of asymmetry based on the mean. Our results showed that the distribution of mean value of LL was more asymmetrical. We think the reason may be relative to the calcification of the LL, causing asymmetrically the gray-scale value. But it has not been confirmed yet.

In the present study, we found that the kurtosis values of LIP was lower than that of LL. Jin indicated that kurtosis was peakedness indicative of whether the histogram distribution was concentrated into an average value and the smaller the kurtosis, the flatter the distribution of the histogram gray-scale values, and the more complex the tumor components\[28\]. This result also illustrated the theory easily. Reportedly, different contents of masses leaded to different average gray values. It will be necessary to compare the
characteristics of CT gray-scale histograms of the LGTs with histopathologic patterns to explore the relationship between image features and histology in the future.

We found that acceptable discrimination was detected between LL and LIP with mean, variance, skewness, kurtosis, 1th, 10th, and 50th percentiles alone (AUC = 0.789, 0.823, 0.716, 0.762, 0.624, 0.719, and 0.666 respectively). Whereas the AUC of the combination of these histogram parameters yielded excellent discrimination between LL and LIP (AUC = 0.961), and when the cutoff was 0.588, the sensitivity, specificity, and Jordan index were 0.889, 0.960, and 0.849, respectively. Reportedly, Wang established a combined model to distinguish between LL and LIP based on MRI manifestations and the optimum texture features[26]. The sensitivity, specificity, accuracy of combined model was 95.23%, 92.00% and 93.47%, respectively, and AUC was 0.96, which indicated that texture analysis based on MR CE-T1WI could effectively distinguish between LL and LIP. This results was justly consistent with ours. Although the both methods to distinguish between LL and LIP in two studies have displayed excellent diagnostic efficiency, CT is estimated to be more accessible, economical and acceptable comparatively.

Some limitations should be noted in our study. The evaluation of each case was retrospective. Also, the lacrimal gland masses existed 3-dimensionally, and the CT image was measured on a 2-D image, which could not always show the whole tumor perfectly, so selection bias is naturally inevitable. Despite selecting the focus ROIs over as much of the the whole tumor as possible, the placement of ROIs was still performed in a manual pattern, which could result in a potential sampling bias. It is hoped that in the future, artificial intelligence technology will help achieve automatic delineation of ROIs to solve this problem. Finally, according to the different proportions of inflammatory cell infiltration and fibrous tissue in the pathological tissues, LIP can be classified into three types generally. So, sub-type gray-scale histogram analysis of histologically different classification in the LIP may be necessary under the condition of increasing the sample size of LIP.

Conclusions

This result suggests a new method for accurate differential diagnosis of LL and LIP in clinical day-to-day work without increasing the economic burden to patients.

Declarations

Ethics approval and consent to participate

The research was approved by the ethics committee of the First Affiliated Hospital of the Medical College. Written informed consent was waived owing to the noninterventional and retrospective nature of this study. The need for informed consent was waived by the ethics committee of the First Affiliated Hospital of the Medical College, because of the retrospective nature of the study. All the methods were performed in accordance with relevant guidelines and regulations.

Consent for publication  Not applicable
Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no conflicts of interest.

Funding  None

Authors' contributions

Siyao Zhang performed formal analysis and wrote the manuscript; Ting Yuan wrote the original draft; Huijuan Wan performed data curation; Xinrong Zhao and Haidong Lian reviewed and edited the manuscript; All the authors commented and approved the final version of the manuscript.

Acknowledgements  The authors would like to thank all the participants.

References


Figures

Figure 1

Flowchart showing the patient recruitment process for current research.

LGTs, lacrimal gland tumors; LL, lacrimal lymphoma; LIP, lacrimal inflammatory pseudotumor;
Figure 2

Female, 68-year-old, lacrimal lymphoma A. Routine orbital CT; B. ROI of routine orbital CT; C. The histogram of ROI in routine orbital CT; D. The lacrimal gland parenchyma, which effaced diffusely, was filled with small, regular lymphocytes with round nuclei (HE×100).

Figure 3
Female, 57-year-old, lacrimal inflammatory pseudotumor A. Routine orbital CT; B. ROI in routine orbital CT; C. The histogram of ROI of routine orbital CT; D. Collagen fibers proliferated significantly, and lymphocytes, plasma cells, and neutrophils infiltrated the lacrimal gland interstitial (HE×100).