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State-of-the-art screening for lung cancer (part 1): the chest radiograph

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A series of studies performed primarily in the 1970s have been interpreted to show that the chest radiograph (CXR) is not an effective method for reducing mortality from lung cancer. While a stage shift was seen for the detected cancers, compared with current or historic controls, mortality was not shown to decrease. Since the 1970s, when these studies were performed, there have been substantial improvements in the technologies for CXRs and for the detection of small nodules on these radiographs. New developments include computed radiography (CR), direct digital radiography (DDR), image processing, energy subtraction (ES), temporal subtraction of serial radiographs (TS), and computer-aided detection (CAD). In this article the term digital radiography (DR) will be used to include CR and DDR. Examples of DR, ES, and CAD are shown in Figs. 1 and 2.

Identified causes of missed lung cancer

Analyses of CXRs for missed cancers [1–4] show that there are identifiable causes for missing lung cancer on CXRs. Small lesions can lie in lightly or darkly exposed portions of the CXR, a problem that can be at least partially overcome by image processing of CR and DR CXRs. Other cancers can be hidden partially or completely behind bony structures, a problem that is decreased by energy subtraction imaging, in which bone structures are made less visible. Other cancers might be simply overlooked, a problem that is partially corrected by CAD, a computer program that alerts the radiologist to findings that might represent lung nodules. These major changes in available techniques for chest radiography have not been incorporated into current lung cancer screening trials. DR, ES, and CAD have been shown to enhance the detection of lung nodules on CXRs when compared with conventional chest radiographic techniques. Most studies to date have reported on synthetic nodules, nodules representing metastases to the lungs, or mixtures of primary and metastatic cancer. CR, DDR, ES, and CAD have received U.S. Food and Drug Administration (FDA) approval. CR has been used in lung cancer screening trials in Japan and at some sites in the United States. The combinations of DR with ES, DR with CAD, and DR with ES and CAD have not been used in prospective studies for lung cancer detection.

Several methods of statistical analysis have been applied in the prior reported studies. Receiver operating characteristic (ROC) is a standard method for analyzing the effect of new methods of imaging on radiologists' interpretation. The most commonly applied statistic for this is the area under the ROC curve (Az). For practical purposes, the Az range is 0.5 to 1.0. The higher the value, the better the system. Az can be interpreted as the sensitivity averaged at all possible levels of specificity. When clinicians write of improvements in sensitivity improvements in an ROC

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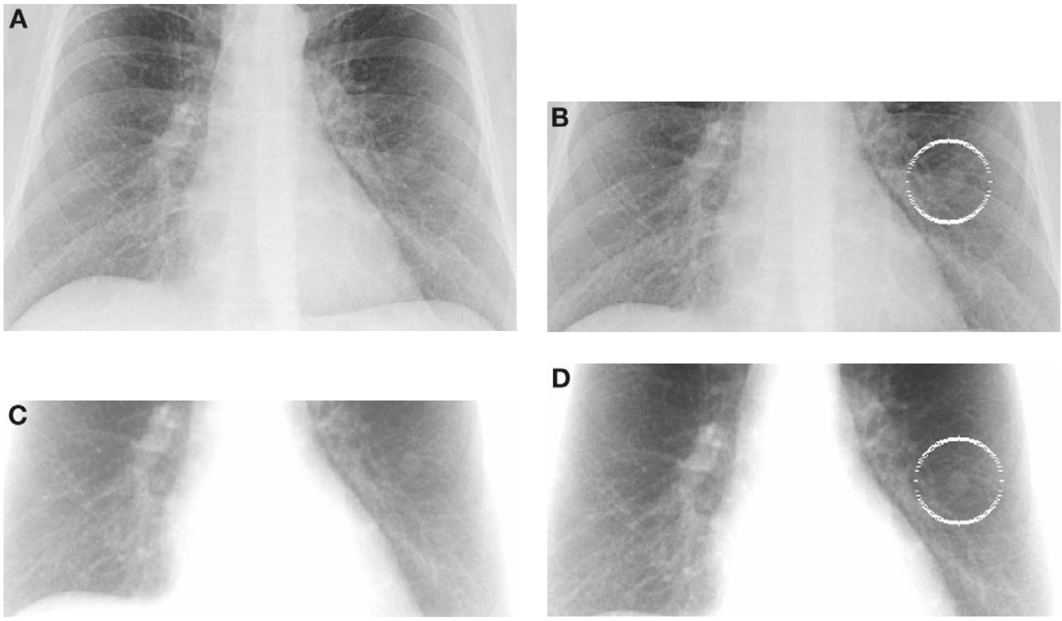

Fig. 1. Case 1. (*A*) Small nodule in the left midlung. (*B*) Circle drawn by CAD program. (*C*) Nodule on ES image. (*D*) Nodule on ES image outlined by CAD program. The CAD product used (RS2000D) is FDA approved for use with digitally acquired CXRs but not for use with ES CXRs. (Courtesy of Deus Technologies LLC, Rockville, MD.)

study, this average improvement in sensitivity for all possible specificity levels is being referenced. Some studies have used free ROC (FROC) and alternate FROC (AFROC), methods that allow multiple findings (in this case one or more nodules) on each image. Identification of the location of the finding is important. There are various methods of reporting the FROC and AFROC statistic. In each case the maximum value is 1.0, and higher values are better.

Digital radiography

CR and DR are different methods for acquiring digital radiographs of the chest. DR with image processing is FDA-approved, and with certain types of image processing it has been shown to increase radiologists' ability to detect pulmonary nodules. It is designed to correct for exposure differences among subjects and within a single subject. Intersubject and intrasubject image optical density is better controlled with digital methods [5–8]. It is well recognized that there is an optimal range of optical densities on chest images for the detection of minimal findings such as small lung nodules. The International Labor Organization has provided standards for conventional CXRs, and similar settings have been recommended by the American College of Radiology [9,10]. The reason for these limits is that film is a nonlinear recorder of exposure, and if the image is too light or too dark the contrast of a small object might be so decreased that it cannot be seen.

DR uses an x-ray sensing system that allows a wider range of exposures to be recorded. This wider range of exposures can then be adjusted by computer vision techniques (usually referred to as image processing) to produce images of optimal exposure (if displayed on film) or luminance (if displayed on a monitor). There are several types of DR that fall into two categories: (1) CR (also referred to in the literature as storage phosphor radiography [SR]) and (2) DDR.

There are analog and digital image processing methods. Fundamental changes that can be produced include changes in optical density, contrast, unsharp masking to balance or correct optical density, spatial frequency filtering, and mathematical methods to enhance specific frequencies in images, resulting in improved contrast for objects of specific sizes or shapes, edge enhancement, and image noise reduction. These processing methods can be applied across the entire image (global processing) or to specific portions of an image (adaptive processing). The process-

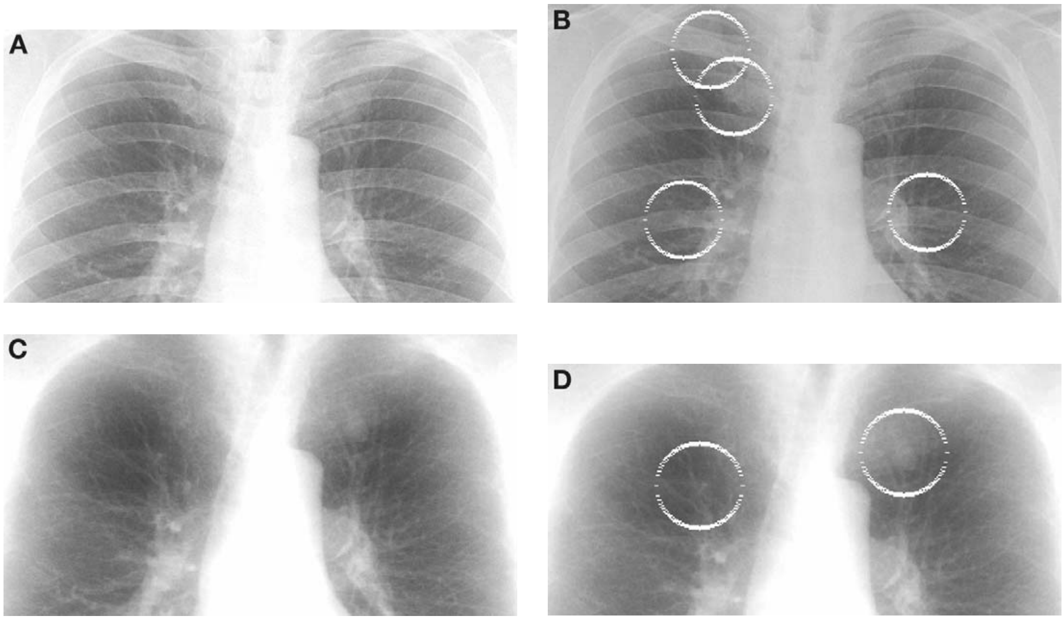

Fig. 2. Case 2. (*A*) Small nodule in the left upper lung on DR chest image. (*B*) Circles drawn by CAD program. The CAD program misses the nodule. (*C*) Nodule on ES image. (*D*) Nodule on ES image outlined by CAD program. On the ES image the performance of the CAD program is improved. The CAD product used (RS2000D) is FDA approved for use with digitally acquired CXRs but not for use with ES CXRs. (Courtesy of Deus Technologies LLC, Rockville, MD.)

ing of specific portions of an image can be based on anatomic regions identified by the computer or on regions of specific optical density.

Initial work with analog processing

Sorenson used analog unsharp masking technique and demonstrated that improving the contrast in the retrocardiac region improved detection of nodules metastatic to the lung in that region [11]. He used FROC analysis with Bunch transform to ROC coordinates. FROC mean true-positives in the retrocardiac region were 0.500 for conventional and 0.700 for the unsharp mask images, a 40% increase in true-positives. For all nodules the conventional mean was 0.625 and for unsharp mask images it was 0.677.

Initial work with image processing of digitized screen film images

Sherrier had eight radiologists interpret digitized CXRs containing 150 nodules [12]. They viewed the images unprocessed, processed with histogram equalization, and with adaptive filtration applied to underexposed regions of the images. The highest performance was seen with the adaptive filtration. Az improved from 0.68 on the unprocessed images to 0.78 with adaptive filtration, a 15% improvement.

Using synthetic nodules superimposed on digitized CXRs, Hoffmann applied optical density correction for under- and overexposed images [13]. In an ROC study, Az for underexposed retrocardiac and retrodiaphragmatic regions improved from 0.708 to 0.849 ($P < 0.01$), a 20% increase in sensitivity. For overexposed lung periphery Az improved from 0.958 to 1.0 ($P < 0.05$). The authors concluded that the improvement resulted from adjusting the contrast at the location of the nodules to the area of steepest contrast gradient in the image.

Initial work on synthetic nodules with digital image acquisition and image processing

Initial work with digitally acquired images and image processing used synthetic nodules and anthropomorphic phantoms or digitally synthesized nodules that were superimposed electronically on digital or digitized CXRs. Prokop reported that in phantoms, simulated nodules in CR chest images, nodule detection was better with large masks than with small masks [14]. Schaefer-Prokop used phantom and simulated nodules superimposed on lung tissue and mediastinum and found no differences between screen film (SF), CR, and a selenium system (Thoravision, Philips Medical Systems, Shelton, Connecticut) in the phantoms but did find an improvement in the detection of micronodules and thin simulated lines with the selenium system [15]. Leppert compared SF, asymmetric SF, and Fuji AC-1, (Fuji Medical Systems, Stamford, Connecticut) images using synthetic nodules placed on human volunteers before obtaining the CXRs [16]. This work showed that the asymmetric SF system was best overall for pulmonary nodules and that the Fuji system and the asymmetric SF combination were better than conventional SF images for synthetic nodules superimposed on the mediastinum. In 1994 (1 year before this report) the Fuji AC-1 was in the process of being replaced by newer Fuji systems (FCR 9000 and AC-3) that had better signal to noise characteristics and new image processing methods that produced images similar to those produced with the asymmetric SF system. It would be expected that these technical advances would result in improved nodule detection. Li used 5 and 10 mm synthetic nodules of two compositions and shapes to simulate dense and less dense nodules in an anthropomorphic phantom [17]. This work showed that image processing changes had no effect on the detection of 10 mm nodules but improved detection of 5 mm nodules. They recommend processing with unsharp masking with midrange frequency suppression and low frequency enhancing filters.

This important work with synthetic nodules superimposed on anthropomorphic phantoms or on digitized or digital CXRs showed that image processing applied to digital images enhanced the detection of smaller nodules, particularly when they occurred in regions of the image that had low contrast (ie, in lightly or heavily exposed regions).

Studies in subjects who had actual lung nodules confirmed by CT

Van Heesewijk obtained SF and selenium images of the chest in patients who had several types of CT-confirmed pulmonary and pleural diseases (eg, pulmonary opacities, interstitial disease, mediastinal disease, and pleural disease) [18]. The patients had 12 solitary nodules less than 2 cm. No differences were found between SF and Thoravision, but the authors might not have stressed the difference with the use of small nodules. No range of nodule size was given.

Muller reported a complex experiment in which he compared two SF systems (200 and 400 speed), digital CR images obtained at the same two exposures, and six filtering masks for the digital images [19]. Two hundred eighty-four CT-documented nodules were evaluated with these methods and rated by six observers. A nodule detectability score was used, with 0 points for nondetection of a nodule and 20 points for a well-visualized nodule; mean nodule detectability scores were then calculated. Overall, CR processed with large kernel sizes was superior to CR processed with small kernel sizes. CR was superior to SF for nodules superimposed on the heart, diaphragm, and mediastinum and for smaller nodules. Properly processed CR was always at least as good as SF and sometimes better. For nodules in lung fields, the mean nodule detectability score for SF was 12.52; for CR it was 14.26. For nodules obscured by the heart, diaphragm, or mediastinum, mean values were 8.63 for SF and 12.81 for CR. Nodules were also studied by size. For nodules less than 10 mm, the mean score was 11.9 for SF and 13.5 for CR. For nodules that were 10 to 20 mm and greater than 20 mm, SF at 200 speed and CR performed the same. For SF at 400 speed, CR at 400 speed was better than SF (SF 9.6, CR 13.2 for nodules 10–20 mm). An improvement in detectability score indicates that the nodules were more conspicuous, but it does not indicate that more nodules were detected.

Woodard compared chest images obtained with the selenium Thoravision and system-optimized SF images obtained at 150 kilovoltage peak (KVp). Selenium and SF images were obtained in 34 subjects who had 78 lung nodules that were identified by CT previously [20]. The nodule size range was 0.5 to 3.5 cm with an average size of 1.5 cm. Overall there was no significant difference in nodule detection (64% SF, 66% digital). For the subgroup of 19 nodules that were less than 1 cm, radiologists detected 53% of the nodules on the selenium images and only 46% on the asymmetric SF images, a 15% increase in nodules detected, which was not significant at the small sample size ($P = 0.69$). For the 13 nodules that were obscured on the postero-anterior (PA) view because they were superimposed on the heart or diaphragm, radiologists detected 46% on the selenium system images and 36% on the asymmetric SF system, a 28% increase in nodules detected, which was not significant at the small sample size of 13 cases.

Krupinski reported a study in which six radiologists compared unprocessed images with five different image processing methods on 168 CR cases of disease that were initially missed on interpretation [21]. There were 38 subtle nodules among the 168 cases. No difference was shown in the Az for these cases or for individual subsets. Enhanced confidence ratings were shown with the use of image processing ($P < 0.0001$), but it is not known if enhanced confidence ratings enhanced disease detection. Diagnostic decisions were not changed in this case.

Yang studied 18 patients who had CT-detected nodules less than 20 mm. Regius CR (Konica, Tokyo, Japan) was used for data acquisition with the original image and two degrees of unsharp mask [22]. Overall, no significant difference was shown. Radiologists interpreting the standard image had an Az of 0.65; with each of the filters the Az was 0.68. Sensitivity increased with tumor size ($P < 0.5$). Tumors that had alveolar lining growth were less visible than those that were solid. While the authors showed no statistically significant difference, eight of the ten measurements showed nonsignificant improvement in Az for the filtered images and one was equivalent.

Awai reported a comparison of CR to selenium-based radiography in 31 patients who had CT-documented solitary noncalcified lung nodules that were 5 to 30 mm [23]. Nineteen nodules were smaller than 10 mm. Five radiologists interpreted the images, comparing the CR and selenium images. Az was 0.64 with the CR system and 0.72 with the selenium system ($P < 0.05$).

Overall, these reports support the assertion that radiologists interpreting images of patients who have lung nodules show improved performance in nodule detection when digital images with appropriate image processing are used when compared with nodule detection with SF systems. The benefit of digital imaging is greatest with the smallest nodules and for those that are obscured by the heart or diaphragm.

Energy subtraction

ES radiography (also called dual energy radiography in the literature) is a well-established research imaging technique that has been implemented in clinical systems over the past 7 years. Energy subtraction is an FDA-approved method for chest imaging and has been shown in several clinical studies to improve the detection of noncalcified nodules superimposed on bony structures.

There are now at least two FDA-approved systems. For clinical use it is still considered to be novel, and no large United States trial has used it for lung cancer screening. With ES, two images of the chest are obtained simultaneously (in CR systems) or in rapid succession (in DR systems). Because of the underlying physical properties of atoms, the ratio of the x-ray absorption of water and calcium varies at different x-ray energies. Because this ratio varies at different energies, image processing methods can be used to take a low and a high energy radiographic image and present them to the viewer as a bone emphasis and a water emphasis image. The work of Stitik [1,2] and Austin [3] show that many cancers missed on CXR screening in clinical practice are missed because they are small or because they are hidden behind ribs or the clavicles. Limited clinical studies have confirmed that ES increases the conspicuity of lung nodules.

Ho evaluated the effect of ES imaging on nodule detection in images of anthropomorphic phantoms that had simulated nodules using analog film as the detector [24]. He compared two methods for ES. He demonstrated that readers of the conventional SF image had an Az of 0.876, those who read dual-exposure ES had an Az 0.945 (an increase of 8% in the mean sensitivity for all potential specificities), and those who read single-exposure ES had an Az of 0.929. Both ES methods were statistically significantly superior to the conventional SF image.

Ishigaki performed an experiment in which 140 subjects had CR ES images taken. In two studies a total of nine radiologists reviewed the images [25]. Sixty images showed primary lung cancer and 34 had metastatic nodules. The others were normal or had nonmalignant findings confirmed by biopsy or follow-up. In the first experiment the sensitivity for nodule detection was 0.47 for CR and 0.72 for ES ($P < 0.05$). Specificity also improved from 0.74 to 0.86 ($P < 0.05$). For the second experiment nodule sensitivity improved from 0.45 to 0.67 ($P < 0.05$) and specificity improved from 0.80 to 0.92 ($P < 0.05$). While improved sensitivity was shown for all nodules, the effect was greater for those that projected under a rib. For these nodules the sensitivity improved from 0.17 to 0.73 in the first study and from 0.13 to 0.68 in the second study ($P < 0.05$). In the second study the radiologists were asked to determine if the nodule showed benign calcification. Sensitivity for calcium detection improved from 0.29 to 0.96 on the ES images.

Kelcz reported on a study of 116 CT nodules in 50 patients [26]. Conventional SF and CR single-exposure ES images were compared. Five observers showed improvements in Az for nodule detection and for characterization of the nodules as calcified. For nodule detection the average Az was 0.597 for SF and 0.695 for ES ($P < 0.005$). For detecting nodule calcification, the Az was 0.815 for SF and 0.958 for ES ($P < 0.05$).

Kido reported a comparison of standard CR with an older and a newer method for detecting CT-confirmed lung nodules [27]. Forty nodules 5 to 20 mm in size were seen in 22 subjects. Fourteen radiologists interpreted the images. AFROC methods of data analysis were used. For all nodules, the average Az for the radiologists was 0.61 with CR, 0.72 with the new ES method ($P < 0.01$), and 0.66 with the older ES method ($P < 0.01$). For nodules that were superimposed on ribs, the average Az for the radiologists was 0.55 on standard CR, 0.71 with the new ES method ($P < 0.05$), and 0.63 with the older ES method ($P < 0.05$). No improvement or decrement was shown among the three methods for the nodules that were not superimposed on the ribs (Az of 0.69, 0.69, and 0.72, respectively).

This evidence demonstrates that ES imaging provides improved lung nodule detection. Sensitivity is improved for the detection of all nodules, but particularly for those that are obscured by ribs. The detection of calcification in nodules is also improved. Patients who had calcified nodules were less likely to be classified as having potentially malignant lesions.

Computer-aided detection

CAD of solitary pulmonary nodules is an FDA-approved method for application to digitized SF and digitally acquired CXRs. The FDA-approved version was validated on primary non-small cell lung cancer (NSCLC) 9 to 27 mm in size.

Computer analysis of radiographs for nodules has been shown to be an effective method for increasing radiologists' detection of small lung nodules. With CAD, the computer searches the image for findings that could indicate the presence of a lung nodule. The radiologist first views the image without CAD information, then the CAD information is provided. If the CAD system indicates sites that contain nodules that the radiologist has overlooked and if the radiologist accepts the information, the radiologist's detection rate for nodules improves. Many of the articles to date cover technical details of the development of these systems. In the fields of computer-aided diagnosis of lung cancer, two types of organizations (academic and commercial) have been conducting investigations for more than a decade. A group of outstanding researchers led by Dr. Kunio Doi has done substantial work [28,29] in pulmonary nodule detection and CAD in other diseases at the University of Chicago [30–32]. Doi's group has presented two effective lung nodule detection methods: (1) evaluation of circularity with incremental thresholding, and (2) evaluation of circularity using a morphological open operation. Their results indicate that these methods achieve a true-positive detection rate of approximately 70% with an average of three to four false-positive detections per chest image [33,34].

The clinical studies are reviewed below. One of the benefits of CAD is that the marking of the lesion appears to enhance its conspicuity. Krupinski reported that the placement of a solid circular boundary around a lung nodule enhanced its detection significantly [35]. When no circle was provided the Az was 0.523; with a dashed circle it was 0.690 and with a solid circle it was 0.800.

Kobayashi assessed the improvement in radiologists' performance using a case sample of 60 normal patients and 60 patients who had a single pulmonary nodule [36]. The mean pulmonary nodule size was 14 mm. Thirty-seven percent of the nodules were confirmed primary lung cancer and 42% had solitary metastases. Sixteen radiologists participated and ROC analysis was used. The Az without CAD was 0.894, and with CAD it was 0.940 ($P < 0.001$), a 5% improvement. MacMahon reported the results of a study in which 20 CXRs containing a single pulmonary nodule and 20 normal CXRs were interpreted with and without CAD [37]. On hundred forty-six observers participated. Chest radiologists' Az improved from 0.825 to 0.889, an 8% improvement; other radiologists' Az improved from 0.810 to 0.876, an 8% improvement. Radiology residents' Az improved from 0.774 to 0.855, and nonradiologists' Az improved from 0.697 to 0.808. All of these improvements were highly statistically significant.

Recently, Deus Technologies LLC received FDA approval for a CAD system for enhanced lung nodule detection on CXRs (FDA PMA000041). The system was validated on cases of NSCLC from the Johns Hopkins Early Lung Cancer Trial, one of the major lung cancer screening trials from the 1970s. Using the RS-2000 (Deus Technologies, Rockville, Maryland) radiologists showed that at their operating points (the point of sensitivity and specificity at which they decided on the need for diagnostic CT averaged for the 15 study radiologists) there was an average increase in cancer detection of 11% for primary NSCLC 9 to 27 mm, 21% for NSCLC 9 to 14.5 mm, and 38% for cancers that had been missed prospectively [38–41]. As defined for this study, a cancer was a missed cancer if the two radiologists at Johns Hopkins who subspecialized in chest radiography both missed the cancer on the film obtained approximately 1 year before actual detection. In ROC numbers the radiologists, on average, went from Az 0.829 to 0.865 for all cancers, from Az 0.798 to 0.848 for cancers 9 to 14 mm, and from Az 0.702 to 0.744 for the missed cancers. The improvement for all cancers and for the cancers 9 to 14 mm in size was statistically significant ($P < 0.05$). For missed cancers the results were not statistically significant for the sample size. The improvement demonstrated in this retrospective study suggests that a prospective screening trial using CAD would result in improved (ie, earlier) detection of NSCLC. A new version of the CAD system, the RS2000D, which uses digitally acquired CXRs, has also received FDA approval.

Computer-aided detection on energy subtraction images

In 2002 Kido provided two reports of CAD on ES images. In the first report [42] 12 patients had CT-confirmed nodules, eight of whom had bronchogenic

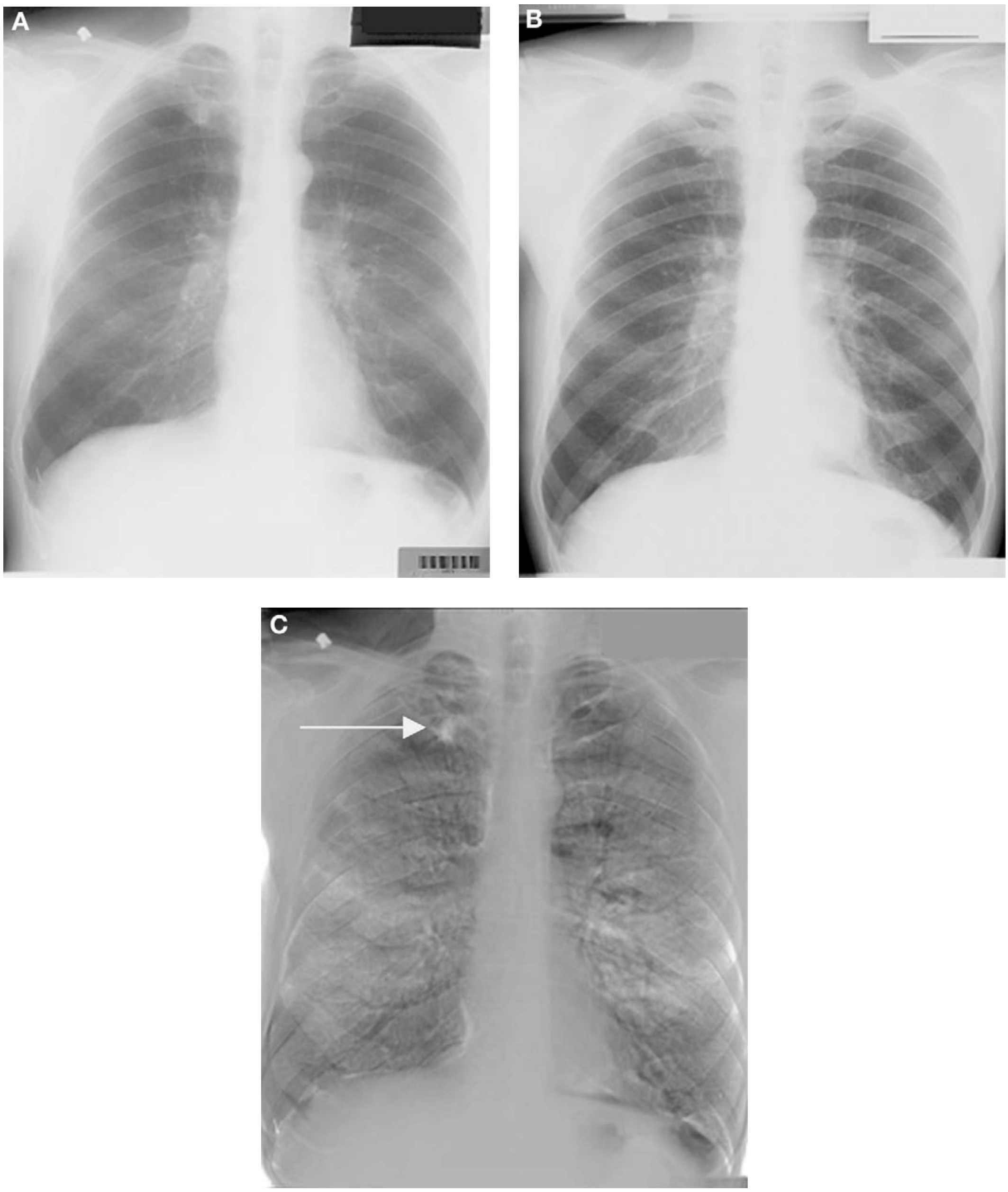

Fig. 3. TS of CXRs. (*A*) Prior CXR. (*B*) CXR obtained 1 year later. (*C*) Subtraction image on which the nodule in the right lung apex can be identified as a white focal nodule. This method is experimental and has not received FDA approval. (Courtesy of S-C Ben Lo, Hui Zhao, and Matthew Freedman, Imaging Science Center, Georgetown University, Washington DC.)

cancer (presumed to have one nodule each, although this is not stated in the article). Four patients had metastases to the lung [42]. In only one of the 12 patients (one patient who had several nodules) did the four radiologists, on average, detect more true-positive nodules than the CAD. In seven patients they were equivalent, and in four patients the CAD system detected nodules that one or more radiologists missed. Overall, the average was 1.60 [standard deviation (SD) 1.03] for the radiologists and 1.83 (SD 1.34) for the CAD system.

In 2002 Kido also reported a study of 25 images of chest phantoms with nylon nodules of three degrees of thickness producing different degrees of contrast on the image [43]. Twenty-five nodules were present. Each lung was viewed separately so there were 25 lungs with nodules and 25 lungs without nodules. Digital chest x-radiograph (D-CXR) and digital chest x-radiograph with energy subtraction (D-CXR-ES) images were studied. For the D-CXR without ES, the CAD system detected 14 of 25 nodules; the 12 radiologists, on average, detected 13.3 of the 25 nodules (SD 2.6; not significant). If one looked at the maximum potential improvement that radiologists could have had if they tested with CAD, the 12 radiologists would have detected 17.7 (SD 1.4) of the 25 nodules, a potential improvement of 4.4 nodules. On the ES images, CAD detected 23 nodules compared with 14 without ES ($P < 0.005$). The average detections of the 12 radiologists on the D-CXR-ES images were 21.2 (SD 2.1) compared with 13.3 (SD 2.6) without ES ($P < 0.005$). If the radiologists had used CAD, the maximum potential nodule detections would have increased from 21.2, on average, to 24.4 (SD 0.5). These articles show the potential contribution of ES when added to D-CXR and CAD when added to D-CXR with ES.

A series of studies have been reported in which evidence is presented that (1) DR CXR with appropriate image processing is superior to standard CXR for nodule detection, (2) DR CXR with ES is superior to DR CXR without ES, (3) CXR and DR CXR with CAD is superior to CXR and DR CXR, and (4) preliminary data suggest that CAD might provide further potential improvements when added to DR CXR with ES.

Temporal subtraction

TS is an important proposed method for enhancing the detection of lung nodules on serial CXRs. In this method two studies of the chest are taken at different times. The older image is then subtracted from the newer image, resulting in increased conspicuity of any change that might have occurred over time. The method is complex because of differences in positioning of the chest on the two radiographs and because of differences in the degree of lung inflation. An example of TS is shown in Fig. 3.

Kakeda reported on a study in which a temporal series of D-CXR images containing 20 solitary lung nodules (10 benign and 10 lung cancers, all less than 30 mm) were assessed by four radiologists and four radiology residents [44]. The radiologists showed improved Az from 0.873 to 0.969 with the use of temporally subtracted images. The residents' Az improved from 0.825 to 0.958. The combined improvement was significant ($P = 0.027$). Similar results for lung infiltrates were reported by Tsubamoto [45].

In a study of sequential radiographs in 30 patients who had CT-confirmed solitary pulmonary nodules, Johkoh [46] showed that temporal subtraction pairs resulted in improved performance among residents but not attending radiologists. The residents' performance improved from Az 0.855 to 0.907 ($P < 0.05$). For the attending radiologists, the Az was 0.964 without and 0.907 with the TS images.

Preliminary data suggest that TS imaging might, in the future, provide additional benefit in the detection of lung nodules, but additional investigation and improvements in this method are needed.

Summary

The chest radiographic methods used in prior studies of lung cancer screening and in current prospective clinical trials of lung cancer screening do not incorporate, as part of their prospective design, the newer methods available for the detection of lung nodules. DR, image processing, ES, and CAD have been shown to enhance lung nodule detection. TS is a promising method but with less supporting data currently available. These techniques, alone or in combination, do not equal the nodule detection capability of lung CT, but they are likely to benefit patients having CXRs for other clinically indicated purposes and when the detection of a nodule is incidental to the clinical indication for the radiographic study.

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