Differential diagnosis of cervical lymphoma and lymph node metastases by dual-source dual-energy CT imaging

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Aims and objectives

Qualitative diagnosis of cervical lymph nodes by CT imaging is challenging. Traditional contrast enhanced CT imaging has been used for diagnosis by measuring the enhancement of lymph nodes (1,2), but this method has disadvantages. Conventional imaging is first of all more restricted in the characteristics of the lymph nodes that can be defined, such as morphology and blood flow. Parameters measured generally include the size and density of the lymph nodes, location, enhancement and so on, which are all characteristics that are difficult to measure in qualitative and quantitative analysis of the lymph node lesions. These characteristics can be limiting in lymphoma and lymph node metastases, as, for example, both present with cervical lymph node enlargement. In addition, conventional imaging results in a high radiation dose to patients and vulnerability to respiratory motion.

Dual-source dual-energy CT (DECT) differs from conventional CT in that the method does not rely on single parameter. Multiple quantitative parameters, including the iodine overlay and iodine content, of the pathological tissues can be obtained with DECT thereby enhancing non-invasive diagnostic capabilities. Material decomposition can be performed based on the attenuation characteristics of material and tissue at different energies. The iodine maps of the lesions are obtained by extraction of the iodine component, and the overlay value and iodine content of the lesions can be determined, thus eliminating the interference of the CT value of the tissue itself. Furthermore, quantitative analysis of the data from DECT scan accurately reflects the blood flow status of cancerous lesions (3,4). Finally, the iodine map intuitively and accurately reflects the differences of the iodine concentration in the diseased tissue, and therefore can reproduce the anatomical detail of the lesions more clearly (5-8). The iodine content and iodine overlay derived from DECT scans were recently shown to differ significantly among normal, inflammatory and metastatic squamous cell carcinoma cervical lymph nodes.

One of the more exciting aspects of DECT is the reconstruction of virtual unenhanced images, which eliminate the need for unenhanced imaging [3,5,10-11]. Their clinical utility is thus drawing increasing attention. Monochromatic energy images at different energy from 40 keV to 190 keV can be reconstructed based on material decomposition analysis. Furthermore, spectral curves depicting changes in the attenuation coefficients (HU) of various lesions under different energy levels can reveal distinguishing features of tissue types. These characteristic curves have already been exploited in the differentiation of tumor and non-neoplastic lesions of the kidney [12] and benign and malignant lesions in the solitary pulmonary nodules [10].

DECT thus provides distinct advantages as a diagnostic strategy as it is possible to both reduce the radiation dose to the patients, and to avoid ROI mismatch due to respiratory movement [3,5,11]. Metastatic disease and lymphoma differ based on cell type composition, raising the possibility of distinguishable contrast enhancement...
behaviors under DECT. The purpose of this study was, therefore, to investigate whether DECT can be used for the differential diagnosis of lymphoma and metastatic cervical lymph nodes.
Methods and materials

A retrospective analysis of the DECT images of 20 patients with cervical lymphoma (56 nodes) and 25 patients with cervical lymph node metastases (46 lymph nodes) was performed. The iodine map, monochromatic energy images (40 ~ 190 keV), and the CT values of the lymph node lesions were obtained and compared.

All patients were imaged using a dual-source CT scanner with supine arteriovenous dual-phase enhanced scans. The 100 kV and 140 kV enhanced scan images were transferred to a Siemens workstation. The Liver VNC mode was applied to derive the iodine map, and mono-energetic CT images were reconstructed from 40 ~ 190 keV. The image processing and parameter measurements were performed independently in a blinded study by two radiologists. The following parameters were measured:

1. CT overlay value in the arterial phase ($CT_{A}$, HU) and iodine content in the arterial phase ($IC_{AP}$, mg / ml) of the lymph node lesions, and the iodine content of the carotid artery in the arterial phase ($IC_{A}$);

2. CT overlay value in the venous phase ($CT_{V}$, HU) and iodine content in the venous phase ($IC_{VP}$, mg / ml) of the lymph node lesions, and the iodine content of the jugular vein in the venous phase ($IC_{V}$);

3. ($NIC_{AP}$, $NIC_{AP}#IC_{AP}/ IC_{A}$) and normalized iodine concentration in the venous phase ($NIC_{VP}$, $NIC_{VP}#IC_{VP}/ IC_{V}$) of the lymph node lesions;

4. CT values of the lymph node lesions on monochromatic energy images from 40 to 190 keV, and the slope $k$ of the energy decay curve, where $k = CT_{1} - CT_{2} / 100 - 40$, and $CT_{1}$ is the CT value of the 40 keV image and $CT_{2}$ is the CT value of the 100 keV image.

Statistical analysis was performed with SPSS 19.0 software (SPSS Inc.; Chicago, IL, USA). Measurement data were expressed as the mean ± standard deviation (m ± SD). The parameters between the two groups were compared using an independent samples t-test. A p-value <0.05 was considered statistically significant.

Receiver operating characteristic (ROC) curves were plotted for iodine overlay and iodine concentrations in the arterial and venous phases. The optimal threshold to distinguish lymphoma and metastases to the lymph nodes was determined, and the diagnostic performance was compared.
Bland-Altman plots were analyzed to demonstrate consistency of analysis between observers [13].
Results

**Iodine overlay and iodine content differ between lymphoma and metastatic cancer**

Measurements were first examined to determine whether any differences were detectable overall between the two groups of patients based on the values from iodine overlay and iodine content. The were overall greater in the lymphoma group than in the metastases group (Table 1). Iodine map differences can be observed between a patient with lymphoma and (Figures 1A and 1B) one with metastatic cancer (Figures 1C and 1D). These results demonstrated that the two groups were distinguishable by any one of these measurements.

Table 1: Comparison of the iodine parameters

<table>
<thead>
<tr>
<th></th>
<th>lymphoma group (n=56)</th>
<th>metastases group (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT&lt;sub&gt;A&lt;/sub&gt; (HU)</strong></td>
<td>32.43±13.24</td>
<td>12.80±9.40</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td><strong>CT&lt;sub&gt;V&lt;/sub&gt; (HU)</strong></td>
<td>40.56±11.48</td>
<td>21.45±11.57</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td><strong>IC&lt;sub&gt;AP&lt;/sub&gt; (mg/ml)</strong></td>
<td>1.78±0.67</td>
<td>0.62±0.45</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td><strong>IC&lt;sub&gt;VP&lt;/sub&gt; (mg/ml)</strong></td>
<td>2.21±0.54</td>
<td>0.90±0.47</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td><strong>NIC&lt;sub&gt;AP&lt;/sub&gt;</strong></td>
<td>0.75±0.07</td>
<td>0.21±0.23</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td><strong>NIC&lt;sub&gt;VP&lt;/sub&gt;</strong></td>
<td>0.40±0.12</td>
<td>0.23±0.18</td>
<td>$p&lt;0.01$</td>
</tr>
</tbody>
</table>

*CT<sub>A</sub>: CT overlay value in the arterial phase; CT<sub>V</sub>: CT overlay value in the venous phase; IC<sub>AP</sub>: iodine concentration in the arterial phase; IC<sub>VP</sub>: iodine concentration in the venous phase; NIC<sub>AP</sub>: normalized iodine concentration in the arterial phase; NIC<sub>VP</sub>: normalized iodine concentration in the venous phase.

**Diagnostic performance**

ROC curves were subsequently used to determine the sensitivity and specificity of the iodine overlay and iodine content values (CT<sub>A</sub>, CT<sub>V</sub>, NIC<sub>AP</sub>, and NIC<sub>VP</sub>) for distinguishing lymphoma from metastatic cancer (Figure 2). The diagnostic performance of CT<sub>A</sub> and CT<sub>V</sub> displayed the greatest sensitivities and specificities of these four parameters (Table 2). The area under the ROC curve for CT<sub>A</sub> was the greatest indicating the highest sensitivity and specificity of all of the tests. The best diagnostic thresholds for CT<sub>A</sub> and CT<sub>V</sub> were at 22.6 and 24.9 HU, where the diagnostic sensitivity and specificity were 79.5% and 95.5%, and 86.8% and 76.3%, respectively. As there were no significant differences
between the areas under the ROC curves for CT_A and CT_V, these measurements had similar diagnostic performance in differential diagnosis of lymphoma and metastatic lymph nodes.

NIC_{AP} and NIC_{VP} also exhibited high diagnostic sensitivity but were lower in terms of specificity. The best diagnostic thresholds for NIC_{AP} and NIC_{VP} were 0.0789 and 0.2, with diagnostic sensitivity of 93.2% and specificities of 71.1% and 57.9%, respectively.

Table 2. Analysis of the ROC curves of CT_A, CT_V, NIC_{AP} and NIC_{VP}

<table>
<thead>
<tr>
<th></th>
<th>Az</th>
<th>S.E.</th>
<th>95% confidence level</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT_A (HU)</td>
<td>0.900</td>
<td>0.0346</td>
<td>0.814-0.955</td>
<td></td>
</tr>
<tr>
<td>CT_V (HU)</td>
<td>0.868</td>
<td>0.0446</td>
<td>0.775-0.932</td>
<td>0.5142</td>
</tr>
<tr>
<td>NIC_{AP}</td>
<td>0.859</td>
<td>0.0424</td>
<td>0.764-0.926</td>
<td></td>
</tr>
<tr>
<td>NIC_{VP}</td>
<td>0.783</td>
<td>0.0528</td>
<td>0.678-0.866</td>
<td>0.1693</td>
</tr>
</tbody>
</table>

*ROC: Receiver operating characteristic; Az: area under the ROC Curve; S.E.: standard error; CT_A: CT overlay value in the arterial phase; CT_V: CT overlay value in venous phase; NIC_{AP}: normalized iodine concentration in arterial phase; NIC_{VP}: normalized iodine concentration in the venous phase

**CT values from monochromatic energy images**

Spectral curves were assessed as a method to differentiate diagnoses. CT values from reconstructed 40 ~ 120 keV monochromatic energy images of the lymphoma group were higher than those of the metastases group (Table 3). The slope determined from the lymphoma group was 1.96, which was statistically significantly greater than that of the metastases group (k2 = 0.66; p < 0.01; Figure 3). This finding demonstrated that attenuation of signals was reproducibly distinguishable between disease states, indicating that differences in tissue composition in lymphoma and metastases were evident in the spectral curves.

Table 3. (HU)

<table>
<thead>
<tr>
<th></th>
<th>lymphoma group (n=56)</th>
<th>metastases group (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 keV</td>
<td>171.48±48.62</td>
<td>80.25±45.36</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
50 keV  121.46±30.30  65.46±28.47  p<0.01
60 keV  91.54±20.60  55.10±24.30  p<0.01
70 keV  75.36±14.90  52.47±13.77  p<0.01
80 keV  63.23±12.19  45.17±12.86  p<0.01
90 keV  57.04±10.81  43.13±10.26  p<0.01
100 keV 51.84±10.20  42.15±10.18  p<0.01
110 keV 50.26±10.32  41.56±10.11  p<0.01
120 keV 46.56±10.21  40.85±10.09  p<0.05

**Inter-observer consistency**

To determine agreement between the measurements based on the operator, a Bland-Altman diagram was plotted with CT_A calculated by two different clinicians from the iodine overlay maps. CT_A measured by the two physicians were compared with a paired t-test, and yielded a t value of 1.403 where p = 0.179. The consistency limits (mean standard error ± 1.96 standard deviation) was -0.79 ± 5.17 HU (Figure 4). These results demonstrated that the measurement data showed no statistical difference between observers.
**Fig. 1:** Representative iodine maps from lymphoma and metastatic cancer obtained by dual-energy CT scans. Iodine maps in the arterial (A) and the venous phases (B) of a 42-year-old man with non-Hodgkin's lymphoma. Multiple enlarged cervical lymph nodes were observed in the left neck. Iodine maps in the arterial (C) and the venous phases (D) of a 55-year-old man with lung adenocarcinoma and multiple lymph node metastases in the neck. The white circles are the ROIs used for calculation.

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Fig. 2: Diagnostic potential of iodine overlay (CT) and iodine content (NIC) in arterial and venous phases is similar. Receiver operating characteristic (ROC) curves were plotted for CTA and CTV (A) and NICAP and NICVP (B), as tests for differential diagnosis of lymph node metastases and lymphoma. CTA: CT overlay value in the arterial phase; CTV: CT overlay value in the venous phase; NICAP: normalized iodine concentration in the arterial phase; NICVP: normalized iodine concentration in the venous phase.

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Fig. 3: Spectral curves distinguish lymphoma and metastatic lymph nodes. CT values obtained from 40 ~ 120 keV monochromatic energy images are plotted to generate the spectral curves for lymphoma (blue) and metastatic lymph nodes (purple). CT values of the lymphoma group were higher than those from the metastases group particularly at the lower energy values.

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Fig. 4: Reliability of CT measurements from iodine overlays based on a Blond-Altman plot. Blond-Altman plot reveals no statistical difference between measurements calculated by two different observers/clinicians. The consistency limits (mean standard error ± 1.96 standard deviation) was -0.79 ± 5.17 HU.

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Conclusion

Improvements in imaging technology/equipment can potentially lead to earlier detection and diagnosis in cancer patients without invasive medical procedures. Whether the current status of the technology enables the clinician to make distinctions between tumor types is currently under intensive investigation. The focus of this study was, therefore, to investigate the utility of DECT in the differential diagnosis of cervical lymphoma and metastatic cervical lymph nodes. The results indicated that the tissues were distinguishable based on several parameters. First, lymphoma and metastatic lymph nodes displayed significantly different values in the iodine overlay and iodine content, especially in the arterial phase. Second, the slope of the two spectral curves was also significantly different demonstrating fundamental differences in the nature of the tissues. Finally, areas under ROC curves for the different parameters indicated that \( \text{CT}_A \), \( \text{CT}_V \), \( \text{NIC}_{AP} \) and \( \text{NIC}_{VP} \) all displayed similar diagnostic performance. However, \( \text{CT}_A \) and \( \text{NIC}_{AP} \) overall exhibited relatively greater differences between the two groups than \( \text{CT}_V \) and \( \text{NIC}_{VP} \). These results indicated that the parameters that may best differentiate between lymphoma and metastatic lymph nodes in the neck are \( \text{CT}_A \) and \( \text{NIC}_{AP} \).

The study illustrates the potential of the technique to make a challenging diagnosis by imaging perhaps routine in the future. Cervical lymphoma was distinguishable from metastatic lymph nodes, first, on the basis of iodine data. The values for the iodine overlay and iodine content of tissues were directly proportional to the concentration of the intravascular and extravascular contrast agent. In both the arterial and venous phases, the values for lymphoma were greater than that of the metastatic lymph nodes, thus reflecting the pathophysiological differences between the two disease types. The biological basis for this finding is potentially due to the fact that metastatic cancer lesions often become necrotic. In necrosis, the blood volume is reduced, so that the values from the iodine overlay and the concentration of iodine within lymph nodes metastases were lower. Lymphoma, however, usually presents with a uniform density, and necrosis rarely occurs, so that the values for the iodine overlay and iodine concentration were generally higher than for metastatic lymph nodes.

Second, the derived monochromatic energy images from 40 to 190 keV revealed differences in CT values at different energies. Structural changes induced by invading metastatic tumor cells would lead to detectable differences in the attenuation coefficient of the lymph nodes. The energy attenuation curve thus reflected the pathological status of the lymph nodes. Injection of the iodine contrast agent highlighted the differences in X-ray attenuation behaviors between lymph nodes with different pathological status, especially at low energy levels. A second study demonstrated that the energy curve was a quite useful parameter in the differential diagnosis of benign and malignant lesions in the neck. Our study also demonstrated that the slope of the energy-attenuation curve of the metastases group was significantly different from that of the lymphoma group, and
that the $CT_A$ values of the lymphoma group at different keV were greater than those in the metastases group.

Differential diagnosis by DECT is, however, dependent on reliability of the measurements. For example, the magnitude of enhancement depends on the concentration of the intravascular and extravascular contrast agent, but individual differences in the amount of contrast agent injected, the scan time, and the flow rate will lead to deviations in the measured parameters. Here, the concentration of iodine was standardized in order to eliminate these individual variations.

One of the more interesting questions that our work does not answer is whether the tissue origin of the metastases influences the CT values of the metastatic lymph nodes. Although our study included lymph node metastases of different primary tumor tissue types, an expanded sample size is necessary to further investigate this possibility. The ability to potentially distinguish tissue of origin by this method is a tantalizing proposition, which would ultimately facilitate pathological diagnosis and treatment in the absence of more invasive procedures.

In summary, DECT imaging demonstrated several advantages for diagnosis of affected lymph nodes. The $CT_A$, $CT_V$, $NIC_{AP}$ and $NIC_{VP}$ values all demonstrated similar diagnostic performance. As $CT_A$ and $NIC_{AP}$ values differed more greatly between the two groups, it is recommended to scan at the arterial phase in order to potentially make a differential diagnosis. Our work represents a promising basis for dual-source DECT imaging as an integral tool in the differential diagnosis of the neck lymphoma and metastatic cervical lymph nodes.
References


