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Research article

Pulmonary nodules: Assessing the imaging biomarkers of malignancy in a "coffee-break"

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ABSTRACT

Introduction: Although nodule volumetry is a recognized biomarker of malignancy in pulmonary nodules (PNs), caution is needed in its interpretation because of variables such as respiratory volume variation and inter-scan variability of up to 25%. CT Texture Analysis (CTTA) is a potential independent biomarker of malignancy but inter-scan variability and respiratory volume variation has not been assessed.

Methods: In this prospective cohort study, 40 patients (20 with an indeterminate PN and 20 with pulmonary metastases) underwent two LDCTs within a 60-min period (the "Coffee-break") with the aim of assessing the repeatability of CTTA and semi-automated volume measurements.

Texture features were extracted from each automatic contoured region surrounding the PN.

Patients were also randomized to two inspiratory control groups: normal breath hold, and controlled lung volume to study the influence of inspiratory control on these measurements.

Results: The mean difference in volume between the two scans was 6.3%,SD:29.9%.

The textural features displayed 95% CI below ± 17.8%, and were less variable than nodule volume (95%CI ± 28.9%). All features had high repeatability, calculated by the concordance correlation coefficient, ($0.84 \leq CCC \leq 0.99$).

All measurements were more repeatable for the controlled lung volume group than the normal breath-hold group.

Conclusion: CTTA repeatability was comparable to automatic volumetric measurements, and appears to be improved using controlled volume breath holding.

Key Points

- Pulmonary nodule (PN) volumetry is a recognized biomarker of malignancy.
- Volumetry measurements are prone to inter-scan variability of up to 25%.
- CT Texture analysis (CTTA) has been shown to be a promising imaging biomarker of malignancy.
- This prospective study demonstrates that CTTA is a highly repeatable measure, comparable to volumetry.
- The repeatability of nodule volumetry and CTTA improves with controlled volume breathing.

1. Introduction

Current methods of determining if pulmonary nodules (PNs) are benign or malignant are not standardised. The US National Lung Screening Trial (NLST) showed that up to 95% of lung nodules detected on CT scans of the chest were falsely positive for malignancy [1]. Detection of non-malignant nodules has the unwanted consequences of unnecessary cost, additional investigations, patient anxiety and increased morbidity. Three studies have reported generic health-related quality of life, anxiety and lung-cancer specific distress data from approximately 2500 screening participants [2–4].

At present for small, sub-centimetre indeterminate nodules, follow up scanning to detect growth as a surrogate biomarker for malignancy is the most common recommendation [5]. Prior studies have shown that there is significant variation of up to 25% in these measurements

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[6]. This has been attributed to patient position, heart pulsation and inspiration levels, which can all influence the assessment of nodule size [7]. Consequently, a change in volume of 25 or 30% (at separate time intervals) has been suggested as a way of avoiding false positives.

Recent studies have shown that incorporating nodule characteristics such as size, growth rate, contrast enhancement and CT texture analysis (CTTA) can improve the accuracy of predicting the risk of malignancy [8,9]. This allows the stratification of PNs into different investigations and/or follow-up pathways based on the predicted risk of malignancy.

CT Texture Analysis (CTTA) represents a novel imaging approach that can potentially be used as an imaging biomarker in tumour characterization. Texture analysis refers to a variety of mathematical methods that provide information about the spatial arrangement of gray scales or intensities of the pixels within an image, producing measures of tissue heterogeneity, irregularity of shape and border and surface smoothness as well as many other features that may not be appreciated by the naked eye.

The reproducibility of CTTA as an imaging biomarker has been studied in patients with non- small cell lung cancer (NSCLC), however this study was based on retrospective imaging data [10].

Conventionally, CT Chest examinations are performed in full inspiration after appropriate instructions are given to the patients. However this results in inconsistent lung volume acquisition, which can alter nodule volume and position. Its effects on CTTA of PNs are not known. A method of reducing this variability in lung volumes is by asking the patients to breathe in a set volume of air.

The primary objective of this study was to prospectively assess the repeatability of CTTA of PNs at low dose multi-detector row computed tomography (CT) and to compare this to the repeatability of nodule volume. The secondary objective was to investigate the influence of two different methods in inspiratory control on CTTA and nodule volume measurements.

The repeatability of CTTA for each nodule for the risk of malignancy was also analysed.

2. Materials and methods

2.1. Patient and nodule selection

The study was approved by the local Research Ethics Committee and written informed consent was obtained from all patients.

Between March and July 2016, 40 adult patients (24 male, 16 female, age range, 43–88 years, mean age 69 years) with PN(s) between 5 and 20 mm were enrolled into the study.

20 patients had known pulmonary metastases previously shown on chest CT. The majority of these patients (n = 17) were referred for chest CT or Positron Emission Tomography (PET) scans as part of cancer surveillance or for baseline chest CT (n = 3) before the start of anticancer therapy.

The underlying primary cancers were sarcoma (n = 15) and colorectal cancer (n = 5).

The other group of 20 patients was enrolled from the virtual pulmonary nodule clinic. This group had indeterminate PN(s) and were referred for CT surveillance. 3/20 of these patients were subsequently diagnosed with non-small cell lung cancer. 7/20 of the patients had completed two years of nodule surveillance and were diagnosed with a benign nodule based on stability. 10/20 of the patients are still undergoing nodule surveillance to date (March 2017).

Only solid, non-calcified nodules were included in both groups because the software used for nodule volumetry and CTTA was not designed for the analysis of sub-solid nodules (SSNs). Juxta-pleural, juxtacardiac and nodules abutting blood vessels were included.

Each patient had one nodule identified that was either under surveillance if indeterminate at the time or the index pulmonary metastasis previously chosen for oncology follow-up.

2.2. Image acquisition

Two low-dose chest CT examinations (LDCT) without contrast material were performed in all cases. Between the two LDCT examinations, patients were asked to get off and on the CT table to simulate the conditions of a repeat examination, with new patient positioning and a new scan localiser performed.

For patients with known pulmonary metastases, a contrast material enhanced standard chest CT examination or PET scan then followed the two LDCT examinations for clinical purposes. For patients with an indeterminate nodule, one additional LDCT examination was performed, with the first scan used for clinical purposes.

All CT scans were acquired using a multi-slice CT scanner GE Lightspeed VCT 64-slice (General Electric Medical Systems, Milwaukee, Wisconsin, USA) at a section thickness of 0.625 mm and reconstructed with a CHEST convolution kernel.

Exposure settings for one additional LDCT examination were 2 millisieverts.

2.3. Inspiration

In order to investigate the influence of two different methods of inspiratory control, patients were randomized to two groups. 20 patients underwent both CT scans with a normal breath hold (as per routine clinical practice [11]; Group A) and 20 underwent both scans with controlled lung volumes (Group B). Patients in Group B were asked to breathe from a pre-filled reservoir bag containing 1L of air whilst lying down prior to the scan. Scanning was then performed during a breath hold for approximately 10 s.

2.4. Nodule contouring and volume measurements

One PN per patient was identified and marked-up on the first LDCT examination (baseline scan) by a single observer (A.T., two years experience in radiology and trained for this specific task) using commercially available software (XD3, Mirada Medical Ltd., UK). Each PN was identified in the second LDCT examination (validation scan) with knowledge of findings from the first study, and matched by using a combination of section number, lung segment and distance to the pleura. All PNs were delineated using a proprietary semi-automatic Otsu based thresholding method that requires a single user click-point inside the nodule to initialize the segmentation (Fig. 1).

2.5. Texture analysis

A number of image signatures previously used in combination to predict nodule probability of malignancy [12] were extracted from each contoured region surrounding the PN (see Fig. 2). A machine-learning model that maps image signatures onto a probability of malignancy score (ranging from 0 to 100%) was applied to the baseline and validation scans.

In previous work, a large number of textural features were computed on an independent dataset [5], including filter-based Laws features [13], Laplacian of Gaussian (LoG) [14], features derived from the grey-level co-occurrence matrix (GLCM) [15] the Fractal Dimension [16] and First Order Statistics derived from grey-level intensity distributions. The 20 most discriminative features in combination were selected using a greedy-algorithm on this independent dataset. A Support Vector Regressor (SVR) and 5-fold cross-validation technique was used to train a model which maps the selected features onto a probability of malignancy score (ranging from 0 to 100%).

The subset of 20 features and the probability of malignancy score was computed for each PN on the baseline and validation scans.

Image analysis tasks were performed using MATLAB 2015a (The Mathworks, Natick, MA, USA) and the LIBSVM library [17].