Clinical Radiology 72 (2017) 433–442

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

A review of lung cancer screening and the role of computer-aided detection

B. Al Mohammad*, P.C. Brennan, C. Mello-Thoms

Faculty of Health Sciences, University of Sydney, Lidcombe, NSW, Australia

ARTICLE INFORMATION

Article history:
Received 9 June 2016
Received in revised form
14 December 2016
Accepted 4 January 2017

Lung cancer is the leading cause of cancer-related death worldwide; however, early diagnosis of lung cancer leads to higher survival rates. The National Lung Screening Trial (NLST) demonstrated that scanning with low-dose computed tomography (LDCT) led to a 20% reduction in mortality rate in a high-risk population. This paper covers new developments in screening eligibility criteria and the possible benefits and the harm of screening with CT. To make the screening process more feasible and help reduce the rate of missed lung nodules, computer-aided detection (CAD) has been introduced to assist radiologists in lung nodule detection. The aim of this paper is to review how CAD works, its performance in lung nodule detection, and the factors that influence its performance. This paper also aims to investigate the effect of different types of CAD on CT in lung nodule detection and the effect of CAD on radiologists' decision outcomes.

Introduction

Lung cancer is the leading cause of cancer death worldwide. According to the World Health Organization (WHO), there were 1.8 million new cases and around 1.6 million lung cancer-related deaths in 2012.[1] It is considered one of the most aggressive cancers, with a 5-year survival of only 10–15%[2]; however, outcomes are significantly better if the cancer is detected in an early stage, with a 10-year survival of stage 1 lung cancer up to 75%.[3]

Computed tomography (CT) is considered one of the key methods in imaging and investigation of lung disease.[4] Features such as morphological lesion characterisation, nodule size measurement, follow-up of nodule growth, and attenuation characteristics of a nodule have made it the examination of choice in lung cancer investigation.[5] Furthermore, because of the three-dimensional nature of CT and its ability to visualise the chest in axial sections, it provides assessment of the chest wall, diaphragm, and mediastinum invasion, in addition to staging of the tumour.[5] The drawback from using CT as a screening method is the fact that radiation can be carcinogenic and the probability of developing cancer increases with higher radiation dose. The optimal solution will be to use the lowest radiation dose possible without compromising image quality. Low-dose computed tomography (LDCT) uses significantly lower radiation exposure than standard-dose computed tomography (SDCT; LDCT radiation exposure is approximately 1.5 mSv/scan, SDCT radiation exposure is around 8 mSv/scan[6]) thus reducing the effective dose delivered by the imaging process. Studies comparing the sensitivity of nodule detection rates have shown that there was no significant difference between sensitivities in SDCT and LDCT.[7,8] As suggested by some authors, the dose can be further reduced by means of iterative reconstruction.[8,9] The

*Guarantor and correspondent: B. Al Mohammad, Faculty of Health Sciences, University of Sydney, 75 East St, Lidcombe, NSW 2141, Australia. Tel.: +61410095070.
E-mail address: baal8200@uni.sydney.edu.au (B. Al Mohammad).

http://dx.doi.org/10.1016/j.crad.2017.01.002
0009-9260/

dose in LDCT ranges from four to 12-times the dose of chest radiography depending on the reconstruction method implemented.[9] Furthermore CT has a high rate of false-positive findings that result in additional unnecessary follow-up and investigations.

Higher anatomical detail improves the sensitivity in lung nodule detection, which can be achieved by thinner sections and overlapping reconstruction; however this comes at the expense of large data sets (depending on factors such as section thickness and reconstruction parameters, the number of sections can range from around 100[10] to more than 500 sections/scan[11]). As a result of this high number of images produced by CT and LDCT during a single scan, if implemented as a screening method, radiologists' workload will significantly increase (the average time for an experienced chest radiologist to interpret a single scan ranges from around 2 minutes[12] to 3.5 minutes[13]). This may lead to an increase in diagnostic error.[14] Errors arising in relation to CT form 62% of radiology errors.[15]

The need for a tool that will assist the radiologist in nodule detection, such as detecting missed nodules, reduce reading time so that the screening process is made possible and helps differentiate between benign and malignant lesions, has led to the development of computer-aided detection (CAD) systems. A CAD system is a computer technology used to assist physicians to decrease observational oversights when examining digital medical images, and as a result, reduce diagnostic errors.[16] The primary goal of CAD is to increase the nodule-detection rate in a way that is more efficient than double reading, will cost less, and will not require employing additional radiologists for the screening procedures; however, researchers have reported a wide span of nodule-detection sensitivity by CAD in LDCT ranging from 38%[17] to 100%,[18] with false-positive rates from one per scan[19] to 8.2 per scan.[20] The range reported was probably due to the use of different CAD systems and different data sets in each of these studies, which makes it difficult to compare the performance of the CAD systems used. Therefore, it is important to examine whether CAD as an adjunct in LDCT can be helpful in the future of lung cancer screening.

The main aim of this paper is to review the performance of CAD systems in lung nodule detection, explore the effect of different types of CAD systems on LDCT for lung nodule detection, the factors that influence the performance of a CAD system, and its effect of CAD on radiologists' decision outcomes. In addition, this paper will briefly discuss updates in the field of lung cancer screening.

Screening for lung cancer

Randomised controlled trials (RCT) using chest radiography, with or without sputum cytology, have been used to screen high-risk populations for lung cancer.[21–26] The results of these studies demonstrated that screening led to earlier lung cancer detection and improved survival rates; however, none of them showed a reduction in lung cancer mortality.

Advances in CT development have produced high-resolution, volumetric imaging and have made CT a more sensitive imaging method than chest radiography in lung-cancer screening. Several studies have demonstrated that screening a high-risk population with LDCT detects more lung nodules and lung cancers at an early stage than chest radiography; however, they did not prove a reduction in mortality.[3,27–34]

In 2011, the results of the largest randomised controlled trial, the National Lung Screening Trial (NLST), were published. The high-risk current or former smokers, mid-50- to mid-70-year-old participants were randomised to an annual LDCT screening group compared to chest radiography group for 3 years. The average ratio of lung cancer incidence between the LDCT group and the radiography group was 13:1. A significant reduction of 20% was demonstrated in lung-cancer-specific mortality.[31]

Lung cancer screening guidelines in the United States are mainly based on the same criteria for which participants in the NLST study were chosen. Expanding the screening eligibility criteria to include individuals >50-years of age, current or former smokers with a ≥20 pack-year smoking history, in addition to at least one risk factor for developing lung cancer will have the potential to save thousands of additional lives annually.[35]

Although the possible benefit of LDCT screening is reduction in mortality rate, probable harms are a high number of false positives (accompanied by unnecessary workup and invasive evaluation), over-diagnosis, and radiation exposure. Furthermore, due to inconsistencies in nodule characterisation and the reporting manner of the screening studies, comparing results is difficult, leading to a common limitation of the LDCT screening studies: the lack of a standard reference. For example, there is a substantial variation in lung nodule definition among radiologists.[36] In consequence, the American College of Radiology has developed a quality-assurance tool, the Lung Imaging Reporting and Data System (Lung-RADS), with the aim of standardising the reporting of LDCT screening results. Lung-RADS focuses on defining a positive finding on lung-cancer screening CT, attempting to decrease the false-positive rate, with a minimum effect on test sensitivity, and suggesting management recommendations.[37] Applying Lung-RADS retrospectively has shown to substantially reduce the false-positive rate; however, there was also a decrease in detection sensitivity.[38]

Although LDCT is currently being implemented for lung cancer screening, the large number of images produced by a single scan and its complexity makes it prone to different types of diagnostic errors.

Errors in lung nodule detection

Around 4% of daily radiological reporting contains diagnostic errors.[39] As a consequence, 30% of abnormal radiological studies are missed.[40] Diagnostic error has been defined as a miss (no diagnosis made), a false diagnosis (a diagnosis that is different from the correct one), or a

delayed diagnosis (sufficient information was available earlier).[40,41] These errors are considered one of the main causes of patient mortality and significant, major, and minor permanent injury.[41] In addition, they are considered the leading type of diagnosis-related legal claims, resulting in billions of US dollars in annual payments.[40]

Kundel *et al.*[44] identified three types of errors: scanning error, when the observer fails to fixate the area of the lesion; recognition error, when the observer fixates the area of the lesion, but has failed to disambiguate the lesion; and decision-making error, which is an incorrect interpretation of a malignant lesion as a benign lesion or normal structure.[42–44] These three types of error together form a part of observer error.[44] System-related errors and cognitive factors are also worth considering when studying diagnostic error.[45] System-related errors include problems with healthcare policies, procedures, teamwork, and communication, in addition to technical and equipment failure.[40] As described by Graber *et al.*,[45] cognitive errors are either from "faulty knowledge", which includes insufficient physician diagnostic skills or knowledge of the patient's condition; "faulty data gathering", when there is a problem in collecting data from patients' tests, examination or interview; or "faulty synthesis", which means incorrect information processing (such as not considering patient-related information that is relevant to the diagnosis). Furthermore, conditions such as increased workload, patient expectations, level of observer alertness, and fatigue also contribute to an increase in diagnostic error.[40,43] In a study by Graber *et al.*,[45] almost half of the diagnostic errors were due to a combination of system-related and cognitive factors,19% were only due to system-related factors, and 28% only cognitive factors.

There is a paucity of studies describing errors in CT, although CT reporting seems to be especially liable to error.[43] Of the documented errors, 88% occur during image interpretation (cognitive error) with the majority of errors being false-negative findings.[15] This might be due to the increasing volume of CT procedures conducted in recent years, the large image sets generated for a single CT examination, the limited time available for the radiologist to perform the reporting, and the radiologist not receiving up-to-date, appropriate training on new advancements in CT technologies.[43] McCreadie *et al.*[15] reported 62% of errors in relation to various CT examinations when studying 256 errors in 222 patients. Quantifying the lung-cancer cases missed by CT, as presented in the literature, is limited probably because of the difficulty in recognising the missed cases among a high number of routine CT examinations performed.[42] Kakinuma *et al.*[46] reported seven missed lung cancers out of 22 cancers at CT screening, and in a more recent study by Li *et al.*,[14] 32 cancers out of 83 were overlooked on CT examinations. In the NLST, 6.2% of the lung cancers were missed in the LDCT-screening arm.[47] Considerable variation in lung nodule detection rates for chest CT has been reported in the literature.[11,48,49] The sensitivity in detection depends on the nodule features (size, shape, edges, density, location, relationship to adjacent structures) in addition to technical factors (section thickness). Small diameter is often more closely associated with missed lung nodules. This was demonstrated in a study by Zhao *et al.*,[50] in which the positive predictive value for double reading by radiologists rose from 35.2% for all nodule sizes to 76.1% for nodules >50 mm in size.

CAD in lung nodule imaging

It has been reported that double reading in radiology has reduced errors and increased diagnostic sensitivity,[7,51] but it is considered a time-consuming procedure and it comes at a higher cost of interpretation when two radiologists are used; in addition, it requires more qualified radiologists to engage. Thus performing double reading for every image may not be feasible.

Software technologies, such as CAD, have the potential to assist radiologists to decrease the rate of missed lung nodules, in a more efficient manner than double reading, with lower costs; however, a major concern is a high false-positive rate derived from the inclusion of benign or non-nodule structures. In the late 1980s, the first CAD systems for lung-nodule detection appeared, but these first attempts were not very successful due to the limited computational resources and inadequate advanced image processing techniques available at that time.[52,53] The purpose of CAD systems was to assist radiologists in the detection of lung nodules and to reduce the reading time required for each scan. Reading time was significantly shorter when CAD was used as a concurrent reader rather than when the reading was done separately first by radiologists alone, then with CAD.[13]

As a general concept on how most CAD systems work, it can be summarised in five main steps: acquisition (obtaining the medical images), preprocessing (techniques applied to improve the quality and increase the precision and accuracy of processing algorithms), segmentation (its function is to separate the study region from other organs and tissues in radiographic images), nodule detection (determining the presence of pulmonary nodules in the image and marking their location), and elimination of false positives[54]; however, it is worth mentioning that CAD system developers reveal very little information about how their specific CAD system works. Fig 1 shows an image of a CAD system marking a nodule on a chest CT image.

CAD has the potential to make a difference in the clinical setting; it can automatically detect a lung nodule and calculate the two-dimensional and volumetric measurements of this nodule in CT images. Using those measures, nodule progression can be tracked over time by assessing its growth. The advantage for clinical workflow is potentially to save valuable radiologists' time spent on each case and produce more repeatable results for nodule follow-up. In addition, radiologists' energy is more efficiently focused on image interpretation[55]; however, integrating CAD system quantitative tools in a clinical workstation has proven to be challenging and, as yet, this has not been efficiently applied.[56]

CAD substantially increased lung nodule detection sensitivity in chest CT examinations; in addition, several studies have established that CAD application on chest CT also has proven useful in detecting lung nodules that were originally

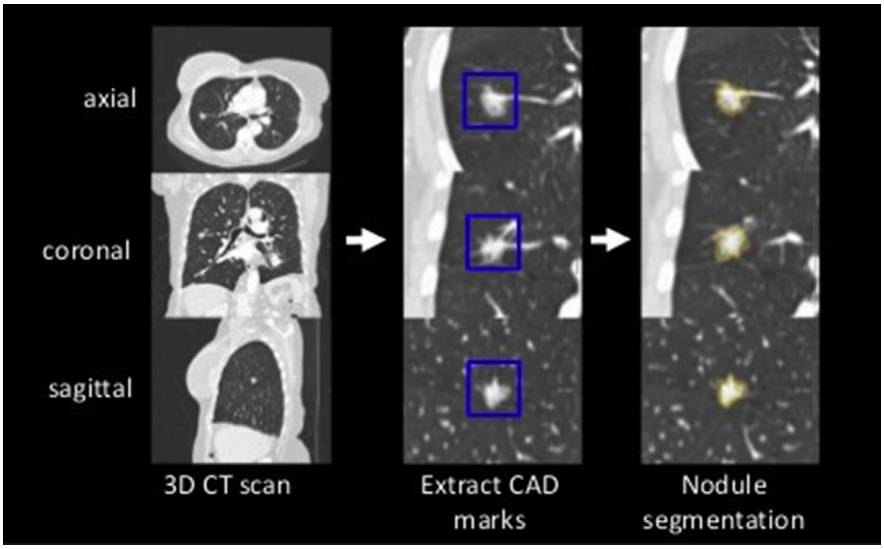

Figure 1 CAD System. Chest CT images with CAD markings of a lung nodule. (Permission from Arnaud Setio).

missed by radiologists.[19,57–59] This was demonstrated in a recent study, in which four CAD systems were tested on 50 lung cancers that were manifested as solid nodules on CT examinations a year before radiologists detected them. At the time when cancers were missed by the radiologists, the CAD systems detected up to 70% of the lung cancers.[60]

In the published literature, CAD proved to have a higher sensitivity in lung nodule detection than double reading. A study was done comparing the performance of CAD versus double reading of two experienced radiologists on 400 LDCT examinations. CAD had a sensitivity of 96.7% (at a false-positive rate of 1.9 per examination) for lung nodule detection compared to 78.1% for double reading; furthermore, around 22% of nodules had been detected by CAD alone.[50] In another study, the authors compared the sensitivity for three radiologists alone (57%, 68%, and 46%), double reading (75%), and reading using a CAD system (94%, 96%, and 94%).[61]

To date, different CAD sensitivities in lung-nodule detection have been reported ranging from 38% to 100%.[10,17,18,50,59,62–73] For more details on CAD system performance see Table 1. CAD sensitivity in nodule detection can be affected by several factors; some relating to the imaging technique used, such as section thickness or dose, and other factors related to nodule size, its position, and the internal content of the nodule (lung nodules are divided into solid, semisolid, and non-solid nodules also called ground-glass opacities[74]); however, it is difficult to compare the performance of different published CAD systems, due to the diversity of detection algorithms used to develop CAD and the lack of a standardised test database.

Factors effecting CAD performance

Section thickness

Various CAD systems have been developed and assessed for the detection of lung nodules, some of these were tested on thick CT sections[17,75–79] and others on thin CT sections.[18,71,80,81] Evidence demonstrates that CAD performance depends highly on section thickness and reconstruction interval, with better results obtained when using thin sections and reconstruction intervals <1 mm, as partial volume effects are reduced.[18,80,82] This trend was observed in other published studies. Brown *et al.*[18] tested their CAD system on a specific region of the chest, using thin section CT image sets, with 1 mm collimation and a 0.5–1 mm reconstruction interval. They reported 100% sensitivity for the detection of lung nodules >3 mm in diameter.[18] Demir *et al.*[10] reported 98% sensitivity in CAD performance (2.45 false-positive readings per scan) when a 1 mm section thickness was used. Studies that used CAD with thick-section CT (5–10 mm) presented a variable performance ranging from 38% to 94% sensitivity with false-positive rates ranging from 0.18–3 false-positives per section.[17,75–79] This resulted in dozens of false-positives per single scan. On thick-section CT images, some nodules will not be clearly visible across contiguous sections, which make 3D characterisation of their features difficult. This combined with volume averaging will result in a high rate of false-positive findings.[80] The shortcomings of using thick-section CT images are that lung cancer nodules may be missed. Small reconstruction intervals can be applied to compensate for the effect of thick sections for improved detection of lung nodules. In a study by Kim *et al.*,[80] by reducing the reconstruction interval from 5 to 1 mm, nodule-detection sensitivity rose for both radiologists by 6% and CAD by 13%. Moreover, the number of false-positive findings detected per patient with CAD decreased from 23.6 to 9.7. White *et al.*[83] demonstrated a CAD sensitivity of 81% when using a 0.9 mm section thickness, but only 51% sensitivity is achieved with a 3-mm section thickness.[83]

Dose

For the purpose of reducing radiation dose in lung cancer screening programmes, researchers have tested the

Table 1
Computer-aided detection (CAD) system performance.

Study	Ref. no.	No. of scans	No. of nodules	Sensitivity	FP rate
Armato *et al.*	62	43 CT scans		70%	1.5 FP/section
Ko *et al.*	76	16 CT scans	380 nodules	86%	
Gurcan *et al.*	63	34 CT scans		84%	5.5 FP/section
Wormanns *et al.*	17	88 /CT scans	135 nodules	38%	5.8 ± 3.6 FP/scan
Brown *et al.*	18	15 CT scans	57 nodules <3 mm	70%	Average of 15 FP/scan
			22 nodules >3 mm	100%	
Bae *et al.*	68	20 CT scans	164 nodules	95.1%	6.9 FP/scan
Murphy *et al.*	20	698 CT scans	268 nodules	84%	8.2 FP/scan
Ye *et al.*	64	108 CT scans	220 nodules	90.2%	8.2 FP/scan
Messay *et al.*	81	84 LIDC CT scans	143 nodules	82.6%	3 FP/scan
Kumar *et al.*	65	40 CT scans	538 nodules	86%	0.3 FP/section
Tan *et al.*	66	125 LIDC CT scans	574 nodules	87.5%	4 FP/scan
Cascio *et al.*	83	84 LIDC CT scans	148 nodules	97%	6.1 FP/scan
Zhao *et al.*	50	400 CT scans	151 nodules	96.7%	3.7 FP/scan
Teramoto *et al.*	67	84 LIDC CT scans	103 nodules	80%	4.2 FP/scan
Torres *et al.*	68	1043 LIDC and other CT scans	NA	80% for M5L	8 FP/scan
Jacob *et al.*	59	888 LIDC CT scans	777 nodules	82%	3.1 FP/scan
Setio *et al.*	77	888 LIDC CT scans	238 solid large nodules >10 mm	94.1%	1 FP/scan
Demir *et al.*	10	100 LIDC CT scans	609 nodules	98%	2.45 FP/scan
Lu *et al.*	69	294 CT scans	631 nodules		
		Training set 196 scans		87%	2.6 FP/scan
		Test set 98 scans		85.2%	3.1 FP/scan

FP, false positive; CT, computed tomography; LIDC, Lung Image Database Consortium.

effect of dose reduction on the performance of CAD systems. Radiation dose can be considerably reduced, by lowering either the tube current–time product (mAs) or tube voltage (kV), without significantly compromising detection rates of CAD systems. To evaluate the impact of dose reduction, Hein *et al.*,[84] compared two CAD systems on a ultra-low dose CT (ULDCT) using 5 mAs and SDCT using 75 mAs. Detection rates using CAD were 62% and 72% for both CAD systems for the SDCT examinations and 56% and 73% for the ULDCT examinations. Both CAD systems did not present significant differences between the detection rates for the SDCT and the ULDCT data sets.[84] Bodelle *et al.*[85] evaluated radiation dose reduction and its effect on CAD sensitivity in detection solid pulmonary nodules by applying different tube voltages of 70 and 100 kV. Detection rates and radiation dose in terms of effective dose (E) were measured. The CAD rates were 94.7% for the 70 kV and 92.4% for the 100 kV CT examination. The effective dose measurements were 0.51 mSv for the 70 kV versus 2.02 mSv for the 100 kV CT examination.[85]

Nodule location

It is evident that CAD sensitivity in nodule detection is influenced by the location of the nodule; according to their location (nodule adjacency to anatomical structure), pulmonary nodules can be divided into: isolated, juxtaplural, and juxtavascular. CAD is most sensitive in detecting isolated nodules, has an average sensitivity for juxtavascular nodules, and is least sensitive for detecting juxtaplural nodules.[71,86] Detection of isolated nodules is at a higher rate probably because they are surrounded by lung parenchyma resulting in a different attenuation and higher contrast. Another reason could be the higher prevalence of these nodules in the training data sets. In addition, detection of juxtavascular and juxtaplural nodules is more challenging because these nodules are not easily differentiated from the surrounding tissue. A study examining the effect on detection sensitivity of the location of the lung nodule divided nodules into three groups; the sensitivity for detecting nodules was 97.4% for isolated, 92.3% for juxtaplural, and 94.1% for juxtavascular nodules. Most of the nodules were not detected with CAD were either juxtaplural or juxtavascular nodules.[71] Conversely, other investigators report that nodule location has no significant influence on detection by CAD or by radiologists.[81]

Nodule size

In general, the sensitivity for nodule detection decreases with decreasing nodule size. In a study undertaken by Brown *et al.*,[18] a detection sensitivity of 100% was achieved using CAD for pulmonary nodules >3 mm in diameter, whereas CAD sensitivity dropped to 70% for pulmonary nodules that were <3 mm. A similar trend, shown by Ko *et al.*,[70] was that the sensitivity decreased from 91% for nodules >3 mm to 86% for nodules of all sizes. In a recent study by Setio *et al.*[87] a CAD sensitivity of 94.1% was achieved (one false-positive per scan) for solid nodules >10 mm. Conversely, in a study by Marten *et al.*,[81] CAD demonstrated a strong performance over various nodule sizes, while radiologists' performance significantly depended on the size of the nodule. The percentage of nodules detected by the radiologists reduced significantly compared to CAD values for nodules <6 mm.[81] In a study that compared the performance of different CAD systems using the same data set, five out of the six CAD systems had better detection sensitivity for smaller nodules

compared to larger ones. This result contradicts the expectation of better performance for larger nodules, which the authors explain by considering smaller nodules as being more frequently isolated, more common, and thus probably appear more frequently in CAD training data sets.[86]

Evaluating CAD in pulmonary nodule detection

The efficiency of the CAD algorithm can be measured by the speed of the CAD system, its ability to detect different shaped nodules, automation level, and correct lung segmentation[88]; however, evaluating CAD performance can be challenging; when working alone, the outcome can serve as an indicator of its sensitivity in lung-nodule detection and the number of false positives per scan. Conversely, when used as a second reader, the performance of CAD systems depends on the interaction between the CAD system and the radiologist, in addition to the radiologist's baseline performance. A large number of CAD performance studies either use small data sets,[83,89] different types of "true positive" (e.g., nodule size),[18,70] or different imaging parameters (section thickness and reconstruction intervals),[18,80] making comparison a difficult task. To assist in the evaluation process, the National Cancer Institute (NCI) and other organisations developed an international, internet-based image collection, the Lung Image Database Consortium (LIDC), which consists of diagnostic and screening lung cancer CT images with marked nodules. It can be used as a source for development and assessment of different CAD systems for the detection of lung cancer.[90] Recent studies have reported on using the LIDC to evaluate the performance of CAD systems.[66,72,73]

Effect of CAD on radiologists' detection of pulmonary nodules

Before implementing CAD in a clinical setting, we need to consider its effect on the performance of radiologists with different levels of experience and whether there is a combination of human observer and a CAD system that will provide optimal sensitivity in lung nodule detection with minimal false-positive findings. Studies have been conducted evaluating the effectiveness of a CAD system in identification of lung nodules when compared to radiologists' performance. With CAD the readers identified significantly more nodules than without CAD,[11,12,61,79,83,89,91–94] with a significant reduction of 40% in reading time with the aid of CAD[95]; however, a study has reported that a nodule-detection software did not improve the diagnostic performance of radiologists.[96] In a study by Jeon *et al.*[93] seven chest radiologists read 134 chest LDCT scans searching for lung nodules. They used CAD for reducing interobserver variability, demonstrating that agreement was increased with the use of CAD from 77% to 84%.[93] Bogoni *et al.*[12] evaluated the performance of five thoracic radiologists reading 48 LDCT scans in different nodule size categories; readers' detection improved significantly in each category when using CAD; from 44% to 57%, 48% to 61% and 44% to 60%, for nodule size $\geq$3, $\geq$4, and $\geq$5 mm, respectively.[12] Other studies have also demonstrated that there is an increase in radiologist's sensitivity with the use of CAD. For more details see Table 2.

In a study that analysed single and combined radiologists' performance including experienced and inexperienced radiologists, results showed that the performance of experienced radiologists with the assistance of the CAD system significantly outperformed experienced radiologists alone, inexperienced radiologists with CAD, and double reading (experienced and inexperienced radiologists).[91] This study demonstrated that CAD can be used to improve the performance of experienced radiologists and as a replacement of an inexperienced second reader. Awai *et al.*,[79] carried out a comparison in performance between board-certified radiologists and radiology residents and also confirmed that there was a significant difference in the performance of both groups of radiologists before the use of CAD and after.[79] Some of the limitations of this study may have affected the outcomes, such as informing the readers about the size and the number of nodules present in each case, which potentially excluded false-positive findings. In some studies, CAD proved to be helpful in the detection of small size nodules; a study by Sahiner *et al.*,[92] has shown evidence that CAD improved the performance of six thoracic radiologists when detecting pulmonary nodules $<$5 mm in diameter, but significance was not achieved before and after the use of CAD for larger nodules.[92] In another study evaluating the effect of CAD on the diagnostic performance of radiologists, 10 board-certified radiologists and nine radiology residents evaluated LDCT images with and without CAD. The study demonstrated that the use of CAD did not significantly improve the diagnostic abilities of the board-certified radiologists; however, it improved the diagnostic performance of the residents significantly.[97]

Despite that CAD is able to enhance radiologist's performance, the application of CAD to a daily clinical practice has not yet been reached; it still needs to be further improved by providing higher sensitivity in nodule detection, with an increased true-positive rate while minimising false-positive rates. This can be done by developing CAD systems that are more sensitive to the variety of lung cancers. Furthermore, as there is a substantial difference in CAD performance, combining CAD algorithms with high sensitivity for different types of lung nodules might prove useful. Most of the currently available CAD systems do not meet all of these requirements.

Conclusion

Lung cancer is by far the major cause of cancer death due to its aggressiveness and advanced stage when detected. Several large randomised controlled trials have demonstrated that screening for lung cancer did not reduce

Table 2
Radiologist versus computer-aided detection (CAD) performance in lung nodule detection.

Study	Ref. no.	No. of cases	Radiologists	Results
White *et al.*	83	109 CT scans	10 radiologists with different chest experience	Mean area under the curve for radiologists without CAD was 86.7% (76.6–90.6%) Mean area under the curve for radiologists with CAD was 88.7% (80.9–93.8%) CAD sensitivity at 0.9 mm section thickness was 81% CAD significantly improved the sensitivity of the radiologists in nodule detection
Sahiner *et al.*	92	85 CT scans	6 thoracic radiologists	At diameter threshold of 3 mm CAD average sensitivity is 54% Radiologists FOM without CAD was 0.66 Radiologists FOM with CAD was 0.71 There was significant improvement in performance for the radiologists after the use of CAD for <5 mm nodules, but significance was not achieved for larger nodules.
Nietert *et al.*	96	131 CT scans	8 radiologists read the scans with then without (CAD) NDS	The mean sensitivity in nodule detection without NDS was 52.3% with 28.2% FPR The mean sensitivity in nodule detection with NDS was 53.8 with 27.3% The NDS: • did not improve the diagnostic accuracy of the readers • did significantly influenced readers confidence
Bogoni *et al.*.	12	48 CT scans	5 thoracic radiologists read the scans without and with CAD	A statistically significant improvement in performance when radiologists used CAD: • Sensitivity of 44–57% for nodules ≥3 mm • Sensitivity of 48–61% for nodules ≥4 mm • Sensitivity of 44–60% for nodules ≥5 mm
Jeon *et al.*	93	134 CT scans	7 chest radiologists	The use of CAD for reducing inter-observer variability showed an increase in mean percentage of agreement between reader pairs on the positivity of screening results from 77% at initial assessment to 84% with CAD.
Zhao *et al.*	50	400 LDCT cases	2 experienced radiologists performed double reading CAD	For all nodule sizes: • CAD sensitivity was 96.7% with 3.7 FP/scan • Double-reading sensitivity was 78.1% with 0.5 FP/scan For nodules >50 mm^3 • CAD sensitivity was 96.7% with 1.9 FP/scan • Double-reading sensitivity was 78.1 with 0.1 FP/scan • CAD and using nodule size of >50 mm^3 as threshold improves the sensitivity compared to double reading.
M Das *et al.*	89	77 scans LDCT and SDCT	1 experienced radiologist 1 inexperienced radiologist	CAD sensitivity: 74% • Experienced radiologist sensitivity: 83% • Inexperienced radiologist sensitivity: 68% • Experienced radiologist + CAD sensitivity: 93% • Inexperienced radiologist + CAD sensitivity: 88% CAD: 4 FP/scan Both radiologists showed a statistically significant increase in sensitivity with the use of CAD
Iwasawa *et al.*	94	60 CT scans	10 observers (6 radiologists and 4 pulmonologists) read the scans with and without CAD	CAD sensitivity was 49% with 0.67 FP/scan Mean FOM without CAD was 0.684 with 0.19 FP/scan Mean FOM with CAD was 0.717 with 0.24 FP/scan The use of CAD significantly increased the performance of the observers

FP, false positive; LDCT, low-dose computed tomography; SDCT, standard-dose computed tomography; NDS, nodule detection software; FOM, figure of merit.

mortality. Conversely, the NLST showed a significant reduction in lung cancer deaths, in a selected population that underwent annual LDCT scans compared with chest radiography. New evidence has shown that lung cancer mortality can be further reduced by widening the eligibility criteria with which individuals are chosen for screening.

Screening for lung cancer is a complex process that involves the selection of individuals at risk, conducting the screening test, and effectively performing lung cancer detection while minimising diagnostic errors. Diagnostic error can be made at any stage of the imaging process. CAD has been designed to aid radiologists in lung nodule detection, reduce diagnostic errors and false-negative rates, and do it more efficiently than having a single radiologist reading the images or double reading[16,50,61]; however, studies have shown a wide range of detection

sensitivities when implementing different CAD systems. Overall, CAD has improved the performance of inexperienced radiologists and in some cases increased detection sensitivity when used by experienced radiologists. Its performance can be affected by several factors involving technical parameters in the scanning process and by the nodule characteristics, but it has a good potential assisting radiologist in lung nodule detection. Valuable features, such as volumetric measures, have helped in the follow-up of nodule size growth.

References

1. World Health Organization. *Cancer fact sheet No. 297*. 2013. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/. Accessed 03.11.2015.
2. World Health Organization. *World cancer report*. 2014. Available at: http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014. Accessed 30.03.2016.
3. Henschke CI, Yankelevitz DF, Libby DM, *et al*. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;**355**(17):1763–71.
4. Neroladaki A, Botsikas D, Boudabbous S, *et al*. Computed tomography of the chest with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination: preliminary observations. *Eur Radiol* 2013;**23**(2):360–6.
5. Gould MK, Donington J, Lynch WR, *et al*. Evaluation of individuals with pulmonary nodules: when is it lung cancer?: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest J* 2013;**143**(5_suppl):e93S–120.
6. Carlile P. Lung cancer screening: where have we been? Where are we going? *J Oklahoma State Med Assoc*. 2015;**108**(1):14–8.
7. Wormanns D, Ludwig K, Beyer F, *et al*. Detection of pulmonary nodules at multirow-detector CT: effectiveness of double reading to improve sensitivity at standard-dose and low-dose chest CT. *Eur Radiol* 2005;**15**(1):14–22.
8. Nagatani Y, Takahashi M, Murata K, *et al*. Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis. *Eur J Radiol* 2015.
9. Gorycki T, Lasek I, Kamiński K, *et al*. Evaluation of radiation doses delivered in different chest CT protocols. *Pol J Radiol* 2014;**79**:1.
10. Demir Ö, Yılmaz Çamurcu A. Computer-aided detection of lung nodules using outer surface features. *BioMed Mater Eng* 2015;**26**(s1):1213–22.
11. Rubin GD, Lyo JK, Paik DS, *et al*. Pulmonary nodules on multidetector row CT scans: performance comparison of radiologists and computer-aided detection. *Radiology* 2005;**234**(1):274–83.
12. Bogoni L, Ko JP, Alpert J, *et al*. Impact of a computer-aided detection (CAD) system integrated into a picture archiving and communication system (PACS) on reader sensitivity and efficiency for the detection of lung nodules in thoracic CT exams. *J Digit Imaging* 2012;**25**(6):771–81.
13. Matsumoto S, Ohno Y, Aoki T, *et al*. Computer-aided detection of lung nodules on multidetector CT in concurrent-reader and second-reader modes: a comparative study. *Eur J Radiol* 2013;**82**(8):1332–7.
14. Li F, Sone S, Abe H, *et al*. Lung cancers missed at low-dose helical CT screening in a general population: comparison of clinical, histopathologic, and imaging findings. *Radiology* 2002;**225**(3):673–83.
15. McCreadie G, Oliver T. Eight CT lessons that we learned the hard way: an analysis of current patterns of radiological error and discrepancy with particular emphasis on CT. *Clin Radiol* 2009;**64**(5):491–9.
16. Castellino RA. Computer aided detection (CAD): an overview. *Cancer Imaging* 2005;**5**(1):17.
17. Wormanns D, Fiebich M, Saidi M, *et al*. Automatic detection of pulmonary nodules at spiral CT: clinical application of a computer-aided diagnosis system. *Eur Radiol* 2002;**12**(5):1052–7.
18. Brown MS, Goldin JG, Suh RD, *et al*. Lung micronodules: automated method for detection at thin-section CT—initial experience. *Radiology* 2003;**226**(1):256–62.
19. Armato SG, Li F, Giger ML, *et al*. Lung cancer: performance of automated lung nodule detection applied to cancers missed in a CT screening program. *Radiology* 2002;**225**(3):685–92.
20. Murphy K, Schilham A, Gietema H, *et al*. Automated detection of pulmonary nodules from low-dose computed tomography scans using a two-stage classification system based on local image features. *Med Imaging* 2007. 651410-651410-651412.
21. Frost JK, Ball Jr WC, Levin ML, *et al*. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in The Johns Hopkins Study 1–3. *Am Rev Resp Dis* 1984;**130**(4):549–54.
22. Melamed M, Flehinger B, Zaman M, *et al*. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. *Chest J* 1984;**86**(1):44–53.
23. Fontana RS, Sanderson DR, Taylor WF, *et al*. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Resp Dis* 1984;**130**(4):561–5.
24. Kubik A, Polak J. Lung cancer detection results of a randomized prospective study in Czechoslovakia. *Cancer* 1986;**57**(12):2427–37.
25. Strauss GM, Gleason RE, Sugarbaker DJ, *et al*. Screening for lung cancer: another look; a different view. *Chest J* 1997;**111**(3):754–68.
26. Fontana RS, Sanderson DR, Woolner LB, *et al*. Lung cancer screening: the Mayo program. *J Occupat Environ Med* 1986;**28**(8):746–50.
27. Bach PB, Jett JR, Pastorino U, *et al*. Computed tomography screening and lung cancer outcomes. *JAMA* 2007;**297**(9):953–61.
28. Blanchon T, Bréchot J-M, Grenier PA, *et al*. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer* 2007;**58**(1):50–8.
29. Infante M, Cavuto S, Lutman FR, *et al*. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Resp Crit Care Med* 2009;**180**(5):445–53.
30. Pegna AL, Picozzi G, Mascalchi M, *et al*. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer* 2009;**64**(1):34–40.
31. Team NLSTR. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;**365**(5):395.
32. Saghir Z, Dirksen A, Ashraf H, *et al*. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012;**67**(4):296–301.
33. Pastorino U, Rossi M, Rosato V, *et al*. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prevent* 2012;**21**(3):308–15.
34. Field J, Duffy S, Baldwin D, *et al*. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2015. thoraxjnl-2015–207140.
35. McKee BJ, Hashim JA, French RJ, *et al*. Experience with a CT screening program for individuals at high risk for developing lung cancer. *J Am Coll Radiol* 2015;**12**(2):192–7.
36. Armato SG, Roberts RY, Kocherginsky M, *et al*. Assessment of radiologist performance in the detection of lung nodules: dependence on the definition of "truth". *Acad Radiol* 2009;**16**(1):28–38.
37. Radiology ACo. *Lung CT Screening Reporting and Data System (Lung-RADS)*. 2014. Available at: http://www.acr.org/Quality-Safety/Resources/LungRADS. 15.07.2016.
38. Pinsky PF, Gierada DS, Black W, *et al*. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015;**162**(7):485–91.
39. Borgstede JP, Lewis RS, Bhargavan M, *et al*. RADPEER quality assurance program: a multifacility study of interpretive disagreement rates. *J Am Coll Radiol* 2004;**1**(1):59–65.
40. Lee CS, Nagy PG, Weaver SJ, *et al*. Cognitive and system factors contributing to diagnostic errors in radiology. *AJR Am J Roentgenol* 2013;**201**(3):611–7.
41. Tehrani ASS, Lee H, Mathews SC, *et al*. 25-Year summary of US malpractice claims for diagnostic errors 1986–2010: an analysis from the National Practitioner Data Bank. *BMJ Qual Safe* 2013;**22**(8):672–80.

42. Romano L, Pinto A. *Errors in radiology*. Naples, Italy: Springer; 2012.
43. Mazzei M, Volterrani L. Errors in multidetector row computed tomography. *Radiol Med* 2015;**120**(9):785–94.
44. Kundel HL, Nodine CF, Carmody D. Visual scanning, pattern recognition and decision-making in pulmonary nodule detection. *Invest Radiol* 1978;**13**(3):175–81.
45. Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. *Arch Intern Med* 2005;**165**(13):1493–9.
46. Kakinuma R, Ohmatsu H, Kaneko M, *et al*. Detection failures in spiral CT screening for lung cancer: analysis of CT findings. *Radiology* 1999;**212**(1):61–6.
47. Team NLSTR. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;**2013**(368):1980–91.
48. Rubin GD, Roos JE, Tall M, *et al*. Characterizing search, recognition, and decision in the detection of lung nodules on CT scans: elucidation with eye tracking. *Radiology* 2014;**274**(1):276–86.
49. Roos JE, Paik D, Olsen D, *et al*. Computer-aided detection (CAD) of lung nodules in CT scans: radiologist performance and reading time with incremental CAD assistance. *Eur Radiol* 2010;**20**(3):549–57.
50. Zhao Y, de Bock GH, Vliegenthart R, *et al*. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. *Eur Radiol* 2012;**22**(10):2076–84.
51. Quekel L, Goei R, Kessels A, *et al*. Detection of lung cancer on the chest radiograph: impact of previous films, clinical information, double reading, and dual reading. *J Clin Epidemiol* 2001;**54**(11):1146–50.
52. Giger ML, Doi K, MacMahon H. Image feature analysis and computer-aided diagnosis in digital radiography. 3. Automated detection of nodules in peripheral lung fields. *Med Phys* 1988;**15**(2):158–66.
53. Doi K, Chan H-P, Giger ML. *Method and system for enhancement and detection of abnormal anatomic regions in a digital image*. Google Patents; 1990.
54. Firmino M, Morais AH, Mendoça RM, *et al*. Computer-aided detection system for lung cancer in computed tomography scans: review and future prospects. *Biomed Eng Online* 2014;**13**(1):1.
55. El-Baz A, Suri JS. *Lung imaging and computer aided diagnosis*.. Boca Raton, FL: CRC Press; 2011.
56. van Ginneken B, Schaefer-Prokop CM, Prokop M. Computer-aided diagnosis: how to move from the laboratory to the clinic. *Radiology* 2011;**261**(3):719–32.
57. Yuan R, Vos PM, Cooperberg PL. Computer-aided detection in screening CT for pulmonary nodules. *AJR Am J Roentgenol* 2006;**186**(5):1280–7.
58. Lee IJ, Gamsu G, Czum J, *et al*. Lung nodule detection on chest CT: evaluation of a computer-aided detection (CAD) system. *Korea J Radiol* 2005;**6**(2):89–93.
59. Jacobs C, van Rikxoort EM, Murphy K, *et al*. Computer-aided detection of pulmonary nodules: a comparative study using the public LIDC/IDRI database. *Eur Radiol* 2015:1–9.
60. Liang M, Tang W, Xu DM, *et al*. Low-dose CT screening for lung cancer: computer-aided detection of missed lung cancers. *Radiology* 2016;**150063**.
61. Fraioli F, Bertoletti L, Napoli A, *et al*. Computer-aided detection (CAD) in lung cancer screening at chest MDCT: ROC analysis of CAD versus radiologist performance. *J Thorac Imaging* 2007;**22**(3):241–6.
62. Armato III SG, Giger ML, MacMahon H. Automated detection of lung nodules in CT scans: preliminary results. *Med Phys* 2001;**28**(8):1552–61.
63. Gurcan MN, Sahiner B, Petrick N, *et al*. Lung nodule detection on thoracic computed tomography images: preliminary evaluation of a computer-aided diagnosis system. *Med Phys* 2002;**29**(11):2552–8.
64. Ye X, Lin X, Dehmeshki J, *et al*. Shape-based computer-aided detection of lung nodules in thoracic CT images. *IEEE Trans Biomed Eng* 2009;**56**(7):1810–20.
65. Kumar SA, Ramesh J, Vanathi P, *et al*. Robust and automated lung nodule diagnosis from CT images based on fuzzy systems. In: *2011 International Conference On Process Automation, Control and Computing (PACC)*. Tamilnadu, India: IEEE; 2011. p. 1–6. 20–22 July 2011 http://ieeexplore.ieee.org/xpl/mostRecentIssue.jsp?punumber=5978854.
66. Tan M, Deklerck R, Jansen B, *et al*. A novel computer-aided lung nodule detection system for CT images. *Med Phys* 2011;**38**(10):5630–45.
67. Teramoto A, Fujita H. Fast lung nodule detection in chest CT images using cylindrical nodule-enhancement filter. *Int J Comp Assist Radiol Surg* 2013;**8**(2):193–205.
68. Torres EL, Fiorina E, Pennazio F, *et al*. Large scale validation of the M5L lung CAD on heterogeneous CT datasets. *Med Phys* 2015;**42**(4):1477–89.
69. Lu L, Tan Y, Schwartz LH, *et al*. Hybrid detection of lung nodules on CT scan images. *Med Phys* 2015;**42**(9):5042–54.
70. Ko JP, Betke M. Chest CT: automated nodule detection and assessment of change over time—preliminary experience. *Radiology* 2001;**218**(1):267–73.
71. Bae KT, Kim J-S, Na Y-H, *et al*. Pulmonary nodules: automated detection on ct images with morphologic matching algorithm—preliminary results. *Radiology* 2005;**236**(1):286–93.
72. Messay T, Hardie RC, Rogers SK. A new computationally efficient CAD system for pulmonary nodule detection in CT imagery. *Med Image Anal* 2010;**14**(3):390–406.
73. Cascio D, Magro R, Fauci F, *et al*. Automatic detection of lung nodules in CT datasets based on stable 3D mass–spring models. *Comput Biol Med* 2012;**42**(11):1098–109.
74. Bellomi M. A classification of pulmonary nodules by CT scan. *Ecancermedicalscience* 2012;**6**:260.
75. Giger ML, Bae KT, MacMahon H. Computerized detection of pulmonary nodules in computed tomography images. *Invest Radiol* 1994;**29**(4):459–65.
76. Armato SG, Giger ML, Moran CJ, *et al*. Computerized detection of pulmonary nodules on CT scans. *RadioGraphics* 1999;**19**(5):1303–11.
77. Armato III SG, Altman MB, La Riviere PJ. Automated detection of lung nodules in CT scans: effect of image reconstruction algorithm. *Med Phys* 2003;**30**(3):461–72.
78. Suzuki K, Armato III SG, Li F, *et al*. Massive training artificial neural network (MTANN) for reduction of false positives in computerized detection of lung nodules in low-dose computed tomography. *Med Phys* 2003;**30**(7):1602–17.
79. Awai K, Murao K, Ozawa A, *et al*. Pulmonary nodules at chest CT: effect of computer-aided diagnosis on radiologists' detection performance. *Radiology* 2004;**230**(2):347–52.
80. Kim J-S, Kim J-H, Cho G, *et al*. Automated detection of pulmonary nodules on CT images: effect of section thickness and reconstruction interval—initial results. *Radiology* 2005;**236**(1):295–9.
81. Marten K, Engelke C, Seyfarth T, *et al*. Computer-aided detection of pulmonary nodules: influence of nodule characteristics on detection performance. *Clin Radiol* 2005;**60**(2):196–206.
82. Qian J, Fan L, Wei G-Q, *et al*. Knowledge-based automatic detection of multitype lung nodules from multidetector CT studies. *Med Imaging* 2002:689–97.
83. White CS, Pugatch R, Koonce T, *et al*. Lung nodule CAD software as a second reader: a multicenter study. *Acad Radiol* 2008;**15**(3):326–33.
84. Hein PA, Rogalla P, Klessen C, *et al*. Computer-aided pulmonary nodule detection-performance of two CAD systems at different CT dose levels. *RoFo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin* 2009;**181**(11):1056–64.
85. Bodelle B, Klement D, Kerl JM, *et al*. 70 kV computed tomography of the thorax: valence for computer-assisted nodule evaluation and radiation dose—first clinical results. *Acta Radiol* 2013. 0284185113513258.
86. van Ginneken B, Armato SG, de Hoop B, *et al*. Comparing and combining algorithms for computer-aided detection of pulmonary nodules in computed tomography scans: the ANODE09 study. *Med Image Anal* 2010;**14**(6):707–22.
87. Setio AA, Jacobs C, Gelderblom J, *et al*. Automatic detection of large pulmonary solid nodules in thoracic CT images. *Med Phys* 2015;**42**(10):5642–53.
88. El-Baz A, Beache GM, Gimel'farb G, *et al*. Computer-aided diagnosis systems for lung cancer: challenges and methodologies. *Int J Biomed Imaging* 2013;**2013**.
89. Das M, Mühlenbruch G, Heinen S, *et al*. Performance evaluation of a computer-aided detection algorithm for solid pulmonary nodules in low-dose and standard-dose MDCT chest examinations and its influence on radiologists. *Br J Radiol* 2014.
90. The Cancer Imaging Archive. TCIA collections. Available at: http://www.cancerimagingarchive.net/. Accessed 02.08.2016.
91. Marten K, Seyfarth T, Auer F, *et al*. Computer-assisted detection of pulmonary nodules: performance evaluation of an expert knowledge-based detection system in consensus reading with experienced and inexperienced chest radiologists. *Eur Radiol* 2004;**14**(10):1930–8.
92. Sahiner B, Chan H-P, Hadjiiski LM, *et al*. Effect of CAD on radiologists' detection of lung nodules on thoracic CT scans: analysis of an observer performance study by nodule size. *Acad Radiol* 2009;**16**(12):1518–30.

93. Jeon KN, Goo JM, Lee CH, *et al*. Computer-aided nodule detection and volumetry to reduce variability between radiologists in the interpretation of lung nodules at low-dose screening CT. *Invest Radiol* 2012;**47**(8):457.
94. Iwasawa T, Matsumoto S, Aoki T, *et al*. A comparison of axial versus coronal image viewing in computer-aided detection of lung nodules on CT. *Japan J Radiol* 2015;**33**(2):76–83.
95. Fraioli F, Catalano C, Almberger M, *et al*. Evaluation of effectiveness of a computer system (CAD) in the identification of lung nodules with low-dose MSCT: scanning technique and preliminary results. *Radiol Med* 2004;**109**(1–2):40–8.
96. Nietert PJ, Ravenel JG, Taylor KK, *et al*. Influence of nodule detection software on radiologists' confidence in identifying pulmonary nodules with computed tomography. *J Thorac Imaging* 2011;**26**(1):48.
97. Awai K, Murao K, Ozawa A, *et al*. Pulmonary nodules: estimation of malignancy at thin-section helical CT—effect of computer-aided diagnosis on performance of radiologists. *Radiology* 2006;**239**(1):276–84.