Use of a Computer-aided Detection System to Detect Missed Lung Cancer at Chest Radiography[1]

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Purpose: To study the ability of a computer-aided detection (CAD) system to detect lung cancer overlooked at initial interpretation by the radiologist.

Materials and Methods: Institutional review board approval was given for this study. Patient consent was not required; a HIPAA waiver was granted because of the retrospective nature of the data collection. In patients with lung cancer diagnosed from 1995 to 2006 at two institutions, each chest radiograph obtained prior to tumor discovery was evaluated by two radiologists for an overlooked lesion. The size and location of the nodules were documented and graded for subtlety (grades 1–4, 1 = very subtle). Each radiograph with a missed lesion was analyzed by a commercial CAD system, as was the follow-up image at diagnosis. An age- and sex-matched control group was used to assess CAD false-positive rates.

Results: Missed lung cancer was found in 89 patients (age range, 51–86 years; mean age, 65 years; 80 men, nine women) on 114 radiographs. Lesion size ranged from 0.4 to 5.5 cm (mean, 1.8 cm). Lesions were most commonly peripheral (n = 63, 71%) and in upper lobes (n = 67, 75%). Lesion subtlety score was 1, 2, 3, or 4 on 43, 49, 17, and five radiographs, respectively. CAD identified 53 (47%) and 46 (52%) undetected lesions on a per-image and per-patient basis, respectively. The average size of lesions detected with CAD was 1.73 cm compared with 1.85 cm for lesions that were undetected (P = .47). A significant difference (P = .017) was found in the average subtlety score between detected lesions (score, 2.06) and undetected lesions (score, 1.68). An average of 3.9 false-positive results occurred per radiograph; an average of 2.4 false-positive results occurred per radiograph for the control group.

Conclusion: CAD has the potential to detect approximately half of the lesions overlooked by human readers at chest radiography.

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Radiology

The diagnosis of subtle lung cancer at chest radiography remains a formidable challenge. Several investigators (1–5) have described the substantial pitfalls of interpretation created by overlapping structures and by the small size and low conspicuity of many lesions. Notwithstanding the difficulty in making the diagnosis, missed lung cancer is the second-leading cause of malpractice action against radiologists (6).

In recent years, there have been multiple technical advances that have the potential to facilitate diagnosis of lung cancer at chest radiography. The development of computed radiography and direct radiography permits more consistent image quality (7). The use of dual-energy and temporal subtraction chest radiographic techniques enables more direct visualization of the lung parenchyma without interference with overlying bone structures (8,9). However, these improvements are largely directed at the hardware component of image assessment and take less account of intrinsic limitations of the human reader.

Computer-aided detection (CAD) systems are increasingly being applied as a "second reader" to assist in the evaluation of images of complex anatomic structure, often in the context of a large data set. Two widely investigated applications are the use of CAD as a second reader for mammography and chest computed tomography (CT) (10–12). CAD systems directed specifically at chest radiographs have become available in recent years (13–16). To determine the potential effect of CAD in patients with early lung cancer, we investigated the frequency that proved lung cancer overlooked at the time of interpretation but visible in retrospect was detected with a commercially available chest radiographic CAD system.

Advances in Knowledge

- More than 50% of lung cancers missed initially by radiologists on chest radiographs were identified by a commercially available computer-aided detection (CAD) system.
- The number of false-positive markings has decreased substantially from that of a previous study, and many of these markings can easily be dismissed.

Implication for Patient Care

- Our study demonstrates the potential of CAD to detect nodules at chest radiography in many instances that were overlooked by a radiologist.

Materials and Methods

The study was supported by a grant from Riverain Medical (Miamisburg, Ohio). One author's (T.F.) salary for the 2007–2008 academic year was partly paid by Riverain Medical. The authors who are not corporate employees had control of the data and the information submitted for publication.

Patients

Institutional review board approval was given for this study. Patient consent was not required, and a Health Insurance Portability and Accountability Act waiver was granted because of the retrospective nature of the data collection. The cancer registries at a university hospital (1998–2006) and a veterans hospital (1995–2006) were reviewed.

Image Selection

On the basis of lung cancer registries in both institutions, 3100 patients with lung cancer were identified. This list was assessed to determine if images were retrievable on the picture archiving and communication system (PACS) at each hospital. Chest radiographs were obtained by using computed radiography systems (Fujifilm Medical Systems, Stamford, Conn; Agfa, Mortsel, Belgium; and Swissray International, Hochdorf, Switzerland). No screen-film images were obtained. Each available radiograph prior to the study on which the cancerous nodule was first detected was surveyed to determine whether the lesion was visible in retrospect. In each instance, a potentially actionable lesion (missed lung cancer) was agreed to by consensus of two experienced thoracic radiologists (C.S.W. and J.J., with 17 and 5 years of experience, respectively) who did not interpret the radiographs originally. If more than one earlier image showed the lesion, all such examinations were included for further analysis. Any radiographs prior to the earliest image on which a lesion was first recognized by the radiologist reviewers were excluded. The presence of each lung cancer and its lobar location were documented on the basis of a subsequent CT study that demonstrated the precise location of the lesion. All lung cancers were proved histologically.

Image Analysis

For each overlooked lesion, the lobar location and size were recorded in consensus by the radiologists. The radiologists reviewed the images on one of two PACS workstations (Agfa, Mortsel, Belgium; or Centricity, GE Medical Systems, Milwaukee, Wis). The full range of PACS tools, including windowing, leveling, magnification, and gray-scale manipulation, was available. The lesion size was measured for each radiograph on which a lung cancer was overlooked. Size was

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Abbreviations:
CAD = computer-aided detection
PACS = picture archiving and communication system

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Guarantor of integrity of entire study, C.S.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, C.S.W., T.F., J.J.; clinical studies, C.S.W., T.F., J.J., J.J.C.; statistical analysis, C.S.W., T.F., J.J.C.; and manuscript editing, all authors

See Materials and Methods for pertinent disclosures.

designated as the average of two orthogonal dimensions. If a clearly defined margin was not present for both measurements, the average of two representative nonorthogonal measurements was used. Tumors were designated as central if they overlapped with or were contiguous to the pulmonary hilum and were designated as peripheral if they did not. A subjective subtlety score ranging from 1 to 4 was assigned to the overlooked lesion on each image (1 = very subtle, 2 = moderately subtle, 3 = moderately apparent, 4 = apparent). The subtlety score was arrived at by consensus of the two thoracic radiologists, neither of whom had interpreted any of the radiographs on which lung cancer was overlooked. The subtlety score was based on a judgment of the conspicuity of the lesion, defined as the obviousness (based on size, opacity, margination) of the lesion in the context of the surrounding adjacent or overlapping structures such as ribs, the clavicle, and hilar structures.

CAD Analysis

All images were analyzed by using a commercially available chest radiographic CAD system (OnGuard 3.0; Riverain Medical). Developmental testing for this system has been performed in patients with pulmonary nodules at chest radiography, including lung cancers, but this system has not previously been evaluated specifically in patients with missed lung cancer. The CAD system is designed primarily to detect solitary pulmonary nodules between 0.9 and 3.0 cm in size on posteroanterior and anteroposterior chest radiographs. The automated detection process requires about 4 minutes. Circles measuring 2.5 cm in radius were placed around areas of the lung suspected of harboring pulmonary nodules.

For a result to be judged as positive, we required that the center of the circle overlie the missed lung cancer. Lesions located eccentrically within the circle (ie, no part of the lesion projected at the center point of the circle) were considered negative. The rationale for this conservative approach is that, by design, lesions detected by the CAD system are placed at the center of the circle. This circle has a finite size, and it would be rare but possible that a lesion not detected by the CAD software would fortuitously be included at or near the edge of the circle. Only two such instances occurred in our study.

Determination as to whether the CAD system correctly identified the lesion was based on consensus of the two thoracic radiologists who initially reviewed the radiographs for overlooked lung cancer. The number of false-positive results, defined as regions of the lung encircled by the CAD system not containing lesions at their center, was recorded for each image. Because there was more than one radiograph on which the lung cancer was missed in some patients, analysis of the CAD system was performed on a per-patient and a per-image basis.

To determine the number of false-positive findings at CAD in a group of patients without cancer, an age- and sex-matched control group was identified on the basis of a random search of our radiology information systems. The lack of cancer was determined in all cases by using results of chest CT studies performed within 18 months of the index chest radiograph. No match was made to account for differences in lung architecture. Chest radiographs in these patients were analyzed by the CAD system, and the number of false-positive results was tabulated.

In addition, the follow-up chest radiograph at the time of lung cancer diagnosis was identified, if available, and was analyzed with the CAD software. Both the detection and false-positive rates were assessed.

Statistical Analysis

Descriptive statistics were used to establish the sensitivity of the CAD software for the detection of missed lung cancer at chest radiography. The Pearson χ^2 test of association was used to compare CAD detection rates between the left and right lobes; between peripheral and central lesions;

Figure 1

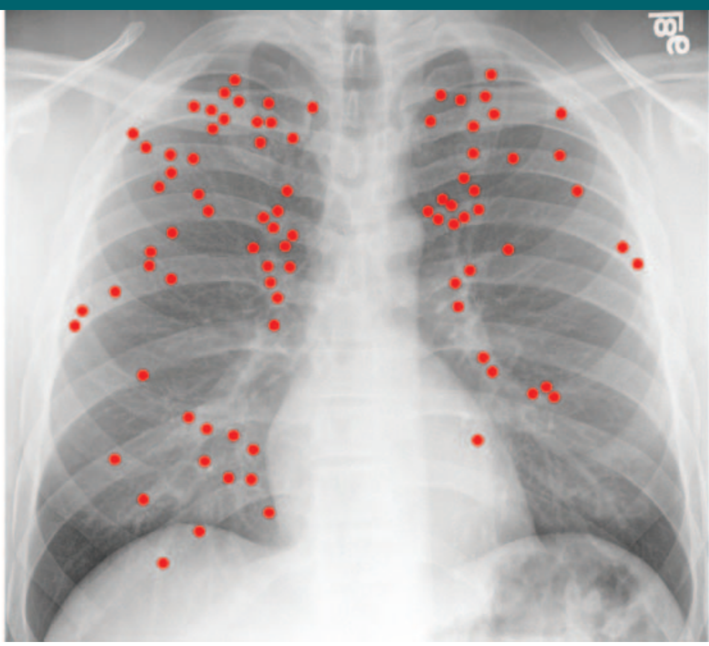

Figure 1: Frontal radiograph shows scatterplot of locations of 89 missed lung cancers at chest radiography.

and between the upper lobes, middle lobe and lingula, and lower lobes. The χ^2 test of trend was used to assess a trend in rates of detection across the subtlety score range. Finally, the independent *t* test was used to compare mean lesion sizes, subtlety scores, and patient ages between CAD-detected and undetected lesions. Many analyses were conducted on a per-patient and a per-image basis. Because some patients had multiple images, per-image analyses used the generalized estimating equation method to correct for within-patient correlation. However, results were nearly identical to the uncorrected analyses, which are the ones presented. A *P* value less than .05 was considered to indicate a significant difference. All analyses were performed with software (SAS, version 9.1; SAS Institute, Cary, NC).

Table 1

Characteristics of 89 Missed Lung Cancers

Location	Total No. of Cases	No. of CAD-Identified Cancers	Percentage of Cancers Identified
Peripheral	63	39	62
Central	26	7	27
Right lung	53	27	51
Left lung	36	19	53
Upper lobe	67	33	49
Middle lobe, lingula	8	6	75
Lower lobe	14	7	50

Figure 2

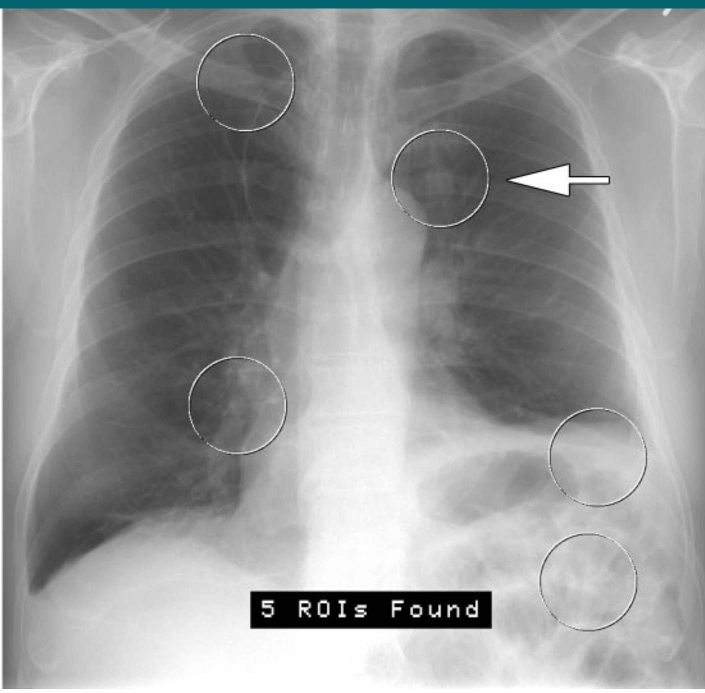

Figure 2: Frontal radiograph in 62-year-old man with lung cancer detected by CAD shows a 1.7-cm nodule (subtlety score = 3) in the left upper lobe denoted by a CAD mark (arrow). Four other CAD marks represent false-positive results. *ROIs* = regions of interest.

Results

Patients

A total of 89 patients (80 men, nine women) with missed lung cancer were found on the basis of review of the lung cancer registries. Seventy-seven patients received treatment at a veterans hospital, and 12 underwent treatment at a university hospital. The average patient age was 65 years, without a significant difference based on sex (age range, 51–86 years; male average, 66 years; female average, 58 years; *P* = .1).

Characteristics of Overlooked Lesions

A single lesion was overlooked in each of the 89 patients (Fig 1). The overlooked lesion was in the right lung in 53 patients (60%) and in the left lung in 36 patients (40%). Most missed lesions (*n* = 67, 75%) were located in the upper lobes (Table 1). Lesions were peripheral in 63 (71%) patients and central in 26 (29%). The average size of the lesion as measured on the initial radiograph on which it was overlooked was 1.8 cm (range, 0.4–5.5 cm). For peripheral lesions, average size was 1.6 cm (range, 0.4–5.3 cm); for central lesions, it was 2.4 cm (range, 1.4–5.5 cm). Ten lesions (11%) measured more than 3.0 cm in diameter and thus were classified as masses. The average time interval between obtaining the radiograph on which the lesion was initially overlooked and ultimate diagnosis was 237 days.

Images on Which Lesions Were Overlooked

The 89 lesions were overlooked on a total of 114 radiographs, of which 92 (81%) were posteroanterior radiographs and 22 (19%) were anteroposterior radiographs (Fig 1). The tumor was overlooked on one radiograph in 72 patients, two radiographs in 10 patients, three radiographs in six patients, and four radiographs in one patient. The lesion subtlety score was 1, 2, 3, or 4 on 43, 49, 17, and five radiographs, respectively. Lesions were overlooked by radiologists without subspecialty training in 99 (88%) instances, thoracic radiologists in 11 (9%), and thoracic imaging fellows in three (3%).

CAD Results for Missed Lung Cancer Chest Radiographs

CAD correctly marked the overlooked lesion on at least one radiograph in 46 (52%) of the 89 patients (Figs 2, 3). On a per-image basis, the CAD software correctly identified the missed lesion on 53 (47%) of the 114 images (Tables 2, 3). The average size of lesions detected with CAD was 1.73 cm compared with 1.85 cm for lesions that were undetected (P = .47) (Figs 4, 5). There was a significant difference (P = .017) in the subtlety score between detected lesions (score of 2.06) and undetected lesions (score of 1.68). When subtlety score was treated categorically, there was a significant trend toward increased detection rate with higher score (P = .018, test of trend), such that 80% of those that had a score of 4 were detected versus 33% of those with a score of 1. On a per-image basis, 46 (54%) of 86 peripheral lesions were detected, and seven (25%) of 28 central lesions were detected, which was a significant difference (P = .009).

There was a significant difference in detection rate based on lobar location, in which lesions on nine (82%) of 11 of the images in the middle lobe and lingula were detected compared with lesions on seven (50%) of 14 images in the lower lobes and lesions on 37 (42%) of 89 images in the upper lobes (P = .040). There were no significant detection rate differences based on laterality (left vs right side) either on a per-patient or on a per-image basis (P > .85). There was an average of 3.9 false-positive results per image (range, zero to five) (Fig 6). A breakdown of false-positive results is given in Table 4. If false-positive results due to erroneous detection of electrocardiographic leads, an obvious cause, were excluded, the false-positive rate would have been 3.6. Moreover, if false-positive results due to erroneous detection of obvious rib crossings and costochondral junctions were discounted, the false-positive rate would have been 2.0.

Figure 3

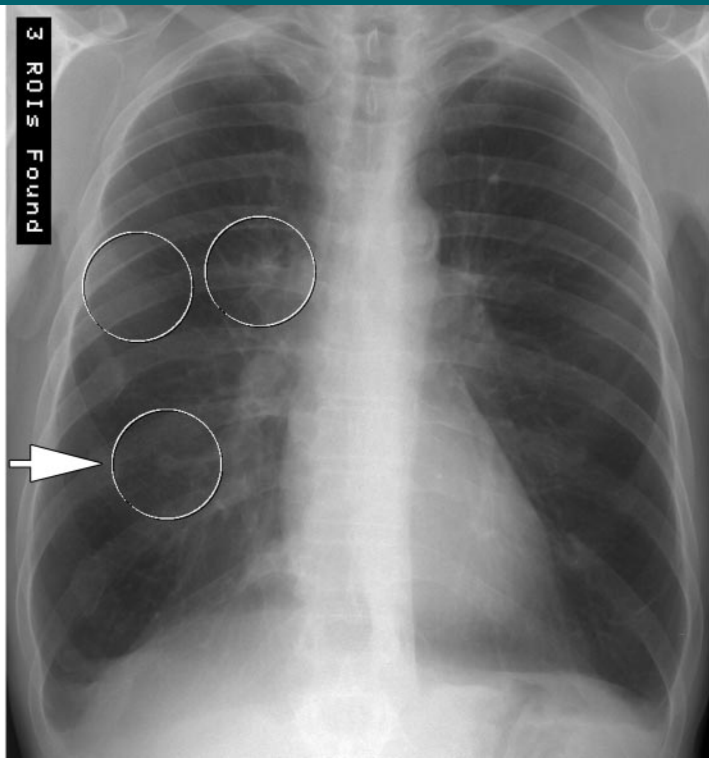

Figure 3: Frontal radiograph in 69-year-old man with subtle lung cancer detected by CAD shows a 1.6-cm nodule (subtlety score = 2) in the right lower lobe denoted by a CAD mark (arrow). The other CAD marks proved to be false-positive results on the basis of subsequent chest CT findings. *ROIs* = regions of interest.

Table 2

CAD Results Grouped according to Subtlety Score on a per-Study Basis

Subtlety Score	Total No. of Cases	Average Size (cm)	No. of CAD-Identified Cases*
1	43	1.3	14 (33)
2	49	1.8	26 (53)
3	17	2.4	9 (53)
4	5	3.6	4 (80)
Total	114	1.8	53 (47)

* Data in parentheses are percentages.

Table 3

CAD Results Grouped according to Size on a per-Study Basis

Size (cm)	Total No. of Cases	Average Subtlety Score	No. of CAD-Identified Cases*
0–1.0	26	1.2	10 (38)
1.1–2.0	54	1.8	27 (50)
2.1–3.0	23	2.3	11 (48)
>3.0	11	2.5	5 (45)
Total	114	1.8	53 (47)

* Data in parentheses are percentages.

CAD Results for Control and Index Chest Radiographs

The control group consisted of 89 patients (80 men, nine women) with an average age of 65 years, identical to the study group. With application of the CAD software, there was an average of 2.4 false-positive results per image (range, zero to five), which was statistically fewer than that on the missed lung cancer images ($P < .01$). Of the index radiographs (image on which lung cancer was identified) in patients with missed lung cancer, 47 (53%) of 89 were available for assessment. Thirty-seven (79%) of 47 tumors were detected by using the CAD software. The false-positive rate was 3.8 per image (range, two to five).

Discussion

Our study showed that CAD-detected nodules that were overlooked at initial interpretation were seen on 47% of radiographs and in more than 50% of patients. No clear difference emerged between size of lesions that were detected and size of those that were not detected by CAD, although there was a significant trend toward increased detection rates with a higher subtlety score. A mixed result was found for location, with a significant difference in detection based on lobar location but not laterality of lesion.

Early detection of lung cancer by using chest radiography is a formidable challenge. The chest radiograph is a two-dimensional projection of a complex array of three-dimensional structures. Pulmonary vessels, bones, and parts of the mediastinum each may project over the lung and partly or totally obscure pulmonary lesions at chest radiography. Some lung nodules are small or inconspicuous because of ill-defined margination or low opacity. A radiologist may fail to detect the lesion or may discount it as a benign structure.

Missed lung cancer is a well-recognized and unavoidable pitfall of interpreting chest radiographs. Lack of detection is attributed to observer error, characteristics of the lesion such as size and degree of opacity, and technical characteristics of image acquisition (17,18). In one classic study (19) of lung cancer detected during the Mayo Lung Screening Project, 45 (90%) of 50 peripheral and 12 (75%) of 16 central lung lesions were visible in retrospect on films obtained 4 months prior to the radiograph on which the diagnosis was established. In several clinical series of missed lung cancer, with numbers of patients ranging from 27 to 40, a fairly large median diameter of such lesions (>1.5 cm) was reported (1–4). Missed tumors were attributed to multiple factors, including failure of perceptual analysis by the radiologist, lack of comparison with previous radiographs, inadequate awareness of clinical information, and deficiencies in film quality (3,4).

Multiple strategies have been recommended to reduce the rate of missed lung cancer. These include scrupulous comparison of the current radiographic study with results of previous examinations, avoidance of distracting findings leading to satisfaction of search error, and double reading of images (6). Each of these approaches has drawbacks related to workflow and limitations of human perception. With improvements in computer technology, CAD has been proposed as a means to assist the radiologist in the detection of malignancy.

An increasing body of literature supports the use of CAD for mammography and in the assessment of lung nodules with chest CT (10–12). The literature regarding the value of CAD to assist in the detection of lung nodules at chest radiography is ample but has received less attention (13–16). MacMahon et al (14) investigated 40 digitized chest radiographs, 20 of which contained nodules, and found that CAD improved nodule detection significantly for radiologists, radiology residents, and nonradiologists. Shiraishi et al (15) found that detection of extremely subtle nodules can be improved with a CAD system if system sensitivity is set at a high level. Kakeda et al (16) determined that the improvement in lung nodule detection at

Figure 4

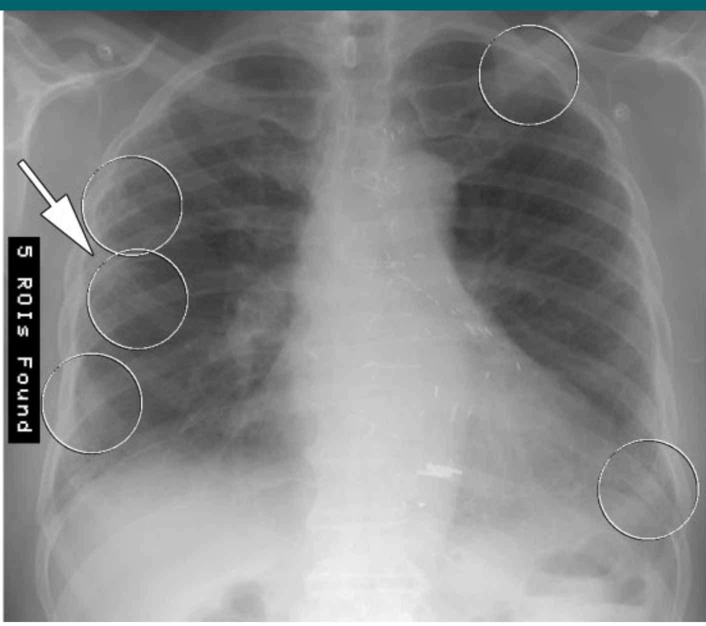

Figure 4: Frontal radiograph in 71-year-old man with lung cancer that was deemed a near miss by CAD shows a 1.7-cm nodule (arrow) (subtlety score = 2). There are two adjacent circles. The lesion is eccentrically located at the superior margin of the lower of the two circles and thus was considered a negative result. *ROIs* = regions of interest.

chest radiography with CAD was greatest for less experienced readers. In each of these studies, the pulmonary nodules were correctly interpreted as abnormal prospectively.

Li et al (20) recently investigated the use of CAD in 34 patients with missed lung cancer. This commercially available CAD system detected the overlooked cancer in 12 (35%) of the patients. However, each image had an average of 5.9 false-positive marks. Our current study used a newer and more advanced algorithm, which likely accounts for our higher detection rate (52% on a per-patient basis, 47% on a per-image basis) and our lower per-image rate of false-positive marks (3.9). In addition, our study consisted of a larger number of nodules than that of Li et al and all previous CAD trials and is, to our knowledge, the largest series of missed lung cancers reported to date.

We believe that our rather substantial rate of CAD detection in overlooked and potentially early lung cancer can be generalized because our lesion group was representative of missed lung cancer characteristics in many respects. The average size (1.8 cm) and location (predominantly peripheral) was similar to those of previous series of missed lung cancer, and many of the overlooked lesions were subtle (1–5). One conspicuous difference was that our series was largely composed of men because the majority of overlooked cancers were identified at a veterans hospital.

A somewhat surprising finding of our study was that there was not a significant difference in nodule detection based on size. One explanation may be the training of the algorithm, which was directed at nodules between 0.9 and 3.0 cm in size. An important consequence of placing an algorithmic limit on the upper size of nodule detection was that in our study the proportion of CAD-detectable missed lung nodules may have been underestimated, because some very large nodules may not have been identified on the basis of these criteria.

In contrast, there was a statistically significant correlation between the subtlety score and detectability with CAD. This finding suggests that conspicuity, or the tendency of a lesion to stand out from adjacent background structures, is a factor that influences detectability for both human observers and the CAD algorithm.

Figure 5

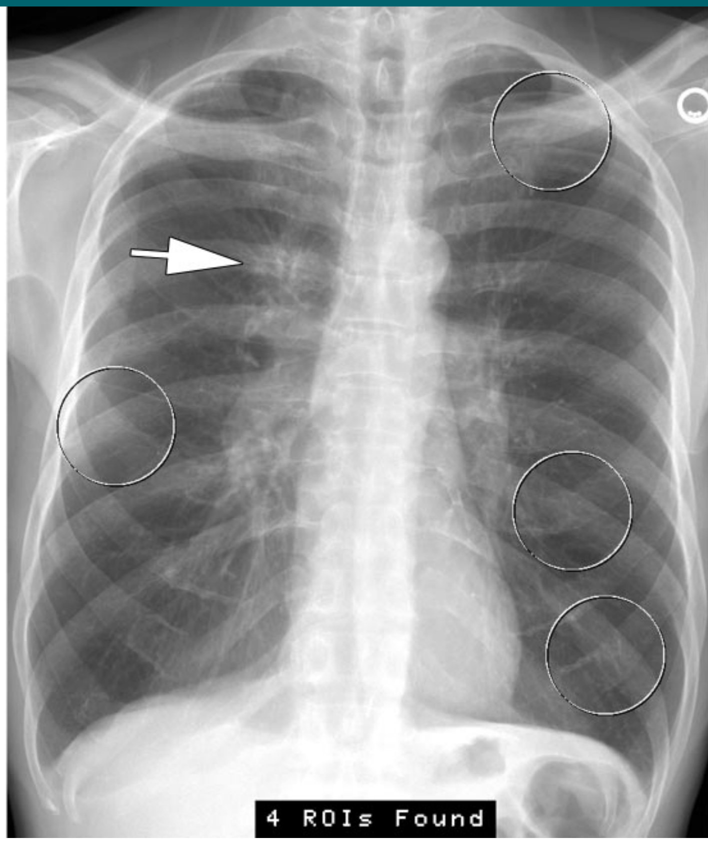

Figure 5: Frontal radiograph in 71-year-old man with lung cancer that was not detected by CAD shows a 2.4-cm central right upper lobe lesion (arrow) (subtlety score = 2) without a CAD mark. Several false-positive CAD results are present. *ROIs* = regions of interest.

We found that the false-positive rate of CAD was lower for our control group than for our missed lung cancer group but was similar on missed lung cancer radiographs and index lesion radiographs. This finding suggests that our missed lung cancer radiographs revealed thoracic architecture (eg, parenchymal scarring) that made a false-positive result more likely than in the control group. The similarity of the false-positive rate between the missed lung cancer and index lesion radiographs supports this premise. However, we did not attempt to match the missed lung cancer and control groups for confounding parenchymal features such as fibrosis. Not surprisingly, the detection rate on the index lesion radiographs was higher than on the missed lung cancer radiographs because of the increased conspicuity of the tumors at the time of diagnosis.

In considering the use of CAD, one must note that chest radiography has not proved effective to help detect lung cancer in screening trials of cigarette smokers. However, the patients in our study and other CAD chest radiography trials were not being screened but rather underwent examination for clinical reasons. Thus, they represent a distinct population in whom detection of early lung cancer may prove valuable, as suggested by previous investigations (21,22).

At least three requirements for the effective use of CAD were evident in our current study. The first was good sensitivity. In our opinion, the correct identification of about 50% of missed lung cancers, many quite subtle, demonstrated the potential of CAD. Whereas we regarded all these overlooked nodules as potentially actionable, we do not know whether a practicing radiologist who viewed the CAD markings corresponding to missed lesions at the time of initial interpretation would have regarded them as suspicious and recommended further evaluation. Thus, the conclusions from this retrospective study regarding CAD cannot be applied to the clinical reading situation.

A second requirement was a reasonable number of false-positive findings. It is clear that there is a trade-off between sensitivity and false-positive findings. The current algorithm still has a somewhat high rate of false-positive results, even though our results were better than those with an earlier algorithm. In many instances, such false-positive markings can be easily disregarded by the radiologist, although care should be taken to exclude an underlying lesion. In particular, bone crossings and medical equipment accounted for almost two false-positive results per image. For lung nodule CAD to become a widely accepted tool and to fit well into the daily workflow, the false-positive rate must be acceptably low. Ongoing investigation suggests that this limitation can be overcome or at least mitigated (23). As suggested by our results, normal cases may have fewer false-positive results than the lung cancer cases, although this possibility requires further investigation.

A third requirement was successful integration of lung nodule CAD into the workflow. This problem is potentially more difficult for chest radiography than for chest CT and mammography because less time and less reimbursement are allotted for interpretation at chest radiography. Thus, there is likely to be less tolerance of any CAD approach that is time-consuming. Much work has already been done to promote the full integration and rapid turnaround that are paramount for the success of CAD at chest radiography. Manufacturers are currently working to integrate CAD into the PACS environment so as not to impede workflow while reading chest radiographs. Overall, our study was directed at the stand-alone performance of CAD in cases of radiographically overlooked lung cancer and did not factor in additional important real-world considerations such as the effect of false-positive results and workflow integration.

The above limitations suggest the need for a prospective study to determine whether radiologists would in fact detect more actionable nodules by using a CAD system. We are undertaking a multiple reader study of overlooked lung cancer to answer this question and to assess the influence of false-positive CAD results and workflow issues.

In summary, our study demonstrates the potential of CAD to detect nodules at chest radiography in many instances that were overlooked by a radiologist. A significant correlation was found between nodule detection by the CAD system and the subtlety score, a qualitative measure of conspicuity. Further work is necessary to determine the value of CAD to detect missed lung cancer in the clinical setting.

Figure 6

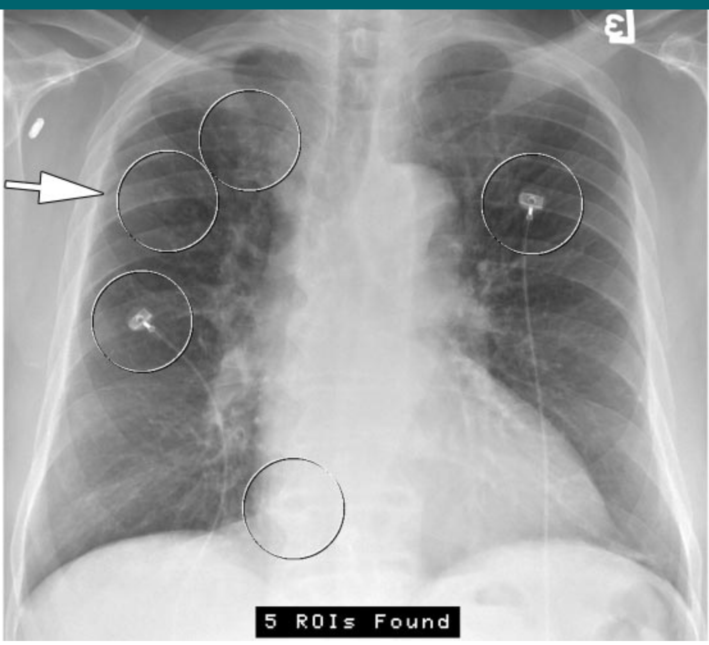

Figure 6: Frontal radiograph in 75-year-old man with false-positive CAD results shows CAD marks on two electrocardiographic leads and two other false-positive marks. The 1.2-cm lesion (arrow) in the right upper lobe (subtlety score = 2) was detected. *ROIs* = regions of interest.

Table 4

CAD False-Positive Causes on a per-Study Basis

Cause	No. of False-Positive Results
Bone crossings	1.4
Hilum	0.7
Equipment	0.3
Costochondral junction	0.2
Upper abdomen	0.2
Other	1.1
Total	3.9

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