Research article

Pulmonary nodule enhancement in subtraction CT and dual-energy CT: A comparison study

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ABSTRACT

Objective: To compare nodule enhancement on subtraction CT iodine maps to that on dual-energy CT iodine maps using CT datasets acquired simultaneously.

Methods: A previously-acquired set of lung subtraction and dual-energy CT maps consisting of thirty patients with 95 solid pulmonary nodules (≥ 4 mm diameter) was used. Nodules were annotated and segmented on CT angiography, and mean nodule enhancement in the iodine maps calculated. Three radiologists scored nodule visibility with both techniques on a 4-point scale.

Results: Mean nodule enhancement was higher (p < 0.001) at subtraction CT (34.9 ± 12.9 HU) than at dual-energy CT (25.4 ± 21.0 HU). Nodule enhancement at subtraction CT was judged more often to be “highly visible” for each observer (p < 0.001) with an area under the curve of 0.81.

Conclusions: Subtraction CT is able to depict iodine enhancement in pulmonary nodules better than dual-energy CT.

1. Background

Lung cancer is the leading cause of cancer death among men and women worldwide [1]. Early characterization of incidental nodules could be an opportunity to reduce negative biopsies and start treatment earlier and increase survival [2–4]. CT imaging can characterize nodules based on morphology, volume and growth [5]. Since these characteristics do not always allow for a differentiation between benign and malignant nodules, other features are being explored. Studies have suggested that nodule enhancement after contrast injection differs between benign and malignant nodules, although overlap exists [6–8].

Several studies have shown the feasibility or potential of characterization of nodules with dual-energy CT acquisition [9–11]. Subtraction CT as an alternative technique to depict nodule enhancement has not been studied yet. Subtraction CT is a recently introduced technique that generates iodine maps of the lungs by subtracting a pre-contrast CT from a contrast-enhanced CT after motion correction [12]. Even with differences in inspiration between the two scans, the iodine enhancement maps with this technique have been shown to be accurate for detection of perfusion defects in the pulmonary parenchyma, with similar diagnostic performance as dual-energy CT [13,14]. However, perfusion defects are relatively large, usually in the centimeter range, while pulmonary nodules of clinical interest are as small as 4 mm [3]. Since the contrast-to-noise and signal-to-noise ratio of subtraction CT has been shown to be better than that of dual-energy CT [15,16], we hypothesize that subtraction CT might be superior to dual-energy CT to depict nodule enhancement.

The goal of our study was therefore to quantitatively and qualitatively compare nodule enhancement on subtraction CT iodine maps to that on dual-energy CT iodine maps using simultaneously acquired CT datasets.
2. Methods and materials

2.1. Study population

For this retrospective analysis, data from a prospective study that recruited 295 patients between July 2016 and April 2017 with ethical board approval (NL56542.091.16, clinicaltrials.gov number: NCT02890706) in the Meander Medical Centre was used [14]. Patients that fulfilled the inclusion criteria were patients referred to dual-energy CT due to suspicion for pulmonary embolism following the Wells criteria. At the imaging site, women below 35 years of age are not referred to dual-energy CT due to concerns about breast irradiation. Therefore, exclusion criteria included males below 35 years old, in addition to patients with hemodynamic instability.

2.2. Generation of images

All included patients underwent the dual-energy CT angiography (Definition Flash, Forchheim, Germany) for pulmonary embolism protocol, with the following settings: 100 kV and 140 kV + Sn filter, reference tube current: 89 mAs and 76 mAs, respectively, rotation time: 0.28 s, and pitch: 0.55. Prior to the contrast-enhanced scan, the participants received a pre-contrast CT scan at 100 kV (reference tube current: 66 mAs), for research purposes only. Breathing instructions were identical for the pre-contrast and the contrast-enhanced scan.

The intravenous contrast injection (5 mL/s) consisted of 60 mL of 350 mg I/mL (Xenetix, Guerbet Group, Paris, France) agent with 40 mL of saline chaser. After contrast-injection, the delay time was 5 s after a relative threshold of 60 Hounsfield Unit (HU) was reached in a region of interest in the pulmonary trunk.

All scans were reconstructed to 1 mm thin slices with an increment of 0.6 mm, with the Q30f filter. Dual-energy virtual iodine maps, which show the iodine enhancement in tissue, were generated with Syngo.Via (Version 3, Siemens Healthineers, Forchheim, Germany). These maps show the whole body cross-section. Iodine maps from subtraction CT were generated by subtracting the pre-contrast 100 kV scan from the contrast-enhanced 100 kV scan using dedicated subtraction software that geometrically registered the pre-contrast scan to the contrast-enhanced scan (SureSubtraction Lung Version 8, Canon Medical Systems, Otawara, Japan). These maps show only the segmented lung parenchyma.

2.3. Lung nodule dataset

All participants with at least one solid lung mass were identified by one radiologist with nine years of experience in thoracic radiology based on the radiological report and the CT angiography data during the prospective study. For this retrospective study, the same radiologist reviewed all those cases, using a dedicated lung screening workstation (Veolity version 1.5, Mevis Medical Solutions AG, Bremen, Germany), and selected patients with nodules with a diameter between 4–30 mm surrounded by pulmonary parenchyma. Consolidations, ground glass nodules, lesions with cavities, calcifications or hilar lesions and previously irradiated lesion were excluded. In patients with multiple nodules, a maximum of 15 nodules were randomly selected.

2.4. Quantitative study

To quantify enhancement in iodine maps from subtraction CT and dual-energy CT, the nodule segmentation obtained on the contrast-enhanced CT scan was transferred directly to the respective iodine maps, and average enhancement of the nodule was automatically calculated from these maps. Transfer of the segmentation of CT angiography to the iodine maps was possible because of identical geometry: the low and high-kV data of the dual-energy share the same geometry and only the pre-contrast scan was registered to the contrast-enhanced CT angiography for subtraction CT. Mean nodules enhancement was measured on grey scale iodine maps in Hounsfield Units (HU), both for subtraction CT and dual-energy CT.

2.5. Observer study

Per patient, the two smallest nodules were selected for the observer study. Three radiologists (one with experience with subtraction CT and nine years’ experience in thoracic radiology, one with experience with dual-energy CT and more than 20 years’ experience in thoracic radiology, and one no experience with either subtraction or dual-energy CT and more than 20 years’ experience in thoracic radiology) scored the visibility of nodule enhancement on a dedicated in-house scoring workstation. An iodine map from either subtraction or dual-energy CT and the 100 kV CT angiography were displayed side-by-side. Observers were able to interactively adapt window with, window level, viewing direction (axial, coronal, sagittal), slice thickness, and viewing mode (average or maximum intensity projection) to simulate a clinical setting. A list of the two nodules was displayed on the workstation next to the CT angiography and the corresponding iodine map. To review each nodule, the observer clicked on each nodule on the list, upon which the correct slice was shown in both images. In addition, a marker was placed on the correct region of the image on the CT angiography. This ensured that the same nodule was being evaluated on both images. Since iodine maps from subtraction images were only displaying the lung fields, while dual-energy iodine maps displayed the whole scan field, the two datasets were easily distinguishable and therefore scored separately in random order.

Observers were instructed to score the visibility of each nodule on the iodine maps on a four-point scale (1: clearly visible, 2: partially visible, 3: hardly visible, 4: invisible). In order to evaluate the potential impact of the difference in diaphragm level between the pre-contrast and contrast-enhanced CT on the visibility of the nodule enhancement in subtraction CT, a subset of all scans with a diaphragm level difference larger than 6.0 mm was selected. This threshold was used since this had been found to be the average difference in the clinical setting [13].

2.6. Statistical analysis

A paired $t$-test was used to determine significance of differences in mean nodule enhancement on iodine maps obtained with dual-energy or subtraction CT. A Wilcoxon-signed-rank test was used per observer to determine any significant difference in visibility scores between subtraction CT and dual-energy CT iodine maps. Furthermore, we used visual grading characteristics (VGC) analysis to determine the difference in visibility scores between the two techniques, which was summarized using the area under the VGC curve of the mean observer [17–20]. To determine if a diaphragm difference $> 6$ mm between the pre-contrast and contrast-enhanced CT scans had a negative influence on the enhancement of the nodule in the subtraction CT iodine map, a Kruskal-Wallis test was performed, by comparing the visibility scores of the images with large diaphragm difference ($> 6$ mm) to the ones with a small difference ($\leq 6$ mm). A paired $t$-test was used to determine if there was a significant difference in radiation dose across techniques.

3. Results

In total, 42 patients were identified to have solid masses or nodules. Eight patients were excluded since the nodules were hilar, were not surrounded by pulmonary parenchyma (4), or were ground glass lesions or consolidations (4). Four had previous radiotherapy. Therefore, the final dataset consisted of 30 patients (16 male, 14 female; age: mean 67.1 ±/- 9.9 years, range 47–80 years) with 95 nodules that fulfilled the criteria. The median dose length product was slightly, but significantly, lower with subtraction CT (154.6 mGy cm than with dual-energy CT (161.8 mGy cm p < 0.001).
3.1. Quantitative enhancement

The median nodule volume was 237.1 mm$^3$ (equivalent to a diameter of 8 mm). Mean nodule enhancement on iodine maps from subtraction CT was 34.9 HU (SD: ± 12.9 HU) compared to a mean enhancement of 25.4 HU (SD: ± 21.0 HU) on the dual-energy CT iodine maps. This difference was significant at $p < 0.001$.

3.2. Observer study

The observers scored 43 nodules (median volume: 223.3 mm$^3$, equivalent diameter of 8 mm) from 30 patients. Fig. 1 shows histograms of each observer ratings for visibility per nodule. It shows that nodules in subtraction CT were judged to be visible significantly more often compared to with dual-energy CT for each observer ($p < 0.001$). Fig. 2 shows the VCG curve, resulting in an area under the curve of 0.81, with preference for the visibility of nodule enhancement in subtraction CT compared to dual-energy CT. Figs. 3–5 show examples of nodule enhancement with subtraction CT and dual-energy CT.

The average diaphragm level difference between the pre-contrast and the contrast-enhanced CTs for all 30 patients was 5.1 mm. Seven patients with nine nodules had a larger diaphragm level difference than the average 6.0 mm. The subtraction CT median score for visibility for all observers in these nodules (median volume: 440.6 mm$^3$, equivalent diameter of 9 mm) was also 1.0 and the statistical test showed a non-significant difference between the visibility scores ($p = 0.97$). Therefore, the large diaphragm differences did not affect nodule enhancement visibility.

Fig. 1. Histograms of visibility scores from each observer and for all observers combined for all 43 nodules evaluated, with the resulting $p$-values from comparing the distributions using the Wilcoxon-signed-rank test. SCT = subtraction CT iodine maps, DECT = dual-energy CT iodine maps.

Fig. 2. The VCG curve of a plot of the proportion of ratings above a certain threshold for the subtraction CT against the same proportion for dual-energy CT at various threshold settings. The Figure shows the separation between subtraction and dual-energy CT (green line). The area under the curve of 0.81 shows a higher visibility in preference of subtraction CT. The blue line is the reference line were both technique shows the same preference (line $y = x$).

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4. Discussion

This study shows that subtraction CT can depict nodule enhancement better than dual-energy CT, and that this depiction is not affected by the difference in diaphragm level between the pre-contrast and contrast-enhanced CT scan, making the technique robust.

No other studies have been performed on characterizing the difference in pulmonary nodule depiction in patient iodine maps between subtraction and dual-energy CT. A phantom-based observer study has shown similar results due to the better depiction of iodine enhancement in plastic tubes in an abdominal phantom in subtraction CT compared to dual-energy CT [15].

Since 1997, researchers have investigated the enhancement in CT angiography scans of pulmonary nodules, as a feature for nodule characterization [21]. In that study by Zhang et al, the clear difference in enhancement between malignant and benign studies was shown. In the studies of Swenson et al. and Yi et al, high sensitivity values were shown, both above 98 % with a threshold of 15 HU and 30 HU, respectively. However, both studies also showed a low specificity (58 % and 54 %, respectively), due to benign nodules also resulting in high enhancement [6,22]. Later, multiple studies tried to improve nodule characterization by investigating the contrast wash-in and wash-out rates [7,8,22]. These showed that with the inclusion of this additional information, the specificity could reach 79 % or higher. In 2014, Ohno et al., with a large prospective study, showed that they were able to characterize pulmonary nodules with dynamic CT angiography. However, it should be noted that, for this, they did not distinguish only between malignant and benign nodules, but added a third category: benign with high biologic activity [23]. This latter group was probably the main reason why there had been overlap between benign and malignant lesions in earlier studies.

This study evaluated the feasibility of visualisation of contrast enhancement by subtraction and dual energy CT. This might help in better characterisation of nodules, but this could not properly be investigated in this study. This is because the CT scans in this study were acquired with early contrast timing, which is not optimal for nodule...
characterisation. The previously described literature on nodule characterisation used later phases or four-dimensional scanning to discriminate between benign and malignant nodules. However, given the better enhancement depiction in subtraction CT, and given the previous characterization results with dual-energy CT, it is likely that with the correct scan timing, subtraction CT could be of added value when attempting to distinguish among benign, malignant, and biologically-active benign nodules. The additional dose that is needed for the pre-contrast CT included in subtraction CT is relatively low compared to that used during full treatment (radiotherapy or additional CTs), while the additional information could be useful for achieving earlier diagnosis. The impact of subtraction CT on any possible earlier diagnosis remains to be investigated, but a clinically-significant reduction in time to diagnosis could improve patient outcome.

The last limitation was that the masking of the lung parenchyma on subtraction CT posed a potential bias against subtraction because seven peripheral nodules were partially or fully excluded from the iodine map, which caused the observers to downgrade their visibility. Better lung masking should therefore shift the results even more in favor of subtraction CT.

In conclusion, subtraction CT is a novel technique that is able to depict the iodine enhancement in pulmonary nodules better than dual-energy CT, no matter the difference in respiratory levels between the pre-contrast CT and contrast-enhanced CT.

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Funding for this research has been provided by Canon Medical Systems Corporation, developers of the subtraction CT algorithm in this study. The study data and results were generated and controlled at all times by the research personnel at Radboudumc, with no influence from Canon.

CRediT authorship contribution statement

Dagmar Grob: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization. Luuk J. Oostveen: Methodology, Software, Formal analysis, Resources, Data curation, Writing - review & editing. Colin Jacobs: Conceptualization, Software, Validation, Formal analysis, Resources, Writing - review & editing. Ernst Scholten: Investigation, Data curation, Writing - review & editing. Mathias Prokop: Investigation, Data curation, Writing - review & editing. Supervision. Funding acquisition. Cornelia M. Schaefer-Prokop: Investigation, Data curation, Writing - review & editing. Ioannis Sechopoulos: Conceptualization, Methodology, Formal analysis, Resources, Investigation, Data curation, Writing - review & editing, Visualization, Supervision, Funding acquisition. Monique Brink: Conceptualization, Methodology, Formal analysis, Resources, Investigation, Data curation, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

Funding for this research has been provided by Canon Medical Systems Corporation, developers of the subtraction CT algorithm in this study. The study data and results were generated and controlled at all times by the research personnel at Radboud University Medical Center, with no influence from Canon. One co-authors has a research grant from Mevis Medical Solution and Royalties from Mevis Medical Solution. We used this software program to calculate nodule enhancement, but did furthermore not influence our research.

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