Lung Cancer Screening Using Multi-Slice Thin-Section Computed Tomography and Autofluorescence Bronchoscopy

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Background: Thoracic computed tomography (CT) for lung cancer screening is sensitive for the detection of early peripheral lung cancer but is not sensitive for detecting central preinvasive and microinvasive cancer. Our hypothesis is that the use of a two-step strategy, using a sputum biomarker, may increase the detection rate of lung cancer by identifying individuals at highest risk.

Methods: We completed a pilot study of 561 volunteer current or former smokers 50 years of age or older, with a smoking history of more than or equal to 30 pack years. All subjects received induced sputum examination and low-dose thoracic CT scan and were offered autofluorescence bronchoscopy.

Results: CT detected 2408 pulmonary nodules, 80% of which were less than or equal to 4 mm in diameter. During 2-year follow-up, 95% of these nodules were stable or resolved, with only 4% showing growth at any time. A total of 28 cancers were detected in 22 subjects: 21 by CT scan and seven by autofluorescence bronchoscopy. Overall, 0.9% nodules were malignant, but growth on more than or equal to two CT scans increased the malignancy rate to 75%. The mean diameter of malignant nodules on detection was 12.8 mm (range, 3 to 36.4 mm). However, 18% of malignant nodules were less than or equal to 4 mm in diameter when first seen.

Conclusions: Multi-detector row CT scanners found multiple small nodules in most subjects screened, but most were stable over the 2-year follow-up. Persistent interval growth increases the probability of malignancy from less than 1% to 75%. One quarter of detected cancers were CT occult and only seen with autofluorescence bronchoscopy. Prescreening using a sputum biomarker improved the detection rate of lung cancer from 3 to 5%.

Key Words: Lung neoplasms, Tomography, X-ray computed, Bronchoscopy, Diagnostic imaging, Cytology.

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METHODS

The methodology has been described in detail in the publication and the online repository of the baseline results.14

Study Subjects

Low-dose spiral thoracic CT scan was added to the early lung cancer detection program at the British Columbia Cancer Agency in April 2000 as a sub-contract of a National Cancer Institute-sponsored chemoprevention trial (N01-CN-85188). Volunteer current and former smokers aged 50 to 74 years with a smoking history of more than or equal to 30 pack years were recruited from the community. After an interview and questionnaire, a sputum sample was obtained using inhalation of nebulized 3% hypertonic saline and high-frequency chest wall oscillations for 12 minutes with a ThAI-Rap Vest (Hill-Rom, St. Paul, MN). The sputum was evaluated using an automated high-resolution image cytometer (Cyto-Savant; Perceptronix Medical Inc., Vancouver, BC, Canada). Sputum atypia was defined as the presence of at least five epithelial cells that had a DNA index greater than 1.2. A low-dose thoracic CT scan was booked at the time of the interview and sputum collection. Subjects were offered an autofluorescence bronchoscopy using the LIFE-Lung device (Xillix Technologies Corp., Richmond, BC, Canada).

Approval was obtained from the Clinical Research Ethics Board of the University of British Columbia and the scientific review committee of the British Columbia Cancer Agency. Written informed consent was obtained from all participants.

Thoracic CT Scan

Baseline screening studies were performed at low dose, with follow-up examinations obtained using the standard diagnostic radiation dose used in our institution. CT scans between June 1, 2000 and August 30, 2001 were performed on a single-detector row GE CTi scanner (General Electric Medical Systems, Wisconsin) using 7-mm collimation, 120-kVp, 1-second scan time, and pitch of 1.0 and either 40 mA (baseline scan) or 200 mA (follow-up scan). Contiguous 7-mm collimation images were reconstructed using the standard (standard) and high spatial frequency (bone) algorithms. After September 1, 2001, scans were performed using either a four-detector row (GE QXi Lightspeed Plus) or eight-detector row (GE QXi Lightspeed Ultra) CT scanner. To make data acquisition uniform between these two machines, both were configured in four-detector row mode using 1.25-mm detector aperture, 120-kVp, 0.5-second rotation time, pitch of 1.5, and either 80 mA (baseline scan) or 320 mA (follow-up scan). Images were reconstructed at a slice width of 1.25 mm at 1.25-mm spacings using both the standard (standard) and high spatial frequency (bone) algorithms. After February 13, 2003, CT scans were performed using a 16-detector row CT scanner (Siemens Sensation Somatom 16; Siemens AG, Medical Solutions, Erlangen, Germany). Images were acquired using a 0.75-mm detector aperture, 120-kVp, 0.5-second rotation time, pitch 1.25, and 80 mA (baseline screen scan) or 200 mA (follow-up scan). Images were reconstructed at 1-mm slice width at 1-mm spacing using the standard (B35f) and high spatial frequency (B60f) reconstruction algorithms.

An abnormal CT was defined by the presence of at least one non-calcified pulmonary nodule or area of non-solid or part-solid density. A nodule was considered benign if it showed benign calcification pattern (central, diffuse, laminated, popcorn). Follow-up was arranged in subjects with an abnormal CT result. Subjects with a normal baseline CT scan were not offered CT scan follow-up. Lesions 4 mm or smaller were re-examined at 6, 12, and 24 months. Lesions 4 to 9 mm were re-examined at 3, 6, 12, and 24 months. Abnormalities 10 mm or larger were assessed on an individual basis for further investigation. The site and size of all detected lesions were recorded in an electronic database using Paradox for Windows software (version 7) (FileMaker, Santa Clara, California). Many nodules that were detected on follow-up examinations could, in retrospect, be seen on previous baseline low-dose or follow-up examinations. These nodules were identified in the database as retrospectively identified nodules.

Growth of a solid nodule was defined as an increase in either maximal long axis or short axis diameter of at least 1 mm. The same size criteria were also used for non-solid opacities, but, in addition, a change in density of the non-solid lesion without a change in maximal long axis diameter was also defined as growth. If these changes were reported in any visible lesion, then a repeat scan was arranged in 3 months. Subjects were referred for surgical resection if there was persistent growth of a pulmonary nodule or change in density or size of a non-solid opacity on sequential CT scans.

RESULTS

A total of 561 subjects were enrolled in the study. All subjects with an abnormal baseline CT scan (259 of 561) were followed with serial CT scans as part of the study protocol until all nodules or non-solid opacities had been observed to be stable in size for at least 24 months, were seen to be benign (calcified), or had resolved. Subjects with a normal baseline CT were not followed unless they were part of the chemoprevention study. The outcome of subjects who did not receive follow-up CT examinations was tracked through the Cancer Registry of British Columbia. By law, pathology laboratories in the province of British Columbia are required to report all newly diagnosed cancers to this Registry. Through January 30, 2005, there were no cases of lung cancer in this cohort except those found by this screening program.

Pulmonary Nodules

A total of 2408 pulmonary lesions were detected. Of these lesions, 92% were solid nodules (2219 of 2408), and only 8% were non-solid or part-solid opacities (189 of 2408). Sixty percent (1456 of 2408) of lesions were visible on the baseline CT scan (prevalence lesions), and 40% (952 of 2408) appeared during follow-up (incidence lesions). Sixty-two percent (1492 of 2408) of all lesions (prevalence and incidence) were detected in retrospect on follow-up examinations, being visible on earlier scans but not identified by the readers. Subjects with a normal baseline scan did not have
follow-up CT scans, and it is likely that some nodules may have been missed in this group.

During 2 years of observation, 95% (2294 of 2408) of lesions remained stable, resolved, or were seen to be benign. In follow-up, 4% of lesions (105 of 2408) showed growth on one CT scan (Table 1). Further CT scan follow-up or investigation of these growing lesions revealed that 12% (13 of 105) were malignant. If the lesions were seen to persistently enlarge on two or more consecutive CT scans, then 75% (12 of 16) were malignant.

By maximal long axis diameter, most detected lesions were small: 78% (1882 of 2408) were 4 mm or smaller, 19% (450 of 2408) were 4 to 10 mm, and 3% (76 of 2408) were 10 mm or larger. Overall, 0.9% (22 of 2408) of all lesions were found to be malignant, including 21 primary lung cancers and one metastatic lymph node (Table 1). In each of these size groups, 0.2% (4 of 1882) of nodules 4 mm or smaller, 1% (5 of 450) of nodules 4 to 10 mm, and 17% (13 of 76) of nodules 10 mm or larger were found to be malignant. The mean size of malignant nodules when first visible was 12.8 mm in diameter (range, 3 to 36.4 mm). However, 18% (4 of 22) of malignant lesions were less than 4 mm, and 36% (8 of 22) were less than 8 mm in diameter when first visible. Detectable growth (increase of 1 mm in maximal long axis diameter) was seen in 75% (6 of 8) of lesions less than 8 mm in diameter within 6 months of detection.

CT-Detected Lung Cancers

A total of 21 primary lung cancers in 11 women and 7 men (mean age 63 years; range, 53 to 77 years) were detected by CT scan (Tables 2, 3, and 4). At enrollment, 12 were current smokers and six were former smokers. There were 16 prevalence and five incidence cancers. Of these 21 cancers, 10 were reported in our baseline results. The histological subtypes of CT-detected lung cancers included 86% (18 of 21) non–small-cell lung carcinoma (NSCLC), 9.5% (2 of 21) small-cell carcinoma, and 4.8% (1 of 21) mixed small- and large-cell carcinoma. Most NSCLC (14 of 18) were adenocarcinoma. Overall, 78% (14 of 18) of the NSCLC was stage I.

Computer software that enabled the performance of volumetric analysis of growing nodules recently became available at Vancouver General Hospital using the Leonardo workstation and LungCare Volumetric Program (Siemens AG, Medical Solutions, Erlangen, Germany). This software was then used to retrospectively evaluate the growing malignant nodules detected on CT follow-up and to calculate volume doubling times of these lesions (Tables 3 and 4). Only one lesion was unable to be evaluated with the software (from subject 9) (Table 3). Tumor volume doubling times were seen to vary widely from 25 days for a prevalence adenocarcinoma (subject 11) (Table 3) to 900 days for an incidence squamous cell carcinoma (subject 11) (Table 4).

Prevalence Cancers

Most of the 16 prevalence cancers were NSCLC (15 of 16), and there was one case of mixed small- and large-cell carcinoma. Of the NSCLC, 80% (12 of 15) was adenocarcinoma.

Half of the prevalence cancers (8 of 16) were large solid lesions (mean maximal long axis diameter 18 mm; range, 10 to 25 mm) that were detected on the baseline screening CT scan and received immediate investigation and resection (Table 2). All cases were treated surgically, and 63% (5 of 8) were stage I. Two subjects (7 and 8) had additional chemoradiation.

The remainder of the CT-detected prevalence cancers (8 of 16) were diagnosed after detection of growth or a change in density during follow-up, and 88% (7 of 8) were stage I (Table 3). The mean diameter when first seen was 9.7 mm; at surgical referral it was 14 mm; and at surgery it was 14.7 mm. There were significant delays in the time to surgery for these lesions with a mean of 25 months (range, 8 to 42 months) from baseline. There were multiple factors that contributed to this prolonged time to surgery. First, some lesions were only detected in retrospect on a follow-up scan. In addition, some subjects delayed surgery or investigations for personal reasons despite strong recommendations from the investigators. All of the lesions except one were surgically resected (Table 3). The non-resected lesion was biopsied.

Incidence Cancers

A total of five incidence cancers were detected by CT scan, including two adenocarcinoma, one squamous cell carcinoma, and two small-cell carcinoma (Table 4). Two of these were second primary cancers in two subjects (subjects 4 and 11) who had previously had a prevalence cancer resected as part of the study.

The two incidence adenocarcinomas were detected in two current smokers (subjects 16 and 17) (Table 4). Both lesions were visible in retrospect on the 3-month follow-up CT scan but were not visible on the low-dose baseline scan. Both follow-up and baseline scans for each patient were performed using the same section collimation, but the follow-up scans were performed using a higher tube current. The incidence of stage IA squamous cell carcinoma was found in a former smoker who had a previous prevalence stage IA adenocarcinoma detected on CT and was undergoing continued follow-up of other nodules (subject 11). This patient developed a new 3-mm nodule during postoperative follow-up that was initially stable for 12 months and then enlarged. All three incidences of NSCLC were surgically resected.
Two small-cell carcinomas were detected on CT scan follow-up in two current smokers (Table 4). The first occurred in a subject with a previous prevalence squamous cell carcinoma diagnosed on the baseline CT scan undergoing continued follow-up of other nodules (subject 4). A 36-mm de novo mass was detected that had not been present on a CT scan performed 12 months earlier. The second small-cell cancer occurred in subject 18 during follow-up. This subject developed a number of new nodules and areas of consolidation seen at the routine 24-month scan after the occurrence of a respiratory tract infection. With further observation, most of the new findings resolved except for a 7-mm nodule that persisted and then enlarged to 10 mm.

### Bronchoscopically Detected Lung Cancers

A total of seven squamous cell carcinomas in four subjects were found using autofluorescence bronchoscopy (Table 5). These lesions were radiologically occult even on retrospective review of the thoracic CT scan by the study radiologist (JM). Half of the subjects had other pulmonary nodules on their baseline thoracic CT scan. The subjects included one woman and three men, and the mean age was 59.6 years. At enrolment, two were current smokers and two were former smokers. There were four prevalence and three incidence cancers. The three incidence cancers were detected on bronchoscopic follow-up in one subject with an occult

### Tables

#### Table 2. CT Scan-Detected Lung Cancers Diagnosed at Baseline Screen

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cell type</th>
<th>CT appearance</th>
<th>Stage</th>
<th>Size first visible (mm)</th>
<th>Size at surgical referral (mm)</th>
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<tr>
<td>6</td>
<td>Adenocarcinoma</td>
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<td>IIA</td>
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<td>IIIA</td>
<td>23</td>
<td>23</td>
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<tr>
<td>8</td>
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CT, computed tomography.

#### Table 3. CT-Detected Prevalence Lung Cancers Diagnosed on CT Follow-up

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<th>CT appearance</th>
<th>Stage</th>
<th>Size first visible (mm)</th>
<th>Size at surgical referral (mm)</th>
<th>Size in resected specimen (mm)</th>
<th>Time to surgery from baseline (months)</th>
<th>Tumor volume doubling time (days)</th>
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<td>11</td>
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NA, not applicable as lesion not resected; CT, computed tomography.

#### Table 4. CT Scan-Detected Incidence Cancers

<table>
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<th>Subject</th>
<th>Cell type</th>
<th>CT appearance</th>
<th>Stage</th>
<th>Size first visible (mm)</th>
<th>Size at surgical referral (mm)</th>
<th>Size in resected specimen (mm)</th>
<th>Time to surgery from first visible (months)</th>
<th>Tumor volume doubling time (days)</th>
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<tr>
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<td>10</td>
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<td>84</td>
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<tr>
<td>4</td>
<td>Small-cell carcinoma</td>
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<td>Limited</td>
<td>36</td>
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</tbody>
</table>

NA, not applicable as lesion not resected; CT, computed tomography.
squamous cell carcinoma detected on the baseline screening bronchoscopy. Surgical resection was performed in two subjects, and endoscopic treatment with electrocautery/cryotherapy was used in two subjects. The one subject with multiple metachronous lesions had a lobectomy for treatment of the prevalence cancer, endoscopic treatment of the incidence cancers, and finally a completion left pneumonectomy because of persistent disease.

False-Positive Surgeries

In addition to the 19 surgeries for lung cancer resection, seven subjects underwent surgery for enlarging pulmonary nodules that were nonmalignant. Most of these nodules (6 of 7) were detected at the baseline thoracic CT scan and showed growth on follow-up. One lesion was new on follow-up and showed rapid growth. Six subjects underwent video-assisted thoracoscopic surgery with wedge resection, and one subject required a lobectomy. The final pathology was lymph node, necrotizing granuloma, cryptococcoma, hamartoma, and inflammatory tissue. Therefore, of the 26 subjects who underwent video-assisted thoracoscopic resection or standard lobectomies, seven resections (27%) were for a benign condition. Of all the subjects screened, 1% underwent unnecessary surgery (7 of 561).

Sputum Results

Of the 561 screened subjects in the cohort, 423 had sputum atypia and 138 had normal sputum by AQC at baseline.
All of the subjects with central CT occult squamous cell carcinoma had sputum atypia. Of the subjects with a peripheral carcinoma, 15 of 18 (83%) had baseline sputum atypia. However, two subjects with normal baseline cytometry developed atypia on repeat testing as the cancers grew on CT scan follow-up, resulting in 17 of 18 (94%) with sputum atypia at the time of resection. Overall, 95% of subjects (21 of 22) with a detected cancer had sputum atypia on quantitative sputum cytometry.

**Lung Cancer Detection**

The use of a sputum biomarker increased the detection of lung cancer in this cohort. If CT scan alone had been used for these subjects, the detection rate would be 3% (18 of 561). By using a sputum biomarker as the first screening step and performing autofluorescence bronchoscopy and CT scan only in subjects with abnormal sputum cytometry, the detection rate would be 5% (21 of 423) (Table 6).

**DISCUSSION**

Only a small proportion of lifelong smokers develop lung cancer; however, lung cancer remains the major cause of cancer death. This is largely a result of the presentation of most patients with inoperable disease. Compared with screening using the chest radiograph, CT screening detects lung cancers at an earlier stage and smaller size. The impact on disease-specific mortality, however, remains to be determined. Given the high prevalence of CT-detected benign nodules in smokers, improved selection of subjects for screening is crucial to develop cost-effective and efficient screening programs.

The definition of a high-risk patient is undergoing change, and the traditional use of demographic and smoking data alone seems to be inadequate. Research regarding a patient’s cancer susceptibility suggests that some individuals have reduced DNA repair mechanisms, which may lead to increased accumulation of genetic mutations and increased risk of cancer development after exposure to cigarette smoke. Further work is underway to identify DNA repair gene polymorphisms that will predict a poor DNA repair capacity. Interestingly, recent research in nonsmoking Chinese patients with lung cancer has revealed an association of lung cancer with polymorphisms of GSTT1 and CYP1A1 genotypes, which suggests that changes in phase I and II enzymes and the activation and detoxification of carcinogens may play a role in lung cancer risk. Ultimately, determination of a high-risk patient’s genotype would be useful in both primary and secondary prevention strategies and in the selection of subjects to be screened for lung cancer.

The use of biomarkers to detect patients with an early lung cancer is also needed to identify those who require second-line investigation for cancer localization. Detection of a circulating serum DNA marker such as hTERT has shown promising results in early case-control studies. Detection of other abnormalities in serum and sputum, such as microsatellite alterations, methylation of the promoter of various tumor suppressor genes, and specific oncogene mutations are also being investigated. In addition to these genomic techniques, imaging of sputum cells with methods such as quantitative image cytometry and detection of malignancy-associated changes is undergoing investigation. An exciting recent development is the use of exhaled breath condensate to detect lung cancer with volatile organic compounds or molecular markers. Phillips et al. reported a sensitivity of 90% and specificity of 83% for detection of lung cancer measuring oxidative stress products such as alkanes and mono methylated alkanes in exhaled breath. It may have a role in screening because it can be incorporated as part of spirometry testing if the technology can be simplified and the chemicals separating patients with cancer from those without cancer are better defined. The potential of a biomarker as the first step in screening is that if we can identify individuals at highest risk of lung cancer, the positive predictive value of more selectively applied spiral CT and autofluorescence bronchoscopy will improve significantly.

The best method of investigation for subjects who are identified as being at highest risk is unknown. Most published screening studies use spiral CT scans with slice widths of 5 to 10 mm and do not evaluate the central airways. Thoracic CT scans detect multiple small pulmonary nodules, and the clinical significance and best observation protocol for these lesions are still uncertain. In this pilot study, thoracic CT scans were initially performed with a 7-mm single-detector
row scanner and then with 4-, 8-, and 16-multi-detector row CT scanners. We have shown that these technical changes substantially increase the detection of peripheral lung nodules, with nearly 80% being 4 mm or smaller in diameter. Long-term follow-up of more than 2000 of these lesions have shown that most are stable or benign over time. However, in this study, the most important indicator of malignant potential was growth on two or more sequential CT scans, in which the risk of malignancy was shown to increase from less than 1% to 75%. In this study, cancers detected on CT scan follow-up because of growth or change in CT appearance were of a smaller size than those detected at the baseline scan, and there was a greater proportion of stage I cancers (88% versus 63%). This has also been previously documented by Henschke et al. An important finding that has not, to our knowledge, been previously reported, is that 18% of malignant nodules were smaller than 4 mm when first visible, which indicates that small pulmonary nodules cannot be ignored. Many of these small lesions had detectable growth within 6 months of detection, indicating that close follow-up is required.

Some important problems that we have found in our study include significant delay to resection in some cases and a significant false-positive surgical rate. When considering a community-based screening program, it is important to consider these factors and to improve our investigational algorithms and techniques to resect cancers at the earliest possible time and reduce unnecessary surgery. Some of these factors were related to delays in attending CT follow-up or intervention by the subjects, and this is always a clinical challenge for the physician. Another factor is that some lesions were only seen in retrospect, which is a common phenomenon in CT scan screening. In our study, we found that 62% of pulmonary lesions were detected in retrospect, and this is most likely a result of using higher tube current and thinner slice width in the follow-up scans, which resulted in improved observer detection. New technologies that assist the radiologist in both the automated detection of pulmonary nodules and the early detection of growth will be extremely important in a lung cancer screening program to identify potential malignant nodules and enable earlier resection. Interestingly, the biological behavior of some of these peripheral lesions resulted in delay to resection. Some lesions seemed to be stable for long periods of time during CT scan follow-up and only showed change after 2 years of observation. The behavior and biology of peripheral adenocarcinoma has stimulated much recent interest, and research is revealing significant differences in biology, pathology, and prognosis in different subtypes of adenocarcinoma.

To reduce false-positive surgical rates, improved preoperative diagnostic techniques are required. However, investigation of small peripheral lesions less than 10 mm in size is limited by both technical skill in fine needle aspiration and limitation of diagnostic yields for bronchoscopy, positron emission tomography scan, and contrast CT scan. These types of investigations are not usually helpful with these small lesions. Novel localization techniques using electromagnetic navigation to aid the early diagnosis of suspiciously behaving peripheral pulmonary lesions and other transtracheal techniques that assist thoracoscopic resection of small growing peripheral lesions look promising.

Evaluation of the central airways is important as revealed in our study in which 25% of detected cancers were radiologically occult, emphasizing the limitation of CT scan in detecting central carcinoma in situ or microinvasive carcinoma. We found that 70% of squamous cell cancers in our cohort were CT occult. This has important implications when considering the population to be screened. In North America, squamous cell carcinoma accounts for approximately 37% of the lung cancers in men and 20% of the lung cancers in women. However, in Europe, a higher proportion of lung cancers are squamous cell carcinoma: approximately 47% and 27% of the lung cancers in men and women, respectively. Thus, if squamous cell carcinoma remains a significant contributor to lung cancer in a screened population, then it is important to evaluate the central airways using a more sensitive technique such as autofluorescence bronchoscopy.

The use of a sputum biomarker (AQC) in combination with autofluorescence bronchoscopy and CT scan in our cohort increased the detection rate of lung cancer from 3 to 5%. The reported detection rate of lung cancer using CT scan alone varies between 0.4 and 2.7%. Our detection rate using CT scan alone (3%) is similar to these rates. The longer term follow-up of this cohort confirms the findings from the early baseline report that more than 90% of lung cancers detected were found in subjects with sputum atypia by automated quantitative cytometry.

The future of cost-effective targeted lung cancer screening relies on the use of biomarkers to identify highest risk subjects and prioritization of cancer localization techniques depending on the patient’s risk profile. The development of new technologies integrated into the screening process will result in earlier detection, diagnosis, and treatment of early central and peripheral lung cancers.

ACKNOWLEDGMENTS

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