Can CT texture analysis aid in the differentiation between normal lymph nodes and nodal metastases in oropharyngeal carcinomas?

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Aims and objectives

CT and MRI currently form the mainstay of assessment of head and neck tumours for local and distal staging. Visual inspection of nodes for features including size, loss of the fatty hilum, evidence of necrosis and pattern of enhancement are all useful for assessing the status of nodes, however these have variable sensitivity and specificity.[1-3]

Texture analysis provides the step from qualitative to quantitative analysis, with the added bonus that it uses routinely acquired images without the need for further tests. It relies on a variety of mathematical models to quantify the relationship of voxels to one another in terms of intensity (whether that be HU, SUV or SI) and in geographical position within the region of interest. This is typically performed using a statistics based technique, which calculates the distribution of local spatial distribution of voxel intensity. This can be performed on a first (one pixel), second (two pixels) or higher order (three or more pixels) basis.[4] Each describes a different form of heterogeneity within the lesion so are often synergistic.

To date texture analysis has been used in CT, MRI and PET in providing further information on the characteristics of tumour with heterogeneity shown to improve software differentiation of tumour from adjacent anatomy, differentiate benign from malignant disease, and predict response to treatment and prognosis.[5-9] A recent study has even used textural analysis to determine the p53 status of oropharyngeal carcinomas. [10] To date the ability of texture analysis has not been used in the assessment of oropharyngeal nodal metastases. Thus the aim of the current study was to ascertain the ability to differentiate between nodal metastases and normal lymph nodes.
Methods and materials

This was a single centre retrospective study, which was performed following institutional review board approval. 15 patients with histologically confirmed surgically resected oropharyngeal squamous cell carcinoma with confirmed local nodal metastases were identified.

All scans were performed on a 64 slice CT scanner (Lightspeed VCT XT, GE, USA). Image acquisition started at 100s, following the injection of 100ml iodine based contrast agent (Iohexol 300, GE Healthcare, USA) at 1ml/s for 100s. In every patient histologically confirmed malignant nodes were chosen and contrasted with normal nodes from the contralateral side in the same nodal zone.

Texture analysis was performed by placing regions of interest over the nodes using MaZda software (Technical University of Lodz, Poland).[11] In every patient a histologically confirmed malignant node was chosen and contrasted with a node from the contralateral side in the same nodal zone. Manual ROI were applied on the raw 0.625mm axial images on every slice that the node was visualized on. A circular region of interest was placed within the solid component of both the normal and malignant nodes on each slice, maximized to include as much soft tissue as possible without including either the fatty hilum of normal nodes nor any necrotic component of malignant nodes. Prior to analysis grey level normalization was performed to standard deviation plus/minus three standard deviations (µ±3#) within the regions of interest, following which grey-levels were then reduced to 64 grey levels as previously described.[12] From this 11 measures of heterogeneity were calculated for each slice and averaged to the number of slices the node was visualized on. Texture features were derived using the co-occurrence matrix (a second order statistical analysis derived textual analysis). Classification of data was performed using Weka software (University of Waikato, New Zealand), with a k-nearest neighbour model (k=3) and a 10-folds cross validation regime.

Results of data classification are reported using classification accuracy (%) and the area under the receiver operator characteristic curve (ROC). Statistical evaluations of differences in raw feature values were made using a Mann-Whitney U test (SPSS;IBM,New York).
Results

The study cohort comprised 15 patients (80% male), with a mean age of 66.4 (range 50-84 years). A total of 80 metastatic nodes were selected in the 15 patients with 26 contralateral nodes in matched nodal zones.

There was a significant difference in the Angular Second Moment, Contrast, Correlation, Difference Entropy, Difference of Variance, Entropy, Inverse Difference Moment, and Sum Variance measures of texture between the metastatic nodes and normal nodes (all p<0.001) - See table 1. No difference was observed in the Sum Average or Sum of Squares measures.

Table 1: Comparison of texture analysis measures between the normal and metastatic nodes.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Normal</th>
<th>Metastatic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular Second Moment</td>
<td>0.04±0.02</td>
<td>0.10±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contrast</td>
<td>189±41</td>
<td>104±64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Correlation</td>
<td>0.02±0.17</td>
<td>0.45±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference of Entropy</td>
<td>0.94±0.27</td>
<td>1.11±0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference of Variance</td>
<td>51±18</td>
<td>39±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Entropy</td>
<td>1.45±0.47</td>
<td>2.16±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inverse Difference Moment</td>
<td>0.08±0.03</td>
<td>0.24±0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum Average</td>
<td>58.6±9.5</td>
<td>63.7±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sum of Entropy</td>
<td>1.07±0.35</td>
<td>1.49±0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of Squares</td>
<td>94.9±15.8</td>
<td>88±36.2</td>
<td>NS</td>
</tr>
<tr>
<td>Sum of Variance</td>
<td>191±57</td>
<td>248±112</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Measure of entropy (attenuation heterogeneity) of the metastatic nodes was 2.16±0.8 compared with 1.45±0.47 for normal nodes (p<0.001, see Figure 1).

Figure 1: Comparison of entropy values in metastatic and normal nodes
When all measures of texture were used, nodal metastases could be differentiated with an accuracy of 96.2% (ROC 0.95), sensitivity of 97.5% and specificity of 92.3%. When only entropy features were used, accuracy was 93.4% (ROC 0.95), sensitivity of 97.5% and specificity of 92.3% (See figures 2 and 3).

**Figure 2:** ROC curve for all texture analysis features
Fig. 2: ROC for all texture analysis features

References: Clinical Radiology, Ninewells Hospital and Medical School - Dundee/UK

Figure 2: ROC curve for entropy
Fig. 3: ROC curve for entropy

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Fig. 1: Comparison of entropy values in metastatic and normal nodes

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Fig. 3: ROC curve for entropy

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Fig. 2: ROC for all texture analysis features

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Conclusion

In this study we have shown the ability of quantitative CT texture analysis to accurately differentiate benign from malignant nodes in oropharyngeal squamous cell carcinomas. When all 10 measures of texture heterogeneity was used this produced a high diagnostic accuracy of 96.2%, with all measures of heterogeneity higher in metastatic nodes.

Our findings are in agreement with a study by Bayanati et al demonstrated similar findings, with sensitivity of 81% and specificity of 80%, with ROC of 0.87 for differentiating mediastinal nodal metastases in primary lung cancer.[12] The ROC in our cohort was higher than in this previous study. This may be due to the effect of contrast on heterogeneity measures as the previous study was performed on non contrast CT images. Alternately it may reflect different architectural changes between lung and oropharyngeal nodal metastases. The effects of contrast on texture analysis measures has not yet been directly studied in CT, however significant differences have been reported in tumour heterogeneity on both non contrast and contrast enhanced CT images. [7, 8] The benefits of contrast in providing better soft tissue characterization is supported by an MRI based paper looking at parotid masses which showed contrast enhanced T1W images provided the best textural analysis discriminator between malignant and benign disease.[9]

In our study entropy was the single best discriminator between malignant and benign disease, and only marginally weaker than a model including all 10 of the assessed second order metrics (accuracy 93.4 vs 96.2%). Entropy measured on CT has previously been shown to be a strong predictor of survival in lung, renal and oesophageal cancers, however this has not be assessed in the current study.[7, 8, 13] The utility of this measure in nodal assessment is mixed however, with another study showing this to be the weakest texture analysis measure of nodal status with higher order texture analysis, including run length non-uniformity and gray-level non-uniformity, providing greater discrimination.[12]

There are several potential limitations within the current study. We have only looked at a small ROI within the solid tissue of the node. Inclusion of the entirety of the nodal solid tissue, or even the entirety of the node may provide more accurate analysis as it provides a more global assessment of the node. The benefit of whole node assessment has been previously demonstrated by a single study in PET, however this has not been assessed in CT yet.[6] We have used a single observer at a single centre with the resultant weakness this entails. Recent work suggests automatic contouring may provide more accurate and reproducible texture analysis quantification.[14] Finally the clinical impact of nodal classification in terms of upstaging/downstaging of the nodal status and the impact of this on survival has not been assessed and further work is required in these areas.
In conclusion, quantitative CT texture analysis shows promise as a useful tool to accurately differentiate between benign and malignant nodal involvement in oropharyngeal squamous cell carcinoma.
References


13. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: