Original Article
Spectral CT imaging improve the differentiation of lymph node metastasis from different tumors

Jingang Liu1*, Weiguang Shao1*, Yu Han1, Xizhen Wang1, Xingsheng Zhao1, Lixin Li2, Wenjuan Wang2, Bin Wang1,3

1Imaging Center of Affiliated Hospital, Weifang Medical University, Weifang 261031, China; 2Department of Radiology, Weifang People’s Hospital, Weifang 261041, China; 3Department of Medical Imaging and Nuclear Medicine, Binzhou Medical University, Yantai, China. *Equal contributors.

Received November 14, 2015; Accepted November 6, 2017; Epub December 15, 2017; Published December 30, 2017

Abstract: Purpose: To investigate the feasibility of differentiating metastatic lymph nodes from lymphoma, lung adenocarcinoma, and lung squamous cell carcinoma using spectral CT imaging. Methods: 64 patients with malignant tumors and an associated 256 metastatic lymph nodes underwent spectral CT imaging during the arterial phase. Eleven sets of monochromatic images with energy levels from 40-140 keV with 10 keV intervals, and material decomposition images using iodine and water as the base material pair were reconstructed and analyzed from the spectral CT imaging during the arterial phase. The iodine and water contents were measured in the iodine and water-based images, respectively. Results: The highest contrast-noise-ratio values for the lymph nodes were obtained at the 70 keV image setting. The CT attenuation values of metastatic lymph nodes at the 11 keV levels were different from each other (P < 0.05). The iodine content of metastatic lymph nodes from lymphoma was 1.93±0.04 mg/mL, which was different from that of lung adenocarcinoma (1.16±0.15 mg/mL) and lung squamous cell carcinoma (1.25±0.21 mg/mL) (all P < 0.001). There was no significant difference for their water contents: 1029.40±20.85 mg/mL from lymphoma, 1024.98±11.19 mg/mL from lung adenocarcinoma, and 1022.12±12.94 mg/mL from lung squamous cell carcinoma (P > 0.05). Conclusions: Spectral CT imaging is a promising method for distinguishing metastatic lymph nodes from different malignant tumors using CT attenuation values at different photon energy levels and iodine content measurements.

Keywords: Lymph nodes, neoplasm metastasis, tomography, X-ray computed, spectral CT imaging

Introduction
The spectral imaging technique gives Gemstone CT the power to obtain spectral images. Gemstone spectral imaging (GSI) broke through the limitations of conventional CT, which only has single parametric imaging. GSI makes material differentiation with monochromatic energy feasible [1]. A dual-energy CT can acquire two-energy images in the same location. Gemstone spectral imaging provides a serial kVp ranging from 40 to 140 kVp and an attenuation curve that displays the attenuation of any tissue across the kVp range. The linear attenuation coefficient of different tissue decreases with an increase of kVp. Different tissue has its own rate of decline, which will enhance the contrast between two different tissues at selected kVp [2]. Monochromatic spectral images generated by GSI range from 40 to 140 kVp providing more details of tissues [3-5]. According to these monochromatic images ranged from 40 to 140 kVp, the contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR) and noise level of background can be optimized [6]. Based on anatomic images, spectral imaging can analyze the tissue component by way of poly-chromatophilic images, such as the monochromatic imaging, iodine-based imaging, water-based imaging and calcium-based imaging. The attenuation curve of GSI has the potential to show the physical character of different tissues. So, GSI plays an important role in CT studies transferring from the macro level to the micro level of the body. Spectral computed tomography has been used to differentiate benign and malignant tumors [7-9].

Metastatic lymph nodes are a common metastatic pattern with malignant tumors, and a key
Spectral CT of Metastatic Lymph Node

indicator of recurrence. In some malignant tumors, lymph node metastases may be found earlier, even before the original tumor is detected using imaging modalities [10-13]. Therefore, detecting and differentiating metastatic lymph nodes plays an important role in tumor staging. However, with conventional CT, the size, shape, and CT value of lymph node were used to identify benign and malignant lymph nodes [14-16]. In these cases, the sensitivities and specificities of conventional CT in detecting metastatic lymph nodes ranged only from 52% to 66% and from 69% to 93%, respectively. The low sensitivity and high false-negative rate of conventional CT limited the usage in N-stage of lung cancer [17-20]. The recently introduced dual energy spectral CT imaging with the rapid tube voltage switch between the low kVp (80 kVp) and high kVp (140 kVp) during a single rotation is capable of generating monochromatic image sets with photon energy levels from 40 keV to 140 keV to provide better contrast resolution and a unique CT attenuation curve as a function of photon energy (spectral HU curve) and material decomposition images to provide material separation. The metastatic lymph nodes have similar biological features to their primary malignant tumors. The cellularity, proliferative ratio, angiogenesis and tissue density in CT of malignant neoplasms were usually different from each other [10-13]. So, we hypothesize that metastatic lymph nodes from different malignant tumors may have inherently unique spectral HU curves. The purpose of our study was to evaluate the feasibility of using dual energy spectral CT to differentiate metastatic lymph nodes from different malignant tumors.

Material and methods

Subjects

Protocols and informed consent provisions were reviewed and approved by Weifang Medical University Review Board. Sixty four patients with malignant tumors were enrolled in our study. There were thirty five males and twenty nine females with an average age of 59 years old (ages from 48 to 77 years). Eighteen of them had lymphoma (Ly) with 72 lymph nodes involved. Twenty four had lung adenocarcinoma (LAC) with 96 lymph nodes involved. The other twenty-two had lung squamous cell carcinoma (LSC) with 88 lymph nodes involved. All the malignancies were confirmed by pathological examination.

CT scanning protocol and data post-process

Pre-contrast scan and enhanced scans in the arterial phase and venous phase were performed using a GE high-definition CT scanner (Discovery CT750 HD, GE Healthcare, USA). The contrast medium iohexol (Urich, Germany) was injected using a high pressure injector at the rate of 3.0 ml/sec via the right ulnar vein. The scan start time for the arterial phase and venous phase was 30 seconds and 55 seconds after injection, respectively. The pre-contrast scan and contrast-enhanced scan in the portal venous phase were carried out using the conventional helical scan mode with the following
Spectral CT of Metastatic Lymph Node

Figure 2. A 66 year old female with LSC. (A) is an enhanced axial monochromatic image of chest showing a large and fused mass in the right hailer. (B) and (C) are an iodine-based image and a water-based image showing the metastatic lymph nodes. Metastatic lymph nodes are more obvious on the iodine-based image than on the water-based image. (D) is the spectrum curve of three ROIs in metastatic lymph node. The shapes of spectrum curves are similar to each other.

Figure 3. A 56 year old female with LAC. (A) is an enhanced axial monochromatic image of the chest showing fused lymph nodes from peripheral lung cancer. (B) and (C) are an iodine-based image and a water-based image. Metastatic lymph nodes are more obvious on the iodine-based image than on the water-based image. (D) is the spectrum curve of three ROIs in metastatic lymph node. The shapes of spectrum curves are similar to each other.

All the statistical analyses were performed using SPSS19.0 (SPSS Inc., Chicago, IL). The CT values of metastatic lymph nodes in different

scan parameters: 120 kVp, auto mA, thickness = 5.0 mm, interval = 5.0 mm, and pitch = 1.375. The contrast-enhanced scan in the arterial

phase was acquired using the spectral imaging mode with single-source, fast tube voltage switching between 80 and 140 kVP. The other scan parameters were: 600 mA, thickness = 5.0 mm, interval = 5.0 mm, pitch = 0.984, 39.37 mm/cycle rotation speed and 0.8s rotation time.

For the spectral CT imaging, two types of images were reconstructed using a single spectral CT scan: monochromatic image sets and material decomposition image sets. These images included 11 sets of monochromatic images with energy levels from 40-140 keV in 10 keV intervals and material decomposition images using iodine and water as the base material pair. Images were sent to an AW4.4 workstation for analysis after reconstructed to a thickness of 0.63 mm. The CT attenuation values and their standard deviations for the lymph nodes and surrounding parenchyma were measured, and contrast-noise-ratios for lymph node were generated in the 11 sets of monochromatic images. The iodine and water contents were measured in the iodine and water-based images, respectively. The monochromatic image set, where the best contrast noise ratio was recorded, was used to observe the metastatic lymph nodes. The attenuation curves in three different regions of interest (ROIs) in the arterial phase images at different keV levels were obtained.

Statistical analysis
keV levels were analyzed using ANOVA followed with a Tamhane test. The content of iodine and water was compared using a T-test. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

**Results**

Lymphadenopathy was found in Ly, LAC and LSC (Figures 1A, 2A and 3A). Images at 70 keV provided the highest CNR for lymph nodes and were used for visual image analysis (Table 1). The metastatic lymph nodes had higher contrast in iodine-based images with clearer boundaries than water-based images (Figures 1B, 1C, 2B, 2C, 3B, 3C). With the increase of voltage, the attenuation of different ROI value decreased (Figures 1D, 2D and 3D). The attenuation curve of different metastatic lymph node tumors was different from each other (P < 0.05) (Table 2). At 70 keV, The CT attenuation values of metastatic lymphadenopathy were 81.36±9.81 HU, 58.33±21.55 HU and 56.47±10.62 HU for Ly, LAC and LSC, respectively. The iodine contents of Ly, LAC and LSC were (1.93±0.04), (1.16±0.15), and (1.25±0.21) g/L, respectively. The water contents of Ly, LAC and LSC were (1029.40±20.85), (1024.98±11.19) and (1022.12±12.94) g/L, respectively. The iodine contents of metastatic lymphadenopathy were different from each other (P < 0.05), except for LAC and LSC (t = 1.77, P = 0.07). There was no difference among the water contents of metastatic lymphadenopathy (P > 0.05) (Table 3).

**Discussion**

Lymph node metastasis is the most common metastatic pattern of lung cancer. Lymphoma is characterized by lymphadenecstasis. Metastatic lymph nodes should have biological features similar to their original malignant tumor with similar cellularity, proliferative ratio, angiogenesis and tissue density in CT [10-13]. In conventional CT, the size, shape, and CT value of a lymph node is used to identify benign and malignant lymph nodes. Due to the limited spatial resolution for lymph nodes and the averaging effects of the polychromatic X-ray source in the conventional CT, the sensitivities and specificities of conventional CT in detecting metastatic lymph nodes ranged are fairly low, and limit the usage of conventional CT in the N-stage of lung cancer [17-20]. By applying two different kV setting simultaneously, dual energy CT is capable of generating a series of monochromatic images corresponding to photon energy levels from 40 keV to 140 keV, thus
Spectral CT of Metastatic Lymph Node

providing images with better contrast resolution and additional information such as CT attenuation as a function of photon energy than conventional CT.

Our results indicate that there is a difference in the attenuation curves among the metastatic lymph nodes of different tumors. In the process of metastasis, normal lymph tissue is replaced by malignant tumor cells. The biological characteristics of lymph nodes are altered by metastasis, which leads to the observation of special attenuation curves. Metastatic lymph nodes are supposed to have similar micro-structures and densities to their original tumors. The small differences between the micro-structures and densities among various tumors are usually covered up by the averaging nature of the polychromatic X-ray in conventional CT. The monochromatic image sets generated in the dual energy spectral CT eliminated the averaging effect and the beam hardening effect associated with the polychromatic X-ray to produce more precise CT values and better contrast-to-noise ratios for lymph nodes and tumors to improving the assessment of this hidden information [21-23].

Blood supply is one of the most important factors of a tumor’s biological behavior. Iodine content in the iodine-based images can be used to quantitatively measure the blood supply. The blood supply of lymph nodes from lymphoma is statistically higher than that of lymph nodes from lung adenocarcinoma and lung squamous cell carcinoma. The attenuation curve will be useful to decide the origin of lymph nodes. Our results are consistent with previous research where the blood supply of the inflammation is more than that of the malignant tumor [24, 25].

**Limitations**

GSI showed promising results in differentiating metastatic lymph nodes by way of quantitative information. However, the sample of this study was relative small. The sensitivity and specificity of GSI in differentiating metastatic lymph nodes is not provided. A larger sample and a ROC curve analysis are necessary in future studies.

**Conclusion**

Dual energy spectral CT imaging is a promising method for distinguishing metastatic lymph nodes from different malignant tumors using CT attenuation values at different photon energy levels and iodine content measurements.

**Acknowledgements**

This study was granted by National Natural Science Foundation of China (81171303), Shandong Provincial Natural Science Foundation of china (BS2012Y038, ZR2010HQ029 and ZR2009CL046) and Technology Development Plan (2010GSF10226), Weifang Science Project (20130167 and 201201242) and Affiliated Hospital of Weifang Medical University innovation fund project (K12QC1040). The research was also supported by project of

---

**Table 2.** The CT values (HU) of different metastatic lymph nodes with multiple KV

<table>
<thead>
<tr>
<th>Tumor</th>
<th>KVP</th>
<th>LY</th>
<th>LC</th>
<th>LSC</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>193.08±32.48</td>
<td>132.44±58.5</td>
<td>133.60±40.61</td>
<td>12.08</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>136.64±21.43</td>
<td>94.63±39.98</td>
<td>94.67±25.32</td>
<td>13.11</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>102.38±14.19</td>
<td>72.29±29.85</td>
<td>70.82±16.10</td>
<td>8.61</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>81.36±9.81</td>
<td>58.33±21.55</td>
<td>56.47±10.62</td>
<td>17.29</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>69.68±69.68</td>
<td>51.81±19.65</td>
<td>46.63±7.00</td>
<td>18.97</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>60.92±4.61</td>
<td>45.99±17.28</td>
<td>41.20±5.78</td>
<td>18.02</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>51.70±6.49</td>
<td>41.93±15.73</td>
<td>36.99±5.00</td>
<td>10.04</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>47.39±6.22</td>
<td>39.08±14.71</td>
<td>33.85±4.88</td>
<td>9.18</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>44.39±5.81</td>
<td>37.08±14.03</td>
<td>31.64±31.63</td>
<td>8.66</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>41.99±5.69</td>
<td>35.53±13.57</td>
<td>30.01±5.12</td>
<td>7.94</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>140</td>
<td>40.12±5.61</td>
<td>34.31±13.20</td>
<td>28.70±5.27</td>
<td>7.4</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

*Tamhane test was used due to heterogeneity of variance.

**Table 3.** Intergroup comparison of iodine and water in metastatic lymph nodes

<table>
<thead>
<tr>
<th>Intergroup</th>
<th>Iodine-based</th>
<th>Water-based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T value</td>
<td>P value</td>
</tr>
<tr>
<td>Ly-LAC</td>
<td>26.29</td>
<td>0.00</td>
</tr>
<tr>
<td>Ly-LSC</td>
<td>16.81</td>
<td>0.00</td>
</tr>
<tr>
<td>LAC-LSC</td>
<td>1.77</td>
<td>0.07</td>
</tr>
</tbody>
</table>
References


