The assessment of chemotherapy and radiation therapy effect in malignant lymphomas with computed tomography and magnetic resonance imaging

Laima Dobrovolskienė, Rasa Griniūtė
Clinic of Radiology, Clinic of Hematology, Kaunas University of Medicine Hospital, Lithuania

Key words: malignant lymphoma, chemotherapy, radiation therapy effect, computed tomography, magnetic resonance imaging.

Summary. Aim of this study was to estimate the diagnostic possibilities of computed tomography (CT) and magnetic resonance imaging (MRI) in the assessment of treatment effect in malignant lymphomas. In the period of 1998 to 2002, 196 patients with histologically proven malignant lymphoma were examined in the Department of Tomography of Kaunas University of Medicine Hospital. The data were processed with SPSS 10.1, including application of standardized t-test and classification of Fisher’s statistics. In this group the density of lymphomatous masses prior and post treatment has no difference on CT images, thus the differentiation of active tissue and relapse is not possible. On MR images the difference of signal intensity of the active component (not treated) and fibrous remnant is significant. MRI is a radiological method which provides information about activity of lymphomatous tissue and is able to delineate the active component (recidive or partial remission) and inactive remnant (total remission) of the tumor mass and thus facilitating the diagnosis of possible relapse of malignant lymphomas for hematology, chemotherapy and radiotherapy specialists.

Introduction
It is possible to diagnose lymphomatous masses of malignant lymphoma (ML) of neck and body region by means of traditional radiographic and ultrasound (US) methods, evaluating size, extent and location of lymphomatous tissue. However, the methods lack information about ML alterations during treatment (1,2). While applying modern radiological methods – spiral computed tomography (CT), angiography with nonionic contrast medium and magnetic resonance imaging (MR), qualitative and quantitative evaluation of ML masses during and after chemo- and radiotherapy course is possible (3-5).

About 10% of all ML are resistant to different kinds of chemotherapy (6). In such case the extent of ML masses is constant during repeated CT evaluation after several courses of chemotherapy. According to other authors, the treatment is considered successful when size of ML masses decreases by 50% (6). When the size of ML masses remains constant or decreases on repeated CT evaluation, uncertainty appears for chemo-, radiotherapists and hematologists: is the mass lymphomatous or fibrous tissue? The key point of this study was to compare diagnostic possibilities of CT and MR in differentiating lymphomatous and fibrous tissue, thus assessing treatment effect.

Materials and methods
One-hundred-ninety six patients with primarily histologically proven neck and body ML were examined by means of spiral CT (Siemens Somatom Plus 4) before and after treatment course in the Department of Tomography of Kaunas University of Medicine Hospital. Neck and body regions were scanned in 5 mm slice and 7.5 mm feed, with and without i/v contrast medium Omnipaque 240/300 injection. In 63 of 196 patients during repeated CT evaluation after 2-4-6-8 chemotherapy courses and complete radiotherapy treatment ML masses or lymphnodes of constant density (+35+60HU) were evident. A group of 20 patients with remnant lymphomatous tissue of more than 1.5 cm in size was selected. Density of ML masses was evaluated prior, during and after treatment course.

Measurements were performed by means of statistical programme of CT unit (Siemens Somatom...
Plus 4), the results were used in statistical calculations: average densities of lymphomatous tissues prior and post treatment, standard deviation as well comparison of the latter in between (Table 1). T-test was applied for average comparison (Table 2). Hypothesis on dependence of variables was checked by means of accurate and asymptomatic $\chi^2$ criterion. Frequences were compared applying accurate and asymptomatic criteria. Significance level was bound to be $p<0.005$. Evaluating the number of necessary investigations, two kinds of mistakes were set: 1st sort mistake $\alpha=0.05$, 2nd sort mistake $\beta=0.1$.

MR investigations in the same patient group were performed and signal intensity (SI) of ML remnant was measured and compared to untreated and fibrous ML tissue SI. MR unit Philips Gyroscan NT-10T was used for this purpose. Neck and body region was scanned in 10 mm axial slices with 10 mm interval. T1W, T2W, SPIR sequences with and without i/v contrast medium Omniscan were performed. It is difficult to evaluate quantitative and qualitative SI alteration of ML tissue during treatment. Thus we tried to evaluate numeral value of SI of active (untreated) and partially active tissue and to compare it with SI of inactive (mature fibrous tissue) tissue. As active ML tissue is best depicted on T2W sequences, SI of active ML tissue was measured on a certain axial slice of this sequence. SI measurement was performed while setting the region of interest (ROI) in three tissues: ML tissue, subcutaneous fat and chest wall muscles (Fig.1,2).

Active, untreated ML tissue contains much water and this is reflected on SI of MR images – low signal on T1W, high on T2W sequences. After specific treatment different histopathological changes take place in ML tissue: fibrous tissue inserts, zones of necrosis, fatty degeneration and inflammatory zones are formed. The latter alterations are reflected in SI changes. Keeping in mind that after treatment ML masses become inhomogeneous, in order to evaluate activity of ML tissue special proportions of average SI of tissues were formed, operating SI values of ML tissue.

**Fig.1.** The arrow show ROI of lymphomatous mass and muscle

![Fig.1](image1)

**Fig.2.** The statistical data of SI measurement and SI histogram

![Fig.2](image2)
tissue, fat and muscle (Lymphomatous/fatty, L/F and Lymphomatous/muscle, L/M). These values of tissues prior and after treatment were compared in between. Mathematical statistical analysis was applied, average rates and standard deviations calculated, regarding ML tissue size (in pixels).

In order to evaluate if investigation of ML tissues by means of MR is reasonable, quantitative difference of various dependent variables was measured. Evaluation of ML tissue activity according to comparative values L/F and L/M and size of remnant was performed applying linear discriminative (Fisher) analysis.

Results

Average SI rates of lymphomatous tissues, standard deviation and interparameter comparisons were evaluated (Table 1). T-test was applied for average comparison (Table 2). After applying of mathematical statistical analysis, t-test and comparisons of ML tissue density average rates on CT it was obvious that average difference was very low (-0.6835) and statistically insignificant, as p>0.05 (p=0.626). Levene’s criterion did not reject the equality of dispersions (p<0.01), and the average rates were compared on the premise of equal dispersions. The following hypothesis was verified:

Average density rate of ML masses prior and post treatment differs.

Standard deviation and average rate of ROI zone corresponding to ML masses was estimated, with regard to area of evaluation (quantity of points) (Table 3). After evaluation of average rates and standard deviations of L/F and L/M, size of ML tissue (similar quantity of points evaluated in muscle and fatty tissues), the hypothesis was verified: L/F and L/M prior treatment differ from L/F and L/M post treatment. t-test and comparison of average rates performed (Tables 4,5).

Coefficients of linear discriminative (Fisher) analysis and classification data are presented in Table 6,7 and Figure 3.

Discussion

In order to evaluate effectiveness of treatment, clinical CT and MR investigations were performed, thus size of ML mass, density and SI measured. According to results of t-test of equality of averages the difference of average densities (HU) of lymphomatous tissue prior and post treatment is not

Table 1. The density measurement data of lymphomatous mass on CT. T-test

<table>
<thead>
<tr>
<th>Value</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density prior treatment (Hv)</td>
<td>20</td>
<td>43.85</td>
<td>7.03</td>
<td>1.57</td>
</tr>
<tr>
<td>Density post treatment (Hv)</td>
<td>20</td>
<td>44.53</td>
<td>6.86</td>
<td>1.53</td>
</tr>
</tbody>
</table>

SE – standard error.
SD – standard deviation.

Table 2. Test of equality of means

<table>
<thead>
<tr>
<th>Value</th>
<th>Levene’s criterion</th>
<th>Test of equality of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p</td>
</tr>
<tr>
<td>Equality of dispersions</td>
<td>0.605</td>
<td>0.005</td>
</tr>
</tbody>
</table>

F – Fischer statistics.
t – t criterion.
df – degrees of freedom.
p – point probability, Levene’s criterion.
SD – standard deviation.
CI – confidence interval of the difference.
Table 3. The signal intensity (SI) measurement on MRI. T-test

<table>
<thead>
<tr>
<th>Value</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI prior treatment</td>
<td>20</td>
<td>1542.32</td>
<td>556.12</td>
<td>124.35</td>
</tr>
<tr>
<td>SI during treatment</td>
<td>20</td>
<td>945.71</td>
<td>40.49</td>
<td>9.05</td>
</tr>
<tr>
<td>SI post treatment</td>
<td>20</td>
<td>608.89</td>
<td>296.33</td>
<td>66.26</td>
</tr>
</tbody>
</table>

SE – standard error.
SD – standard deviation.

Table 4. Measurement of ratio L/F ir L/M on MRI

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/F:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior treatment</td>
<td>20</td>
<td>0.8545</td>
<td>0.18466</td>
<td>0.4129</td>
</tr>
<tr>
<td>post treatment</td>
<td>31</td>
<td>0.4000</td>
<td>0.17686</td>
<td>0.3177</td>
</tr>
<tr>
<td>L/M:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior treatment</td>
<td>20</td>
<td>3.8755</td>
<td>1.37660</td>
<td>0.30782</td>
</tr>
<tr>
<td>post treatment</td>
<td>31</td>
<td>1.5655</td>
<td>0.73644</td>
<td>0.13227</td>
</tr>
</tbody>
</table>

SE – standard error.
SD – standard deviation.

Table 5. Test of equality of group means

<table>
<thead>
<tr>
<th>Value</th>
<th>Levene’s criterion</th>
<th>Test of equality of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p</td>
</tr>
<tr>
<td>L/F equality of dispersions</td>
<td>0.238</td>
<td>0.628</td>
</tr>
<tr>
<td>L/F inequality of dispersions</td>
<td>8.724</td>
<td>39.403</td>
</tr>
<tr>
<td>L/M equality of dispersions</td>
<td>14.630</td>
<td>0.0001</td>
</tr>
<tr>
<td>L/M inequality of dispersions</td>
<td>6.895</td>
<td>26.101</td>
</tr>
</tbody>
</table>

F – Fischer statistics.
t – t criterion.
df – degrees of freedom
p – point probability, Levene’s criterion.
SD – standard deviation.
CI – confidence interval of the difference.
Table 6. Fisher’s classification of linear discriminant function coefficients

<table>
<thead>
<tr>
<th>Value</th>
<th>Activity of mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>active</td>
</tr>
<tr>
<td>L/RB $x_2$</td>
<td>23.385</td>
</tr>
<tr>
<td>L/RM $x_3$</td>
<td>0.738</td>
</tr>
<tr>
<td>Constant</td>
<td>-12.114</td>
</tr>
</tbody>
</table>

$x_2, x_3$ – size of remnant mass (percent).

Discriminant functions:

\[
f_1 = -12.1 + 0.74 \times L/RM + 23.38 \times L/\text{RB}
\]
\[
f_2 = -3.17 - 0.12 \times L/RM + 12.87 \times L/\text{RB}
\]

Canons of classification: active mass if $f_1 > f_2$,
inactive mass if $f \leq f_2$.

Table 7. Results of classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Predicted group membership</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Inactive</td>
</tr>
<tr>
<td>Original</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>90.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Cross-validated</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>85.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

\(^1\) cross-validation is done only for those cases in the analysis.

Table 6 statistically significant, therefore density on CT is not capable to differentiate active untreated lymphomatous masses from remnant fibrous tissue (post treatment) (Table 4).

Also, according to t-test results it is evident that SI and SD of ML tissue on MR prior, during and post treatment differs. Data in Table 5 indicate that relative L/F and L/M values of inactive fibrous tissue, partially active and untreated active ML masses differ. In Table 6 t-test results are presented, indicating that relative values L/F and L/M of active (untreated) and fibrous tissue (post treatment) differ. Average differences are: L/F – 0.45 and L/M – 2.3. In case of comparison of L/M values Levene’s criterion rejected possibility of equality of dispersions (p=0.13), so averages were

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Fig. 3. The dependence of activity mass on ratio signal intensity L/F and L/M
compared on the premise of unequal dispersions, applying a modified criterion. According to 2nd sort mistakes (p=0.0001 in both cases) we can predicate that average values L/F and L/M differ significantly.

In case of untreated ML (active masses) L/F=0.85 ± 0.18 and L/M=3.81.37; while after treatment (fibrous remnant) L/F=0.40.17, L/M=1.50.73; during treatment course L/F 0.67-0.57, L/M 2.43-0.77.

According to relative values L/F and L/M values the average accuracy of prediction of state of lymphomatous tissue is 88.2%. Active state and relapse, as well as partial remission are detected with 90% accuracy, inactive state and thorough remission – with 87.1% accuracy.

Classification results of Fisher’s discriminative functions indicate that based on L/F and L/M it is possible to diagnose activity of remaining lymphomatous tissue, as well as verify the size of masses, and component part of remnant in 90% of cases. The results prior and post treatment differ significantly; constants of classified functions differ evidently: prior treatment - 12.11, post treatment – 3.168. In this manner thorough evaluation of treatment effectiveness and tactics is possible (7,8).

According to our results there is significant difference between treated and untreated ML mass SI on T2W MR images. Active ML possesses high SI on T2W, while inactive – low SI (9). As during treatment MR signal of ML masses becomes inhomogeneous, in order to decrease the degree of inhomogeneity the ratio values of SI of ML mass and SI of fat, as well as SI of ML mass and of muscle tissue were calculated. Based on these results it is possible to conclude that active ML and relapse ML tissue presents value L/F≥0.85±0.18, while L/M ≥ 3.8±1.37 (p=0.04). Partially active ML tissue as well as partial remission – 0.85 < L/F >0.4 and 3.8< L/M >1.5 (p=0.001), while inactive ML masses and thorough remission – L/F=0.4±0.17, and L/M =1.5±0.73 (p=0.001).

Zerhouni EA, Fishman EK et al. performed MR investigation in 34 patients with histologically proven ML, prior and during treatment and concluded that ontologically active ML presents L/F ratio more than 0.9, while L/M – more than 0.3 (4). Nyman RS, Rehn SM et al. found out that active ML presents L/F ratio more than 0.85, while L/M – more than 0.4. These authors state that SI of post treatment ML fibrous tissue on T2W MR images, compared to that of fatty tissue decreases significantly and approaches the SI of muscle tissue (5,9).

Thus, our data are in consensus with other authors. After comparing diagnostic possibilities of CT and MR it is evident, that MR is the only method to differentiate (with 88-90% accuracy) fibrous remnant and active ML tissue of relapsing ML.

Conclusions
1. Density of lymphomatous masses prior and post treatment on computed tomography images is not sufficient to delineate activity of tumor masses.
2. Signal intensity of active (untreated) and fibrous remnant on T2W magnetic resonance images differs significantly.
3. Magnetic resonance allows evaluation of activity of malignant lymphoma tissue remnant and assessment of effectiveness of treatment, as well as remission or relapse of the disease.

Piktybinų limfomų chemoterapijos ir spindulinio gydymo veiksmingumo įvertinimas kompiuterine tomografija ir magnetiniu rezonansu

Laima Dobrovolskienė, Rasa Griniūtė

Kauno medicinos universiteto klinikų Radiologijos kliniką, 1Hematologijos kliniką

Raktažodžiai: piktybinė limfoma, chemoterapija, spindulinis gydymas, gydymo veiksmingumas, kompiuterinė tomografija, magnetinis rezonansas.

Santrauka. Darbo tikslas – nustatyti kompiuterinės tomografijos ir magnetinio rezonanso galimybes įvertinant piktybinės limfomos chemoterapijos ir spindulinio gydymo veiksmingumą.

Darbo medžiaga ir metodai. 1998–2002 m. Kauno medicinos universiteto klinikų Radiologijos klinikose Tomografijų skyrėje ištirti 196 ligoniu, kuriems histologiskai buvo diagnozuota kaklo ir liemens rūšių piktybinė limfoma, iš jų 20 ligonių prieš gydymą ir po jo ištirti kompiuteriniu tomografu („Siemens Somatom Plus 4“) ir magnetiniu rezonansu („Philips Gyroscan NT-T10 1Tesla“).

Rezultatai. 20 ligonių limfominių masių tankio vidurkių prieš gydymą ir po gydymo skirtumas buvo statistiškai nereikšmingas.


Adresas susirašinėjimui: L. Dobrovolskienė, KMUK Radiologijos klinika, Eivenių 2, 3007 Kaunas
El. paštšas: dobro@takas.lt

References

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