ORIGINAL ARTICLE

Management of Lung Nodules Detected by Volume CT Scanning

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ABSTRACT

BACKGROUND

The use of multidetector computed tomography (CT) in lung-cancer screening trials involving subjects with an increased risk of lung cancer has highlighted the problem for the clinician of deciding on the best course of action when noncalcified pulmonary nodules are detected by CT.

METHODS

A total of 7557 participants underwent CT screening in years 1, 2, and 4 of a randomized trial of lung-cancer screening. We used software to evaluate a noncalcified nodule according to its volume or volume-doubling time. Growth was defined as an increase in volume of at least 25% between two scans. The first-round screening test was considered to be negative if the volume of a nodule was less than 50 mm^3, if it was 50 to 500 mm^3 but had not grown by the time of the 3-month follow-up CT, or if, in the case of those that had grown, the volume-doubling time was 400 days or more.

RESULTS

In the first and second rounds of screening, 2.6% and 1.8% of the participants, respectively, had a positive test result. In round one, the sensitivity of the screen was 94.6% (95% confidence interval [CI], 86.5 to 98.0) and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). In the 7361 subjects with a negative screening result in round one, 20 lung cancers were detected after 2 years of follow-up.

CONCLUSIONS

Among subjects at high risk for lung cancer who were screened in three rounds of CT scanning and in whom noncalcified pulmonary nodules were evaluated according to volume and volume-doubling time, the chances of finding lung cancer 1 and 2 years after a negative first-round test were 1 in 1000 and 3 in 1000, respectively. (Current Controlled Trials number, ISRCTN63545820.)

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The use of multidetector computed tomography (CT) has increased the chance of finding noncalcified pulmonary nodules,[1,2] and as a result, clinicians often face the problem of deciding on the best course of action with respect to such nodules when they are found in asymptomatic subjects who have an increased risk for lung cancer.[3] This difficulty is especially evident in CT-based screening programs for lung cancer. The current practice is to refer participants in these programs for additional diagnostic evaluation if they have a noncalcified nodule that is larger than 5 mm in diameter.[4-9] In designing the Dutch–Belgian randomized lung cancer screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON]), we adopted a strategy that was meant to provide an inexpensive and simple follow-up process without increasing the false negative rate of the screening test.[10] The strategy entailed the use of the volume and volume-doubling time of a noncalcified nodule as the main criteria for deciding on further action. In this article, we report an evaluation of this strategy, which involved the tracking of individual nodules and the collection of 2-year follow-up data from the screened population of the NELSON trial.

Methods

Participants

We randomly assigned eligible participants in NELSON, who were recruited as described previously,[11] to undergo CT screening at baseline (first round), 1 year later (second round), and 3 years later (third round, 2 years after the second round), or no screening. The purpose of the trial is to determine whether at 10 years after randomization CT screening will have reduced mortality from lung cancer by at least 25%. The trial was approved by the Dutch Minister of Health and the ethics board at each participating center. All participants gave written informed consent.

Screening Strategy

A 16-detector CT scanner (Somatom Sensation 16, Siemens Medical Solutions or, at the screening site in Utrecht, 1x Mx8000 IDT or Brilliance-16P, Philips Medical Systems) was used at each of the screening sites. Data sets were derived from images of the lung with a thickness of 1 mm that were reconstructed at overlapping 0.7-mm intervals. Isotropic data sets allowed for volume measurements with good reproducibility, even in the case of small lesions.[12] Data acquisition and scanning conditions were standard across screening sites and were the same for all rounds of screening.[10] At each site, CT data were analyzed on one type of digital workstation (Leonardo, Siemens Medical Solutions) with the use of software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions).[13,14] In the case of inappropriate segmentation (i.e., nodules that were attached to a fissure or to a vessel), the radiologist was allowed to enter manual measurements, which overruled the automatically generated volumes. Data generated by the LungCare software were uploaded into the NELSON Management System, which automatically detected whether a nodule was new or had been present previously and which calculated the percentage change in volume and the volume-doubling time in days (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

A nodule was classified as noncalcified if it did not meet previously specified criteria for a benign lesion.[4] For solid pleural-based and nonsolid pulmonary nodules, the diameter was determined manually, and the volume-doubling time was calculated as described previously[10] (Fig. 1 in the Supplementary Appendix). In the case of pleural-based nodules, the diameter was measured at a point perpendicular to the costal pleura. In the case of partially solid lesions, only the volume of the solid region was used. The diameter was defined as the average of the maximum length and width of the nodule. Growth was defined as a change in volume of at least 25% between the first and second scans or between the second and third scans. The 25% threshold was based on three zero-change data sets in which the variation in volume of individual nodules was assessed between two low-dose CT scans. After the first of these scans, the patient returned to the examining table for the second scan to simulate the condition of a repeat examination for the follow-up of a pulmonary nodule. In these studies, the volume measurement error varied between 20% and 25%.[12,14,15] Growing nodules were classified into three growth categories according to their volume-doubling time (<400, 400 to 600, and >600 days).

CT scans were independently read by first

and second readers. The experience of the 13 first readers ranged from none to more than 20 years of experience reading thoracic CT scans (median, 6 years); both second readers had 6 years of experience. The second readers matched the nodules they had identified with nodules identified by the first readers according to location and size and compared their results with those of the first readers. If the results were discrepant, the readers reevaluated the scan to reach a consensus. If no consensus was reached, a third radiologist arbitrated the results.

FIRST-ROUND (BASELINE) SCAN

A test was considered to be positive if on the CT scan any noncalcified nodule had a solid component that was more than 500 mm^3 (>9.8 mm in diameter) and was considered to be indeterminate if the volume of the largest solid nodule or of the solid component of a partially solid nodule was 50 to 500 mm^3 (4.6 to 9.8 mm in diameter) or if the diameter of a nonsolid nodule was greater than 8 mm.[10] In subjects with an indeterminate result, a follow-up scan was obtained 3 months after the baseline scan to assess the growth of the lesion. If at that time the lesion had a volume-doubling time of less than 400 days, the final result was declared to be positive; otherwise, it was considered to be negative. Subjects with positive screening tests were referred to a chest physician for workup and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and left the screening trial; if no lung cancer was found, the regular second-round CT scan was scheduled for 12 months after the baseline scan.

SECOND-ROUND SCAN

When one or more new nodules were found on the second-round scan, the interpretation (positive or negative result) was based on the size of the nodule, as it had been in round one; if the result was indeterminate, a follow-up scan was obtained 6 weeks later.[10] In the case of nodules that had been detected previously, the second-round result was based on the volume-doubling time. If there was no growth, or if the volume-doubling time was more than 600 days, the screen was classified as negative. If the volume-doubling time was less than 400 days, or if a new solid component had emerged in a previously nonsolid nodule, the scan was considered to be positive. When the volume-doubling time was 400 to 600 days, the test result was considered to be indeterminate and a follow-up scan was obtained 1 year after the second-round scan. At that time, if the volume-doubling time was less than 400 days, the final result was considered to be positive; otherwise it was considered to be negative. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the result. All participants with a negative second-round test result were invited to undergo the third round of screening 2 years after the second round. A cancer detected on screening was classified as a first-round or second-round cancer if it was diagnosed after a workup during the first year after a positive first-round or second-round screen, respectively. Lung cancers that were detected during the first year after a negative first-round or second-round screening test were classified as interval cancers. They were identified through linkage with the national pathology database, information from participants and general practitioners, and, in the case of round-one interval cancers, linkage with the National Cancer Registry. The workup, staging, and treatment were standard across all screening sites and were performed according to published guidelines.[10,16,17]

All the authors contributed to the data collection and the decision to submit the manuscript for publication, and all the authors vouch for the accuracy and completeness of the data.

STATISTICAL ANALYSIS

The diagnostic sensitivity was defined as the ratio between the number of true positive results (participants who were diagnosed with lung cancer during the first year after a positive screening test) and the number of true positive results plus the number of false negative results (interval cancers detected during the same time period). Diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were calculated at the participant level, and 95% confidence intervals were determined with the use of SPSS software, version 15.0 (SPSS). The standard for a negative baseline or second-round test result was based on the retrospective information that lung cancer was absent 2 years after the first round of screening and 1 year after the second round. Normally distributed data are shown as means ±SD. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

FIRST ROUND

The mean (±SD) age of the screened participants was 59±6 years, and the mean number of pack-years smoked was 42±19; a total of 16% of the participants were women. The first round of screening was conducted from April 2004 through December 2006 (Fig. 2 in the Supplementary Appendix). Of the 7557 participants, 50.5% had a total of 8623 noncalcified pulmonary nodules, of which 98.0% were solid. Automated volumetric data were manually adjusted in the case of 6.3% of the nodules. The screening results were determined to be negative in 5987 participants (79.2%), indeterminate in 1451 (19.2%), and positive in 119 (1.6%) (Fig. 1). A total of 1536 follow-up scans were obtained 100±19 days, on average, after the baseline scan in participants with an indeterminate result. Including the outcome of these follow-up scans, the results from round one of the screening were negative in 7361 participants (97.4%) and positive in 196 (2.6%).

Of the 196 participants with a positive scan, 177 were referred for workup; 19 were not referred (9 because of a decision by the tumor board, 3 because of an administrative error, and 7 because they were already receiving treatment from another specialist). Lung cancer was diagnosed in 70 of the 177 participants who had a positive scan (39.5%); the diagnosis was made mainly by means of an invasive procedure (85.7%). These 70 participants had 72 lung cancers, of which 46 (63.9%) were classified as pathological stage I. In three subjects, no tissue for a histologic diagnosis could be obtained. These subjects received high-dose radiotherapy because the lesions were growing and were assessed as positive on a positron-emission tomographic (PET) scan. Of the remaining 107 subjects with a positive scan, 100 had benign disease and 7 had metastases from another cancer. In round one, the proportion of invasive procedures that revealed benign disease was 27.2%.

The lung-cancer detection rate in round one was 0.9% (70 of 7557 subjects). There were four interval cancers, all of which were stage IV adenocarcinomas; three of these were new noncalcified nodules, and one, which had been seen in the first round, had a volume-doubling time of more than 600 days at the 3-month follow-up. The sensitivity of round-one screening was 94.6% (95% confidence interval [CI], 86.5 to 98.0), the specificity 98.3% (95% CI, 98.0 to 98.6), the positive predictive value 35.7% (95% CI, 29.3 to 42.7), and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). Thus, in a subject with a positive CT screening test, the probability that the lesion would be malignant was 36%; with a negative screening test, the probability that a participant would not have lung cancer was 99.9%.

Among the 7361 negative CT scans in round one, 20 lung cancers were detected during the 2 years of follow-up: 3 were round-one interval cancers, and 17 were detected in the round-two screening. On the basis of this information, the negative predictive value was 99.7% (95% CI, 99.6 to 99.8). All 126 participants with a positive screening result at round one but with a negative workup returned to the screening program. After a mean follow-up of 785±263 days, 10 of these 126 subjects received the diagnosis of pulmonary adenocarcinoma, which appeared to have originated from a suspicious nodule that was detected in round one (Table 1 in the Supplementary Appendix).

SECOND ROUND

In accordance with the trial's protocol, all the participants in the first round of screening, except those in whom lung cancer had been diagnosed, were invited to undergo screening in the second round,[12] which was conducted from April 2005 through April 2008. A total of 7289 participants underwent screening 384±59 days after the round-one screening (Fig. 1 in the Supplementary Appendix). In 1588 (21.8%) of these participants, a total of 2320 new nodules were detected, 29.2% of which had a volume of less than 15 mm^3 or had been missed in round one. Automated volumetric data were manually adjusted in the case of 5.4% of the new nodules and 1.9% of previously existing nodules. The second-round screening result was negative in 6719 participants (92.2%), indeterminate in 480 (6.6%), and positive in 90 (1.2%) (Fig. 2). Among participants with an indeterminate result, 276 had a follow-up scan 77±36 days after the second-round screening and 231 had a follow-up scan 364±36 days after the second-round screening. The follow-up scans were positive in 38 subjects, and when the results of these positive follow-up scans were added to the results of the 90 positive screening scans, there were 128 subjects (1.8%) with positive second-

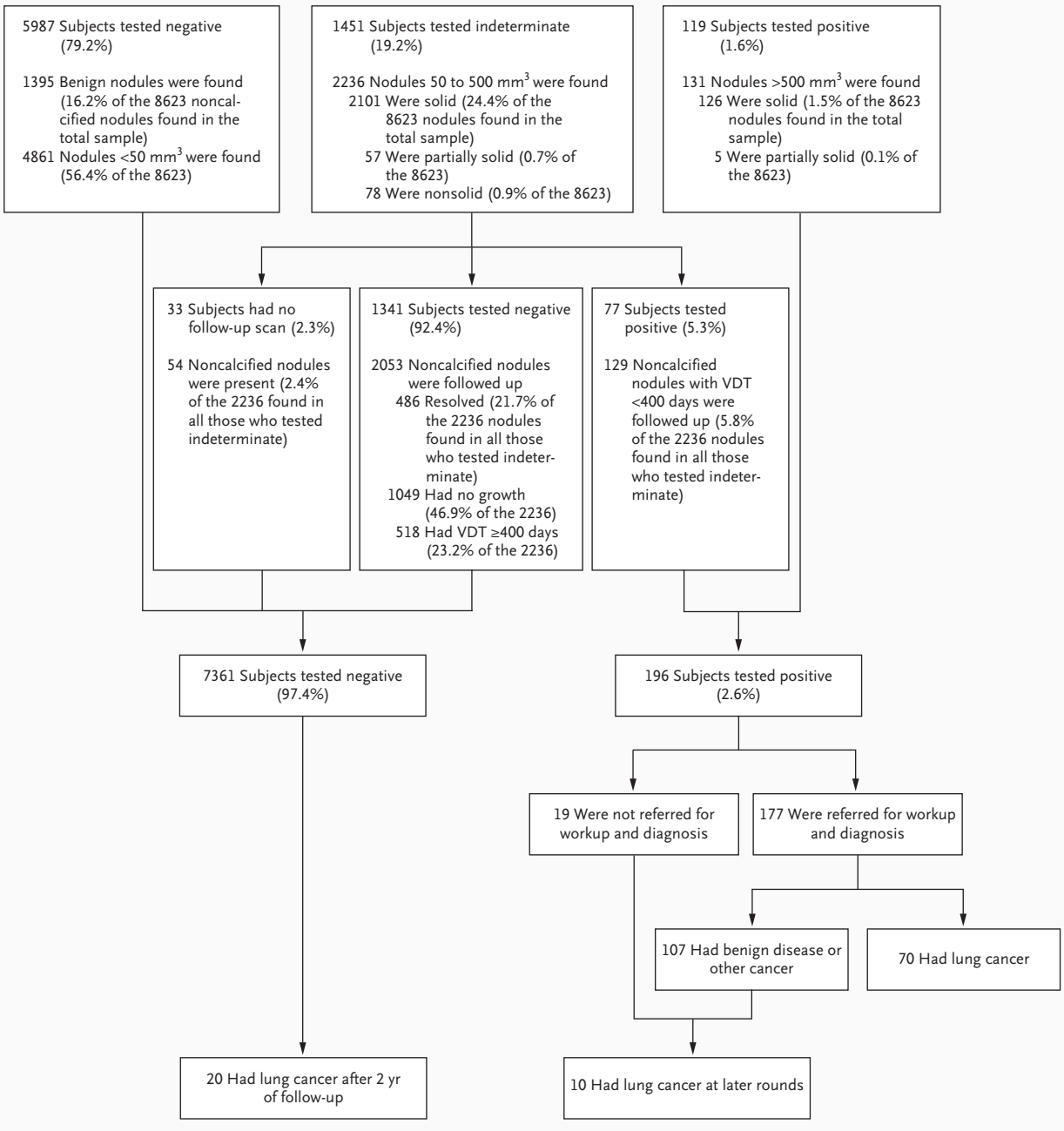

Figure 1. Results of the First Round of Screening.

Some participants had more than one nodule. VDT denotes volume-doubling time.

round scans. Of these 128 participants, 1 patient died as a result of a metastatic colon carcinoma and 118 were referred for workup; 54 of the 118 who were referred for workup (45.8%) received the diagnosis of lung cancer, mainly after undergoing an invasive procedure (88.9%). The nine participants who were not referred for workup (four because of a decision by the tumor board, four because of an administrative error, and one because the patient was already receiving treatment from another specialist) were invited to participate in the third round of screening 2 years later. In

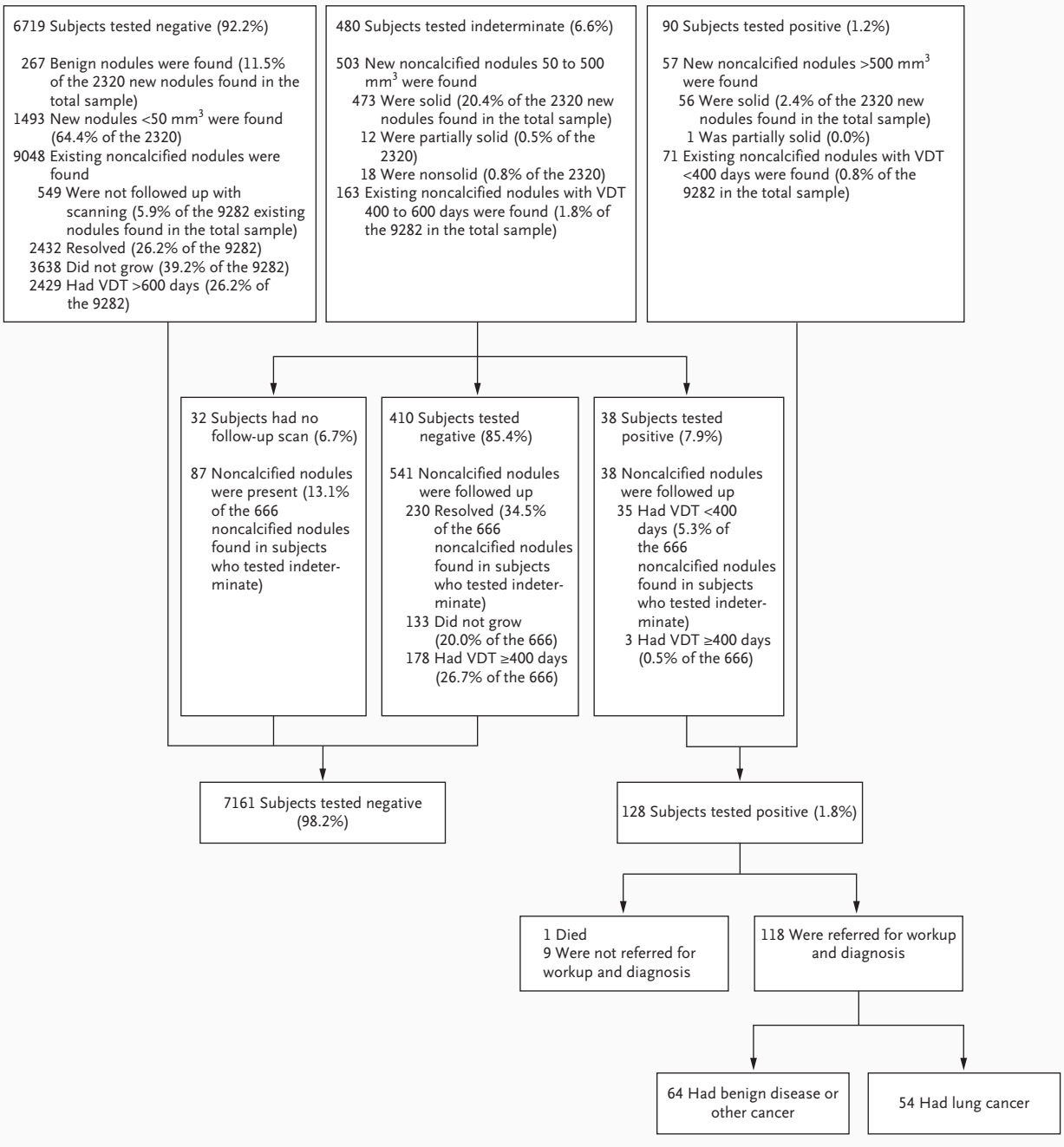

Figure 2. Results of the Second Round of Screening.

Some participants had more than one nodule. VDT denotes volume-doubling time.

one of these nine, lung cancer was found 23 months after the first detection of the nodule in a nodule that had not been seen previously. Of the remaining 64 subjects with a positive scan, 62 had benign disease and 2 had another cancer (1 a thymoma and 1 lymphoma).

There were two subjects with suspicious lesions from whom no tissue could be obtained for histologic diagnosis. These subjects were treated with high-dose radiotherapy because the lesions were new and growing and were positive on a PET scan. The 54 participants with lung cancer

had 57 cancerous nodules, 42 of which (73.7%) were classified as pathological stage I, including 3 that were synchronous double tumors. The lung-cancer detection rate was 0.5% (40 of 7289) during the first year after the second-round screening and 0.8% (57 of 7289) for the entire 2-year period after the second and third rounds of screening. One stage IV small-cell and one stage IV large-cell interval carcinoma, both of which were present in nodules that had been absent at the time of the second-round screening, were diagnosed during the first year after the second-round screening. The sensitivity of the second-round screening was 96.4% (95% CI, 86.8 to 99.1), the specificity was 99.0% (95% CI, 98.7 to 99.2), the positive predictive value was 42.2% (95% CI, 33.9 to 50.9), and the negative predictive value was 99.9% (95% CI, 99.9 to 100.0).

ADDITIONAL DIAGNOSTIC INVESTIGATIONS

The recall rates for CT scans among participants with indeterminate test results were 19.0% and 3.8% in rounds one and two, respectively (Table 2 in the Supplementary Appendix). No diagnostic PET or PET–CT scanning was performed in participants with positive test results, and fine-needle biopsy procedures were performed in less than 1% of the subjects. The rate of invasive diagnostic procedures was 1.2% in round one and 0.8% in round two.

DISCUSSION

In a population that was at an increased risk for lung cancer, our strategy of screening for lung cancer with the use of volume CT diminished the need for follow-up evaluation in participants with an indeterminate test result. This strategy was especially useful during the second-round screening. It reduced the number of follow-up examinations in participants with a positive test result without reducing the overall sensitivity of the technique, as compared with that reported in the literature.[4-8,18-23] This report concerns itself only with how to deal with an abnormality that has been detected on a CT scan in this population; it does not address the usefulness of screening for lung cancer with the use of CT scanning.

The rate of interval cancers that were found in participants in our trial was similar to that found in participants in other trials.[20] The proportion of early (stage I) lung cancers detected in round one (63.9%) was similar to that found in other randomized trials,[18,19,23] but lower than that found in nonrandomized trials (e.g., the proportion in the International Early Lung Cancer Action Program [I-ELCAP] was 86%, and the proportion in a trial performed at the Mayo Clinic was 75%).[6,7,20] The lung-cancer detection rate in round one in I-ELCAP was higher than that in NELSON (1.3% vs. 0.9%),[7] despite similar median ages of the participants and a higher number of pack-years smoked by participants in NELSON. The discrepancy was probably due to the fact that the proportion of women, who tend to have slow-growing cancers,[24,25] was higher in I-ELCAP than in NELSON. Moreover, in I-ELCAP surgeons removed any nonsolid nodule that was larger than 8 mm, instead of waiting for the nodule to grow before removing it, as was done in NELSON. In our trial of subjects who had an increased risk of lung cancer, we found that the chances of finding lung cancer on a CT scan at 3 months, 1 year, and 2 years after a negative first-round test were 0, 1 in 1000, and 3 in 1000, respectively.

In round one, the proportion of invasive procedures that revealed benign disease was 27.2%, which is similar to that found in other trials.[5,6,19,21,22,26-30] The advantages of volumetric measurements become fully apparent when a volumetric comparison can be made with a previous indeterminate CT scan. Because there were no comparative CT scans available at round one, the first-round recall rate was almost as high as that in other trials (Table 2 in the Supplementary Appendix). The LungCare software version that we used is not proprietary and can be used with any CT data set, regardless of the CT system, for evaluation of solid nodules and the solid component of partially solid noncalcified nodules smaller than 500 mm^3. With manual correction, the mean relative deviation from the true lesion volume was only −0.3±6.5% for these types of lesions.[13]

As an absolute standard for negative test results, we used the absence of lung cancer after 2 years of follow-up, a period that is considered to be sufficient for concluding that a nodule is benign.[2] The 400-day threshold for volume-doubling time that we used was based on current opinion that lung cancers with a volume-doubling time of 400 days or more are overdiagnosed cases.[24,31] A volume-doubling time of 500 days

is regarded as the upper limit for lung cancer, even though some tumors may grow more slowly[32-34]; our upper limit was set at 600 days. If a lower upper limit had been used, the rate of false negatives would have increased, but the rate of false positives would have decreased. Therefore, the ranges for volume-doubling time that we used are not definite and could be improved. Finally, before we can make clinically directive recommendations, our strategy requires validation in an independent study.

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