Texture Analysis of Subsolid Nodules- Definitions and Applications

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Learning objectives

• The learner should understand:
1. Definition of terms used in texture and histogram analysis.
2. How texture analysis can be used to differentiate temporary from persistent subsolid nodules.
3. How texture analysis can be used to differentiate pre-invasive from invasive adenocarcinoma lesions.
Background

- Lung cancer is leading cause of cancer deaths worldwide [1]

- Incidentally detected nodules with “ground-glass attenuation” or “sub-solid” has a higher risk of malignancy than an incidentally detected solid lung nodule with 75% of sub-solid nodules representing adenocarcinoma [2]

Spectrum of Persistent Pure Ground Glass Opacity (GGO) to Solid Nodules

Pure GGO
DDX scar, AAH, AIS, organizing pneumonia

Sub-solid/part solid GGO
DDX AIS/adenoca

Solid nodule
DDX lung cancer, metastasis, lymphoma, infection
Subsolid (part-solid) nodules

- Subsolid nodules may have purely ground glass attenuation, partly solid or have mixed solid and ground glass attenuation.
- Ground glass density is defined as lung opacity that does not obscure surrounding pulmonary vessel visualization.

- Subsolid nodules:
  - Temporary - represent infection, inflammation, haemorrhage.
  - Persistent - represent neoplasm; Vary from precursor lesions to adenocarcinomas [3]
Persistent subsolid/GGO Nodules

• Sub-solid/GGO nodules grow slowly & new ground glass nodules may develop during surveillance

• CT guided biopsy is often problematic owing to a low diagnostic yield from lack of or a low percentage of solid component in pure ground glass and sub-solid nodules respectively [3]

• FDG-PET often false negative
Note the development of solid component over time typically representing development of invasive adenocarcinoma.
Value of initial short-term follow-up of benign GGNs. 

A, B, Target reconstructed 5-mm-thick (A) and 1-mm-thick (B) sections through right upper lobe show a focal ground-glass lesion (upper arrow in A), within which a few dilated peripheral airways can be identified. This appearance is strongly suggestive of a peripheral adenocarcinoma. Lower arrow in A points to normal lung.

C, D, CT scans obtained with 5-mm-thick (C) and 1-mm-thick (D) sections 3 months later at same level as A and B show near-complete disappearance of lesion, likely representing focal nonspecific inflammation. Arrows in C indicate subtle new foci of ground-glass attenuation appearing in the interval, again consistent with nonspecific inflammation.

David P. Naidich; Alexander A. Bankier; Heber MacMahon; Cornelia M. Schaefer-Prokop; Massimo Pistolesi; Jin Mo Goo; Paolo Macchiarini; James D. Crapo; Christian J. Herold; John H. Austin; William D. Travis; 

Significance of texture analysis

- Need for surveillance CT for subsolid nodules, but how long?
- Increased radiation risk
- Who needs surgical resection?
- Tissue characterisation of sub-solid nodules can identify patients at higher risk and who may benefit from surgery
- Can we predict pathology using texture analysis of the nodule?
### Fleischner Society 2013 guidelines

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Management Recommendations</th>
<th>Additional Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary pure GGNs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 mm</td>
<td>No CT follow-up required</td>
<td>Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>Initial follow-up CT at 3 months to confirm persistence then</td>
<td>FDG PET is of limited value, potentially misleading, and therefore not recommended</td>
</tr>
<tr>
<td></td>
<td>annual surveillance CT for a minimum of 3 years</td>
<td></td>
</tr>
<tr>
<td>Solitary part-solid nodules</td>
<td>Initial follow-up CT at 3 months to confirm persistence. If</td>
<td>Consider PET/CT for part-solid nodules &gt;10 mm</td>
</tr>
<tr>
<td></td>
<td>persistent and solid component ≤5 mm, then yearly surveillance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT for a minimum of 3 years. If persistent and solid component</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5 mm, then biopsy or surgical resection</td>
<td></td>
</tr>
<tr>
<td>Multiple subsolid nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure GGNs ≤5 mm</td>
<td>Obtain follow-up CT at 2 and 4 years</td>
<td>Consider alternate causes for multiple GGNs ≤5 mm</td>
</tr>
<tr>
<td>Pure GGNs &gt;5 mm without a</td>
<td>Initial follow-up CT at 3 months to confirm persistence and</td>
<td>FDG PET is of limited value, potentially misleading, and therefore not recommended</td>
</tr>
<tr>
<td>dominant lesion(s)</td>
<td>annual surveillance CT for a minimum of 3 years</td>
<td></td>
</tr>
<tr>
<td>Dominant nodule(s) with part-solid</td>
<td>Initial follow-up CT at 3 months to confirm persistence. If</td>
<td>Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for</td>
</tr>
<tr>
<td>or solid component</td>
<td>persistent, biopsy or surgical resection is recommended,</td>
<td>lung cancer</td>
</tr>
<tr>
<td></td>
<td>especially for lesions with &gt;5 mm solid component</td>
<td></td>
</tr>
</tbody>
</table>

*Note: GGNs = Ground Glass Nodules*
# Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Size</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ground glass</td>
<td>No routine follow-up</td>
<td>CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years. In certain suspicious nodules &lt; 6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).</td>
</tr>
<tr>
<td>Part solid</td>
<td>No routine follow-up</td>
<td>CT at 3–6 months to confirm persistence. If unchanged and solid component remains &lt; 6 mm, annual CT should be performed for 5 years. In practice, part-solid nodules cannot be defined as such until ≥ 6 mm, and nodules &lt; 6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥ 6 mm should be considered highly suspicious (recommendations 4A-4C).</td>
</tr>
<tr>
<td>Multiple</td>
<td>CT at 3–6 months. If stable, consider CT at 2 and 4 years.</td>
<td>CT at 3–6 months. Subsequent management based on the most suspicious nodule(s). Multiple &lt; 6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A).</td>
</tr>
</tbody>
</table>

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What is texture analysis

- Tumor spatial heterogeneity is an important prognostic factor
- Image texture analysis is an approach of quantifying heterogeneity
- Texture analysis could improve the diagnosis, tumor staging, and therapy response assessment [5]
Texture analysis

• Variety of mathematical methods used to evaluate the gray-level intensity and position of the pixels within an image to derive so-called ‘texture features’ that provide a measure of intraläsional heterogeneity [5]

• Involves 2 steps: automated segmentation and calculation of texture features
Texture analysis features

- Histogram features - mean attenuation, standard deviation, skewness, kurtosis, entropy, homogeneity, and percentile CT numbers
- Volumetric features - volume, mass, effective diameter, and surface area
- Morphologic features - sphericity, discrete compactness, gray-level co-occurrence matrix inertia, gray-level co-occurrence matrix inverse difference moment, and gray-level co-occurrence matrix contrast
Example of automatic lesion segmentation

Images courtesy of P. Salazar, Vital Images
Figure 1. Linear measurements in Lung nodule analysis following GGO probe

Volume measurement (mm$^3$)
Linear measurements: mean diameter, maximum diameter, short axis diameter (mm)
Density measurements: min, max, mean CT attenuation (HU).

Images courtesy of P. Salazar, Vital Images
Terms used in texture analysis

- Kurtosis
- Skewness
- Entropy and heterogeneity
• **Kurtosis** (flatness of the histogram) - defined as any measure of the “peakedness” of the probability distribution of a real-valued random variable in a histogram, compared to the normal distribution.

*Baek HJ et al. Radiology. 2012 Sep;264(3):834-43*
• **Skewness** describes the asymmetry of the histogram. It is the measure of the asymmetry of the probability distribution of a real-valued random variable in a histogram [6].

**Skewness**. A negative skewness indicates an elongated tail on the left side of the mean, with most values lying to the right of the mean. A positive skewness indicates an elongated tail on the right side of the mean, with most values lying to the left of the mean

*Baek HJ et al. Radiology. 2012 Sep;264(3):834-43*
Entropy and heterogeneity - heterogeneity within the nodule is assessed with entropy and homogeneity. Homogeneity is the measure that increases with less contrast in the window and calculated by histogram. High entropy and low homogeneity increases the heterogeneity of the nodule [7].
Histogram analysis involves 3 types of data:

1. classic moment-based histogram parameters (mean, skewness, kurtosis, etc.)
2. Robust quantile-based histogram parameters (quantile kurtosis, peakedness, tail weights, etc.)
3. Gaussian mixture decomposition to extract and quantify material components (lipidic, calcified, etc.) from heterogeneous 3D regions
The ground glass opacities will be segmented using automated lung nodule probe of commercial software Vitrea v6.7. If needed the GGO contours will be edited, especially in proximity of vessels.

*Linear measurements in Lung nodule analysis following GGO probe*

- Volume measurement (mm³)
- Linear measurements: mean diameter, maximum diameter, short axis diameter (mm)
- Density measurements: min, max, mean CT attenuation (HU)

*Courtesy P. Salazar (Vital images)*
Automatic lesion registration in dual volume CT (before user confirmation)

Courtesy P. Salazar (Vital images)
Density histogram / density curve for segmented ground glass opacification
Transverse thin-section CT image showing manual segmentation of a part-solid nodule (PSN). Segmentation of the PSN was manually conducted using an in-house software program and texture features of the nodules were automatically extracted and calculated by the program. One radiologist segmented the outer boundary of the whole PSN (A) and inner solid portion boundary.

The histogram of a composite segmented 3D region such as a subsolid lung nodule will be analyzed into different components using statistical Gaussian mixture decomposition. The resulting analysis provides peak values and weights for each component that correspond to different typical material densities contained in the 3D region (fibrous, calcified, etc.)
Histogram analysis for pure GGO nodule. Notice the more homogeneous density curves (lack of a second density curve seen with part solid nodules)
How texture analysis can help

Helps in differentiation of temporary from persistent subsolid nodules

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Transient PSNs (n = 31)</th>
<th>Persistent PSNs (n = 46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole nodule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean attenuation</td>
<td></td>
<td></td>
<td>0.005 *</td>
</tr>
<tr>
<td>Standard deviation</td>
<td></td>
<td></td>
<td>0.054 *</td>
</tr>
<tr>
<td>Skewness</td>
<td></td>
<td></td>
<td>0.009 *</td>
</tr>
<tr>
<td>Kurtosis</td>
<td></td>
<td></td>
<td>0.154 *</td>
</tr>
<tr>
<td>Ratio of mean attenuation</td>
<td></td>
<td></td>
<td>0.002 *</td>
</tr>
<tr>
<td>(whole PSN: portion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoid fitting slope</td>
<td></td>
<td></td>
<td>0.149 *</td>
</tr>
<tr>
<td>Inner solid portion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean attenuation</td>
<td></td>
<td></td>
<td>0.095 *</td>
</tr>
<tr>
<td>Standard deviation</td>
<td></td>
<td></td>
<td>0.066 *</td>
</tr>
</tbody>
</table>

Data are means ± standard deviations of PSNs' attenuation values.

*Independent sample t test

PSNs = part-solid nodules.

doi:10.1371/journal.pone.0085167.t003

Lee et al. Usefulness of Texture Analysis in Differentiating Transient from Persistent Part-Solid nodules (PSNs): A Retrospective Study. PloS One 9 (1): e85167.
An example of texture analysis of a transient PSN. (A) Thin-section CT scan shows a 17 mm PSN (arrow) with an ill-defined margin in the left upper lobe in a 49-year-old female. (B) Texture analysis of this PSN shows a low mean attenuation and high positive skewness (2570.2 Hounsfield units and 0.856, respectively). The PSN disappeared at follow-up CT after one month.

An example of texture analysis of a persistent PSN. (A) Thin-section CT scan shows an 18 mm PSN (arrow) with fissural retraction in the right lower lobe in a 62-year-old male. (B) Texture analysis of the PSN shows high mean attenuation and low negative skewness (2305.5 Hounsfield units and 20.378, respectively). As this PSN was persistent, he underwent lobectomy and was diagnosed as having adenocarcinoma.

How texture analysis can help

• Helps in differentiation of subsolid pre-invasive lesions from invasive lesion as significant differences in histograms and with volumetric parameters (such as mass, kurtosis, and entropy) exist between them

• Pre-invasive lesions had typically smaller mass and higher kurtosis

CT scan shows a 14-mm part-solid GGN (arrow) with a small solid portion in the superior segment of the left lower lobe in a 52-year-old woman. This nodule was confirmed as AIS at pathologic analysis. Texture analysis showed the mass of the lesion was 652.28 mg than the invasive adenocarcinoma (857.41 mg). The CT number distribution of the AIS had a higher peak, which meant that it had higher kurtosis (0.031).

*Hee-Dong Chae; Chang Min Park; Sang Joon Park; Sang Min Lee; Kwang Gi Kim; Jin Mo Goo; Radiology 2014, 273, 285-293.
DOI: 10.1148/radiol.14132187
2014 by the Radiological Society of North America, Inc*
CT scan shows a 15-mm part-solid GGN (arrow) with a lobulated border in the anterior segment of the left upper lobe in a 69-year-old man. This nodule was confirmed as adenocarcinoma at lobectomy. Texture analysis showed mass of this invasive adenocarcinoma was (857.41 mg). This lesion had a negative kurtosis (−0.469) with a lower and wider peak on the histogram.

Hee-Dong Chae; Chang Min Park; Sang Joon Park; Sang Min Lee; Kwang Gi Kim; Jin Mo Goo; Radiology 2014, 273, 285-293.
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Future application of texture analysis

• Risk prognostication of subsolid nodules to minimise radiation exposure to the patient from unnecessary CT follow ups
• Correlation of CT texture analysis features with survival data to understand which parameters are more predictive of long term outcome
• Help distinguish benign from malignant nodules
• Threshold density percentage of solid component to predict invasive adenocarcinoma
Summary

1. Definition of terms used in texture and histogram analysis are explained.
2. How texture analysis can be used to differentiate temporary from persistent subsolid nodules.
3. How texture analysis can be used to differentiate pre-invasive from invasive adenocarcinoma lesions.
References


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