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Advanced imaging tools in pulmonary nodule detection and surveillance☆

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ABSTRACT

Lung cancer is a leading cause of death worldwide. The National Lung Screening Trial has demonstrated that lung cancer screening can reduce lung cancer specific and all cause mortality. With approval of national coverage for lung cancer screening, it is expected that an increase in exams related to pulmonary nodule detection and surveillance will ensue. Advanced imaging technologies for nodule detection and surveillance will be more important than ever. While computed tomography (CT) remains the modality of choice, other emerging modalities such as magnetic resonance imaging provides viable alternatives to CT.

1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide. The National Lung Screening Trial (NLST) represents the first and only screening program thus far that demonstrated significant reduction in lung cancer specific mortality in patients screened with low dose computed tomography. With the success of the NLST, it is expected that an increase in exams related to pulmonary nodule detection will ensue. Advanced imaging technologies for nodule detection and surveillance will be more important than ever. Herein we aim to provide an overview of such imaging tools.

2. Radiography

Chest radiography remains the most commonly performed thoracic exam due to wide spread availability, relatively low radiation exposure and low cost. However, despite newer dual energy technique, advanced image processing methods such as digital tomosynthesis and digital bone and temporal subtraction [1], and computer-aided detection (CAD) [2], nodule detection and surveillance via radiographs remains inferior to computed tomography (CT) [3].

3. Computed tomography

Computed tomography is currently the modality of choice for nodule detection and surveillance. Advancement in CT imaging techniques has allowed for ultra-low doses of radiation and CT will likely continue to be the gold standard for nodule imaging. Both solid and subsolid nodules have been reported to be adequately detected on such ultra-low dose CT exams [4,5]. It is known that simple visual detection of nodules on CT can suffer from reader errors and high variability in nodule detection rates [6,7]. Perhaps the simplest computer-aided nodule detection tools that have been successfully incorporated into most radiology practices are volume rendering (VR) and maximum intensity projection (MIP). Peloschek et al. reported that VR is superior compared to MIP for solid noncalcified nodule detection [8]. However, according to Angelelli's group, MIP is the most sensitive reconstruction technique for detecting small pulmonary nodules, especially ones less than 5 mm [9]. Such findings have been confirmed by multiple other research studies [9–14]. In particular, Park, et al. conducted a large study of 514 nodules where they compared the performance of 4 thoracic radiologists in detecting nodules on 1-mm section CT images with and without MIP and CAD [12]. The study showed statistically significant improvements in nodule identification with the aid of MIP and CAD with no significant difference between MIP- and CAD-aided nodule detection.

Computer-aided detection or computer-aided diagnosis of pulmonary nodules has been in existence at least as far back as 1994 and has been established to improve diagnostic accuracy [12,15]. Studies have shown that CAD improves pulmonary nodule detection rates and compensates for deficient reader performance [16,17]. Multiple segmentation approaches and detection schemes have been explored to improve nodule detection [15,18–21]. False positive rates can be reduced by incorporating two-dimensional (2D) local information with the normally employed three-dimensional (3D) global data or by using massive training artificial neural networks [22–23]. Studies have demonstrated that CAD works well with low dose CT, various scanning parameters and reconstruction methods [24–25]. In addition to automated nodule detection, more

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advanced CAD systems can automatically obtain nodule measurements and some even perform automated nodule matching whereby nodules identified on a follow up exam are compared to those seen on a prior study, significantly decreasing interpretation time [Fig. 1, 26].

In addition to being robust in various situations for solid nodules, more recent CAD systems also work well with subsolid nodules due to improved segmentation techniques that are better optimized for identifying these low density lesions [Fig. 2, 27,28]. As a matter of fact, subsolid nodule segmentation has become robust enough that semiautomatic quantification of the solid component of a part-solid nodule is now possible [29], in addition to subsolid nodule volumetry.

With studies showing successful CAD integration into picture archiving and communication system [30] and an increasing number of exams, it is a matter of time before CAD becomes mainstream in radiology practice.

Nodule size on CT is the most important characteristic that dictates the surveillance regimen. Both the Fleischner Society and the American College of Radiology have put forth guidelines for nodule surveillance based on nodule size in the setting of incidentally detected nodules and in the setting of lung cancer screening respectively. These recommendations are based on 2D measurements, typically performed in the axial plane along the axis of the longest diameter or averaging a set of 2 diameters perpendicular to each other. However, the Dutch–Belgian randomized lung cancer screening trial, which was conducted based on 3D volumetric measurements, has raised the question of whether volumetry should play a role in nodule surveillance in the setting of lung cancer screening. Volumetric assessment of a nodule can be performed based on diameter measurements or by direct segmentation and calculation from pixel size data. Less reproducibility and precision were observed in several studies for small nodules on the order of 5 mm or less [31–33], as a result of increased percentage of surface area voxels in relationship to the overall nodule volume which increased partial volume artifact. However, it has been shown in a large screening trial and meta-analysis that nodules less than 5 mm tend to be benign, even in the high-risk population [34]. Moreover, Bolte et al. has shown that volumetry achieves significantly less interobserver variance compared to diameter measurements and advanced volumetry algorithms are independent of observer experience [35]. In fact, such a finding was confirmed by other recent studies [36]. It has been shown that volumetric measurement reproducibility and accuracy are preserved even with different dose settings and iterative reconstruction, which is often used for low dose or ultra-low-dose settings [37–42]. According to Knoss et al., density measurements based on volumetry is more robust than regular 2D measurements. Moreover, in addition to solid nodules, studies have now demonstrated usefulness of volumetry for subsolid nodules [43–44]. Although volumetry has become robust enough to be considered for clinical integration, there are certain pitfalls that one needs to be cautious when using volumetric measurement to follow nodule growth. It has been shown that scanning parameters, such as slice thickness, inspiratory effort, radiation dose, and reconstruction techniques, need to be similar between the follow up scans and it is advisable for the radiologist to review the segmentation of nodules to assure segmentation quality. Moreover, de Hoop et al. [45] has shown that mean nodule volume can differ significantly between different software packages within the same vendor as well as amongst different vendors and therefore it is recommended that one utilize the same segmentation algorithm and software for initial and follow-up measurements.

In addition to nodule size, CT attenuation based advanced imaging tools have also been explored. The correlation of these quantitative measures with histology and survival outcomes has been explored with varying levels of agreement [45–51]. Combining nodule volume and attenuation characteristics, de Hoop et al. [52] proposed the concept of nodule mass, showing decreased intraobserver and interobserver variability when nodule mass calculations were compared with volume measurements. Such encouraging findings need to be confirmed by additional studies.

4. Positron emission tomography

Although CT is the most widely used imaging exam for pulmonary nodule detection and evaluation, assessment is still based solely on nodule morphology. Since the 1990s, metabolic imaging with ^{18}F-flourodeoxyglucose (FDG) positron emission tomography (PET) and PET/CT have been promoted to be more efficacious than CT at distinguishing benign from malignant findings [53–57]. Given its high sensitivity of 96.8% [58], PET/CT is an excellent tool for detecting nodules>8 mm with the added benefit of physiologic information. Various automatic PET/CT nodule detection methods have been proposed [59,60]. However, detection of small nodules still relies on the CT portion of the exam since detection based solely on PET is unreliable as small nodules may not demonstrate sufficient glucose analog uptake and because such detection may suffer from partial volume effects. Therefore, PET/CT is not a cost-effective initial test for screening or surveillance due to nodule size limitations and its higher cost compared to CT.

5. Magnetic resonance imaging

Repetitive application of CT and/or PET/CT may negate the benefits of lung cancer screening due to the cumulative radiation in long term

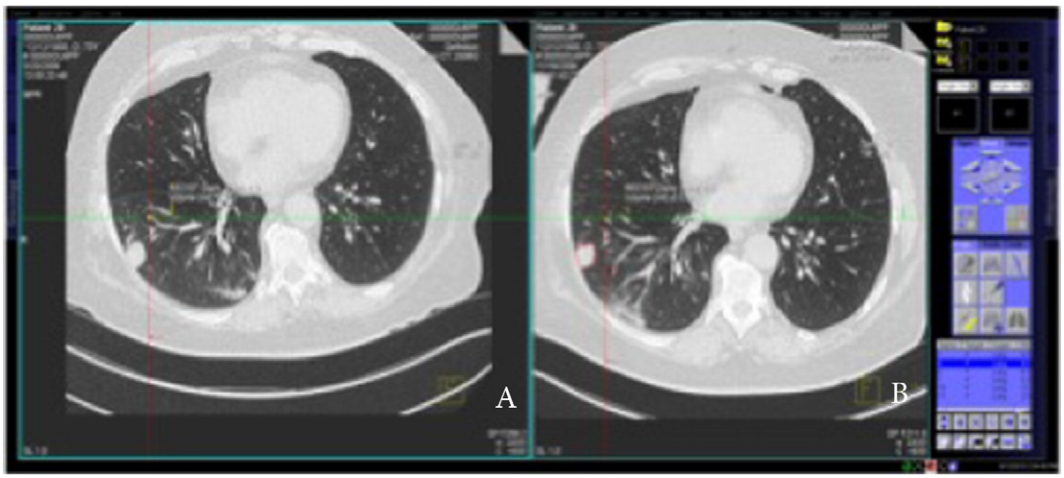

Fig. 1. A 67-year-old man with solid pulmonary nodules. Transverse baseline (A) and follow-up (B) images were loaded. Subsequently all markers for the identified nodules were loaded onto the baseline image followed by automated matching and flagging of corresponding nodules on the follow up CT exam.