Texture analysis of iodine maps and conventional images for k-nearest neighbor classification of benign and metastatic lung nodules

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Abstract

**Background:** The purpose of this study was to analyze if the use of texture analysis on spectral detector CT (SDCT)-derived iodine maps (IM) in addition to conventional images (CI) improves lung nodule differentiation, when being applied to a k-nearest neighbor (KNN) classifier.

**Methods:** 183 cancer patients who underwent contrast-enhanced, venous phase SDCT of the chest were included: 85 patients with 146 benign lung nodules (BLN) confirmed by either prior/follow-up CT or histopathology and 98 patients with 425 lung metastases (LM) verified by histopathology, 18F-FDG-PET-CT or unequivocal change during treatment. Semi-automatic 3D segmentation of BLN/LM was performed, and volumetric HU attenuation and iodine concentration were acquired. For conventional images and iodine maps, average, standard deviation, entropy, kurtosis, mean of the positive pixels (MPP), skewness, uniformity and uniformity of the positive pixels (UPP) within the volumes of interests were calculated. All acquired parameters were transferred to a KNN classifier.

**Results:** Differentiation between BLN and LM was most accurate, when using all CI-derived features combined with the most significant IM-derived feature, entropy (Accuracy:0.87; F1/Dice:0.92). However, differentiation accuracy based on the 4 most powerful CI-derived features performed only slightly inferior (Accuracy:0.84; F1/Dice:0.89, p=0.125). Mono-parametric lung nodule differentiation based on either feature alone (i.e. attenuation or iodine concentration) was poor (AUC=0.65, 0.58, respectively).

**Conclusions:** First-order texture feature analysis of contrast-enhanced staging SDCT scans of the chest yield accurate differentiation between benign and metastatic lung nodules. In our study cohort, the most powerful iodine map-derived feature slightly, yet insignificantly increased classification accuracy compared to classification based on conventional image features only.

**Keywords:** Lung nodules, Staging, Diagnosis, Differentiation, Dual-energy CT, Spectral detector CT, Texture analysis, Lung metastases, Oncologic imaging

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Background
Lung nodules are one of the most common incidental findings in chest computed tomography (CT) [1]. Different imaging features depicted in CT of the chest can be used to facilitate prediction of malignancy, especially large nodule size, part-solid appearance and/or spiculation [2–4]. While nodules in non-cancer patients are mostly benign, probability of malignancy is much higher when found in cancer patients at staging examinations [5]. However, for cancer patients, Fleischner criteria are not applicable [6]. Hence, cancer patients with ambiguous lung nodules often undergo either additional follow-up to detect size increase or biopsy of the referring lesions [7, 8]. The necessity for follow-up implies the risk of delayed diagnosis and additional radiation exposure, while biopsies may lead to perinterventional complications such as pneumothorax or pulmonary hemorrhage [9]. Furthermore, uncertainty regarding metastatic status may even alter therapy [10].

Several approaches have been suggested to investigate differentiation of lung nodules within one examination without further need for additional follow-up. Until now, the majority of referring studies were primarily focused on discrimination between benign lung nodules and primary lung cancer [11–15]. However, with regards to differentiation of benign lung nodules and lung metastases at contrast-enhanced staging CT, data is much sparser. As one of the approaches proposed to this regard, it has been revealed that first order texture features derived from contrast-enhanced chest CT scans could be a feasible method to distinguish between benign and metastatic lung nodules [16, 17]. Another technique that has been investigated in this setting was the application of dual-energy CT derived iodine maps [18]. These maps can be calculated based on the separate acquisition of Photoelectric and Compton-weighted datasets [19]. It has been shown that such maps may be advantageous for the purpose of classification of pulmonary nodules as they reflect lesion vascularity [20–22]. However, accuracies obtained with either of the two methods have not been sufficiently high to pave the way to clinical application.

Our hypothesis was that texture analysis and dual-energy CT-derived iodine maps may work synergistically to facilitate lung nodule differentiation; we focused on first order texture analysis which has been described to be more reproducible than higher-order features, which we assumed to be favorable when applying it to DECT data [23]. Consequently, the study purpose was to examine the differentiation between benign lung nodules and metastases based on first-order texture features obtained from spectral-detector-CT derived iodine maps and conventional CT images.

Methods
Patients
A retrospective database query was executed to identify oncologic patients (≥ 18 years) who underwent clinically indicated, contrast-enhanced, venous phase SDCT of the chest and who were diagnosed with visually uncalcified, metastatic or benign lung nodules according to the radiological report. Subsequently, lung nodules with a diameter equal or greater than 5 mm were selected by an experienced radiologist and all nodules were correlated with ground truth as indicated below; if ground truth was absent, patients were excluded. Figure 1 shows the workflow for inclusion and exclusion of study subjects.

Ground truth correlation and lesion annotation
Before study inclusion, each lesion was correlated with a reference standard. For the subgroup of lung metastases, this was based either on

1. Histopathologic confirmation of metastatic disease and/or
2. Unequivocal radionuclide uptake in referring FDG-PET/CT examinations and/or
3. Unequivocal increase in size over the course of multiple follow-up examinations or change in size during anticancer treatment.

Eligibility criteria for benign lung nodules were:

1. Histopathologic confirmation of inflammation/post-inflammatory changes without malignancy and/or
2. Constant size without treatment compared to prior or follow-up CT for a period of at least 6 months, no history of lung metastases

Image acquisition and reconstruction
All scans were performed on a clinical dual-energy CT scanner (IQon; Philips Healthcare, Best, the Netherlands) with the following scan parameters: supine patient position, inspirational breath hold, pitch=0.67; rotation time=0.33 s, collimation=64 \times 0.625 mm; matrix=512 \times 512; tube voltage=120 kVp; tube current modulation enabled (DoseRight 3D-DOM; Philips Healthcare). For acquisition of contrast-enhanced scans (mainly combined chest/abdomen examinations), all patients received a body weight–adapted bolus of iodinated contrast media (<55 kg: 1 ml/kg; 55–120 kg: 100 ml; >120 kg: 120 ml; Accupaque, 350 mg/mL; GE Healthcare, Chicago, IL) which was administered via a peripheral vein with a flow rate of 3.5 mL/sec and followed by a saline flush of 30 mL. Bolus-tracking technique with a delay of 50 s was enabled to receive venous phase scans of the chest (and abdomen, if clinically indicated). For
reconstruction of conventional images (CI), a hybrid-iterative reconstruction algorithm was used (iDose 3, filter YA, Philips Healthcare) and standard lung window was chosen. Iodine maps (IM) were reconstructed using a dedicated spectral reconstruction method (Spectral, filter B, level 3, Philips Healthcare); 2 mm slice thickness and 1 mm section increment were chosen throughout all datasets.

Post-processing
CT datasets were transferred to a proprietary software for oncologic follow-up (mint lesion research, Mint Medical GmbH, Heidelberg, Germany). Lung nodules were semi-automatically contoured based on CI. CI and IM were co-registered, and segmentations were transferred from CI to IM. After that, segmentations were double-checked in order to warrant consistent volumes of interest between both reconstructions. Volumetric Hounsfield unit attenuation (HU), iodine concentration (IC [mg/ml]) as well as first order texture features (entropy, kurtosis, mean of the positive pixels (MPP), skewness, uniformity and uniformity of the positive pixels (UPP)) within the referring volumes of interests from both datasets were obtained (supplementary Table 1).

Pre-processing and feature analysis
Values for HU and IC and referring first order texture features were exported. Mean HU and IC between the two groups were compared. 15 benign lesions with a HU higher than one standard deviation above the mean HU were excluded due to suspected calcification.

Features were tested individually (scikit-learn 0.21.3) by means of area under the receiver operator characteristic curve (AUC), F-statistics and Mutual Information (MI).

Multiparametric classification
Features were normalized (zero mean and unit variance) and data was transferred to a k-nearest neighbor (KNN) classifier with 10 neighbors using Euclidean distance metric. The classifier was then evaluated with 5-fold and Leave One-Out Cross Validation.

Statistical analysis
Quantitative attenuation and iodine values were compared using Wilcoxon test. Statistical significance was determined as $p \leq 0.05$. For feature testing, MI was calculated. For classification evaluation, F1 score, accuracy, specificity and sensitivity were computed (supplementary Table 2).

Results
Study cohort
183 cancer patients (96 men and 87 women, mean age 63.2 ± 13.0) who underwent SDCT of the chest were included: 85 patients with 161 benign lung nodules and 98 patients with 425 lung metastases. Median time of available imaging follow-up for ground truth correlation was 22.5 months, ranging from 6 months to 79 months. Table 1 gives an overview on patient characteristics. 425 metastases and 146 benign lesions were used for training and testing comprising approximately 70 and 30% of the data, respectively. Accordingly, the training group was composed of 105 benign lesions and 294 metastases, while the testing group comprised 41 benign lesions and 131 metastases. Figure 2 gives an overview on the methodological workflow of the study.

Monoparametric analysis
Hounsfield unit attenuation and iodine concentration were both significantly higher in metastatic (Attenuation: $-80.1 \pm 192.0$ HU; IC: $1.6 \pm 0.5$ mg/ml) than in benign lung nodules (Attenuation: $-170.5 \pm 173.5$ HU; IC: $1.4 \pm 0.5$ mg/ml; both $p \leq 0.05$). However, for both
Table 1 Patient characteristics

|                                | Patients with benign lung nodules | Patients with lung metastases |
|--------------------------------|-----------------------------------|------------------------------|
| **Patients**                   | 85                                | 98                           |
| **Patient demographics**       |                                   |                              |
| Sex (men/women)                | 47/38                             | 49/49                        |
| Mean age (years)               | 62.7 ± 12.2                       | 63.7 ± 13.8                  |
| Mean Dose (CTDvol)             | 14.3 ± 6.7                        | 14.6 ± 6.9                   |
| **Underlying diseases**        |                                   |                              |
| Melanoma                       | 18                                | 32                           |
| Esophageal cancer               | 8                                 | 5                            |
| Sarcoma                        | 7                                 | 6                            |
| Breast cancer                  | 4                                 | 9                            |
| Lymphoma                       | 11                                | 1                            |
| Colorectal cancer              | 3                                 | 9                            |
| Pancreatic cancer              | 6                                 | 5                            |
| Renal cell cancer              | 1                                 | 8                            |
| Urothelial carcinoma           | 2                                 | 5                            |
| Testicular cancer              | 4                                 | 1                            |
| Liver cancer                   | 1                                 | 3                            |
| Ovarian cancer                 | 0                                 | 4                            |
| Other oncologic diseases       | 16                                | 10                           |
| No oncologic diseases          | 4                                 | 0                            |
| **Ground truth**               |                                   |                              |
| Follow-up                      | 80                                | 80                           |
| Pathology report               | 5                                 | 17                           |
| PET/CT                         | 0                                 | 1                            |

Fig. 2 Methodological workflow from study inclusion and image reconstruction to image segmentation, feature extraction, testing and KNN-based classification
parameters, a significant data overlap was observed between the two lesion types (Fig. 3). Consequently, area under the ROC analysis revealed a low AUC of 0.67 and 0.58 for HU and IC, respectively, regarding benign and metastatic nodule differentiation. Pertaining to texture features, kurtosis, skewness and uniformity derived from CI showed significant differences between benign nodules and lung metastases, while for iodine map derived features, significant differences were found for entropy, kurtosis, uniformity and UPP; Table 2 shows the comparison of mean values of all tested features between benign and metastatic lung nodules. Figure 4 depicts exemplary cases of metastatic and benign lung nodules with entropy feature maps, which was the most powerful iodine map-derived feature.

Feature analysis
For feature analysis, only the training cohort was used. Individual feature testing identified entropy, uniformity and skewness as well as mean HU value derived from conventional images as the four most powerful features for lung nodule differentiation. The most powerful iodine map-derived feature was entropy. Table 3 includes AUC, F-statistics and MI values for each feature tested.

Multiparametric classification
Applied to the training cohort, KNN using 5-Fold Cross Validation yielded optimal nodule differentiation when the best 4 CI-derived features were used (Accuracy: 0.87; F1/Dice: 0.91). When combining the 4 best CI-derived features with the best IM-derived feature (Entropy_{IM}), accuracy was on a comparable level (Accuracy: 0.86; F1/Dice: 0.90).

When using all iodine map-derived features without CI-derived features, classification accuracy was lower (Accuracy: 0.73; F1/Dice: 0.83). When applied to the testing cohort, KNN yielded the best nodule differentiation when using all CI-derived features and iodine-derived entropy (Accuracy: 0.86; F1/Dice: 0.91). Here, the 4 best CI-derived features yielded a lower accuracy, yet without statistical significance (Accuracy: 0.84; F1/Dice: 0.89). Tables 4 and 5 provide an overview on the results of KNN-based multiparametric classification in the training and testing cohort, respectively.

Discussion
This study evaluated differentiation between benign and metastatic lung nodules at staging spectral detector CT (SDCT) of the chest based on first-order texture features derived from quantitative iodine maps (IM) and conventional images (CI).

Distinguishing metastatic from non-metastatic lung nodules is a clinical scenario of high relevance. Our results suggest that the proposed method may help to improve M staging in the context of lung metastases which is important for determining prognostic outcome as well as therapeutic approaches of many oncologic diseases. Although lung metastases demonstrated a

Fig. 3 Attenuation and iodine concentration of benign lung nodules and lung metastases. Both were significantly higher in lung metastases yet overlap between the two lesion types was large
Fig. 4 Examples of benign nodules as shown in conventional images (CI; left column), iodine maps (IM; second column from the left) and
entropy texture maps derived from CI and IM (right columns). It is revealed that some benign and metastatic nodules may be clearly
distinguished by means of their iodine uptake (top row vs bottom row) while some benign nodules show comparable iodine concentration
values as metastases (second vs third row), hampering accurate differentiation.

Table 2 Mean values of all tested features for benign and metastatic lung nodules

|                          | Benign lung nodules | Lung metastases | p-value |
|--------------------------|---------------------|-----------------|---------|
| Attenuation<sub>CI</sub> | −170.49             | −80.12          | p≤0.05  |
| Attenuation SD<sub>CI</sub> | 173.54              | 191.96          | p≤0.05  |
| Entropy<sub>CI</sub>     | 6.70                | 8.01            | p≤0.0001|
| Kurtosis<sub>CI</sub>    | 3.90                | 4.26            | p≤0.0001|
| MPP<sub>CI</sub>         | 94.61               | 98.09           | p=0.18  |
| Skewness<sub>CI</sub>    | −0.21               | −0.80           | p≤0.0001|
| Uniformity<sub>CI</sub>  | 0.01                | 0.01            | p≤0.0001|
| Iodine concentration     | 1.44                | 1.58            | p≤0.05  |
| Iodine concentration SD  | 0.47                | 0.49            | p=0.24  |
| Entropy<sub>IM</sub>     | 4.90                | 5.21            | p≤0.0001|
| Kurtosis<sub>IM</sub>    | 3.67                | 4.34            | p≤0.0001|
| MPP<sub>IM</sub>         | 1.45                | 1.60            | p≤0.05  |
| Skewness<sub>IM</sub>    | 0.42                | 0.31            | p=0.06  |
| Uniformity<sub>IM</sub>  | 0.05                | 0.04            | p≤0.0001|
| UPP<sub>IM</sub>         | 0.04                | 0.04            | p≤0.0001|
Table 3 Results from individual feature testing including area under the receiver operating characteristics curve (AUC), F1 score and mutual information (MI score)

| Feature                        | AUC   | F1 score | MI    |
|--------------------------------|-------|----------|-------|
| Attenuation                    | 0.67  | 1.48 X 10^-12 | 0.08 |
| Attenuation SD                 | 0.58  | 6.07 X 10^-31 | 0.02 |
| Entropy_CI                     | 0.83  | 7.45 X 10^-31 | 0.17 |
| Kurtosis_CI                    | 0.63  | 2.97 X 10^-31 | 0.02 |
| MPP_CI                         | 0.64  | 2.70 X 10^-7  | 0.03 |
| Skewness_CI                    | 0.74  | 3.05 X 10^-9  | 0.07 |
| Uniformity_CI                  | 0.82  | 7.75 X 10^-26 | 0.15 |
| UPPCI                           | 0.56  | 1.41 X 10^-11 | 0.11 |
| Iodine concentration           | 0.58  | 1.06 X 10^-22 | 0.00 |
| Iodine concentration SD        | 0.52  | 4.71 X 10^-31 | 0.00 |
| Entropy_WM                     | 0.64  | 1.36 X 10^-32 | 0.03 |
| Kurtosis_WM                    | 0.62  | 1.68 X 10^-31 | 0.00 |
| MPP_WM                         | 0.58  | 9.74 X 10^-33 | 0.00 |
| Skewness_WM                    | 0.55  | 4.49 X 10^-31 | 0.03 |
| Uniformity_WM                  | 0.59  | 4.93 X 10^-31 | 0.02 |
| UPWM                           | 0.60  | 8.59 X 10^-31 | 0.02 |

Table 4 Results of the training cohort. KNN-based lung nodule classification with 5-fold cross validation using different combinations of CI- and iodine-derived texture features

| Combination                      | Accuracy | F1 / Dice  | Sensitivity | Specificity |
|----------------------------------|----------|------------|-------------|-------------|
| 4 best CI-derived features       | 0.87 ± 0.03 | 0.91 ± 0.02 | 0.94 ± 0.03 | 0.69 ± 0.06 |
| 4 best CI-derived features + Entropy_WM | 0.86 ± 0.04 | 0.90 ± 0.03 | 0.95 ± 0.04 | 0.65 ± 0.05 |
| All CI-derived features          | 0.86 ± 0.02 | 0.91 ± 0.02 | 0.95 ± 0.02 | 0.64 ± 0.07 |
| All iodine-derived features      | 0.73 ± 0.02 | 0.83 ± 0.02 | 0.92 ± 0.04 | 0.28 ± 0.08 |
| All CI-derived features + Entropy_WM | 0.86 ± 0.02 | 0.90 ± 0.02 | 0.96 ± 0.01 | 0.61 ± 0.08 |
| All features                     | 0.83 ± 0.06 | 0.89 ± 0.04 | 0.95 ± 0.03 | 0.56 ± 0.12 |
indicated that in conventional CT, contrast-enhancement did not improve texture analysis-based subclassification of lung adenocarcinoma [30] which supports the results we found. Regarding the use of texture analysis of conventional CT, our results are in line with previous studies that reported an accurate nodule differentiation: for differentiation of metastatic and benign lung nodules, Cho et al. reported an AUC of 0.86 [17]. Other studies particularly elucidated the potential of entropy and the absence of uniformity for differentiation between benign nodules and adenocarcinoma of lung nodules, which was also the most powerful feature for nodule differentiation.

Our study is subject to several limitations that need to be addressed. First, we did not assess higher order texture features. As the combination of DECT-derived iodine maps and texture analysis has not been tested before for differentiation of benign and metastatic lung nodules, we wanted to focus on first order features as they were previously described as more robust compared to higher order features [23]; yet, subsequent studies with higher order features should be encouraged. Second, our study comprised a much larger number of lung metastases than benign nodules which introduces class imbalance. Third, histopathologic information was available only in a small proportion of nodules included which is owed to the limited number of patients that underwent biopsy especially in case of benign lung nodules. While the diagnosis of the metastatic nodules we included can be assumed to be relatively certain based on unequivocal changes in follow-up imaging and diagnosis of underlying diseases, the benign nodules often remained unspecific and will predominantly comprise granulomas, scar tissue from previous infections and hamartomas; despite long follow-up periods and refraining from including patients with known history of pulmonary metastases, a small number of non-vital metastatic residuals may have been present in this subgroup. However, this reflects the typical clinical scenario in oncological patients for which the non-invasive characterization is most important for individual optimized treatment planning. Last, most of the patients we included were diagnosed with oncologic diseases; this limits generalization to non-oncologic patients with low probability of lung nodule malignancy.

**Conclusions**
To conclude, our study revealed that KNN classification based on first order texture features improves differentiation of benign and metastatic lung nodules in contrast-enhanced staging SDCT of the chest compared to mono-parametric differentiation. Texture features derived from iodine maps did not significantly improve differentiation compared to the same features obtained from conventional images. Further investigation of possible underlying technical limitations of SDCT as well as analysis of other material-specific maps for lung nodule differentiation should be pursued.

**Supplementary Information**
The online version contains supplementary material available at https://doi.org/10.1186/s40644-020-00374-3.

Table S5: Results after application of the classifier to the test cohort showing lung nodule classification based on different combinations of CI- and iodine-derived texture features.

| Feature combination                      | Accuracy | F1/Dice | Sensitivity | Specificity |
|------------------------------------------|----------|---------|-------------|-------------|
| 4 best CI-derived features               | 0.84     | 0.89    | 0.89        | 0.69        |
| 4 best CI-derived features + EntropyIM   | 0.86     | 0.91    | 0.91        | 0.71        |
| All CI-derived features                  | 0.87     | 0.91    | 0.92        | 0.71        |
| All iodine-derived features              | 0.74     | 0.84    | 0.90        | 0.24        |
| All CI-derived features + EntropyIM      | 0.87     | 0.92    | 0.93        | 0.67        |
| All features                             | 0.84     | 0.90    | 0.93        | 0.52        |

**Abbreviations**

BLN: Benign lung nodule; CI: Conventional images; DECT: Dual energy CT; IM: Iodine maps; KNN: K-nearest neighbor classification; LM: Lung metastasis; SDCT: Spectral detector CT

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**Authors’ contributions**

SL, TP and LC conducted study design. AM built the database and conducted lesion segmentations. SS and DZ contributed to data consolidation and quantitative analysis. SL drafted the manuscript and provided project administration. HCR, RKT, DM, TP, NGH, AM, DZ contributed to manuscript preparation and revision. LC and NGH conducted the statistical analysis. The author(s) read and approved the final manuscript.

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Availability of data and materials
Please contact the corresponding author for data requests.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board and informed consent was waived due to the retrospective character of the study.

Consent for publication
Not applicable.

Competing interests
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