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Original Research

PULMONARY PROCEDURES

The Role of Conventional Bronchoscopy in the Workup of Suspicious CT Scan Screen-Detected Pulmonary Nodules

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Background: **Up to 50% of the participants in CT scan lung cancer screening trials have at least one pulmonary nodule. To date, the role of conventional bronchoscopy in the workup of suspicious screen-detected pulmonary nodules is unknown. If a bronchoscopic evaluation could be eliminated, the cost-effectiveness of a screening program could be enhanced and the potential harms of bronchoscopy avoided.**

Methods: **All consecutive participants with a positive result on a CT scan lung cancer screening between April 2004 and December 2008 were enrolled. The diagnostic sensitivity and negative predictive value were calculated at the level of the suspicious nodules. In 95% of the nodules, the gold standard for the outcome of the bronchoscopy was based on surgical resection specimens.**

Results: **A total of 318 suspicious lesions were evaluated by bronchoscopy in 308 participants. The mean ± SD diameter of the nodules was 14.6 ± 8.7 mm, whereas only 2.8% of nodules were > 30 mm in diameter. The sensitivity of bronchoscopy was 13.5% (95% CI, 9.0%-19.6%); the specificity, 100%; the positive predictive value, 100%; and the negative predictive value, 47.6% (95% CI, 41.8%-53.5%). Of all cancers detected, 1% were detected by bronchoscopy only and were retrospectively invisible on both low-dose CT scan and CT scan with IV contrast.**

Conclusion: **Conventional white-light bronchoscopy should not be routinely recommended for patients with positive test results in a lung cancer screening program.**

Trial registration: **Nederlands Trial Register; No.: ISRCTN63545820; URL: www.trialregister.nl.**

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Abbreviations: ACCP = American College of Chest Physicians; NELSON = Dutch-Belgian Randomized Lung Cancer Screening Trial; NPV = negative predictive value; VDT = volume-doubling time

Depending on the geographic region, 26% to 51% of participants in multidetector CT scan lung cancer screening trials showed at least one noncalcified pulmonary nodule on their CT scan.[1-4] The likelihood of these nodules being malignant depends on size.[1,5] The Fleischner Society guideline recommends a recall CT scan, PET scan, or biopsy for nodules > 8 mm detected on a CT scan[5] but not by bronchoscopy. The American College of Chest Physicians (ACCP) guideline recommends only evaluation by bronchoscopy under the condition that an air bronchogram is present on CT scan or in centers with expertise in newer techniques.[6,7] Literature on the role of newer techniques, such as ultrathin bronchoscopy, autofluorescence bronchoscopy, and CT scan-guided bronchoscopy in lung cancer screening settings is sparse. To our knowledge, a study by McWilliams et al[8] is the only one to report on the role of autofluorescence bronchoscopy in a lung cancer screening trial. The diagnostic yield of bronchoscopy to evaluate solitary pulmonary nodules outside a CT scan screening program varies

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from 51% to 76%[9-14] and highly depends on the size and location of the nodule.[9,10,13-15]

The nodule management strategy of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) is only based on the size and the volume-doubling time (VDT) of nodules detected by CT scan without the use of fine-needle aspiration, PET scan, or evaluation after antibiotics.[1] Positive test results were referred for the workup of suspicious nodules, which included a physical examination, a standard CT scan with contrast, and bronchoscopy.[5,6,16,17]

Recently, a large randomized lung cancer screening trial showed a 20% mortality reduction with low-dose CT scan screening.[20] In the low-dose CT scan arm, 320 subjects (1.8% of positive test results) underwent bronchoscopy without biopsy or cytologic testing, whereas 391 subjects (2.2% of positive test results) underwent bronchoscopy with biopsy or cytologic testing. The investigators did not report on the diagnostic performance of bronchoscopy in their study. In the National Lung Cancer Screening Trial, McWilliams et al,[21] offered all participants an autofluorescence bronchoscopy to detect central airway lesions, and 67% (378 of 561) underwent the procedure. Ideally, all subjects should have undergone bronchoscopy for this purpose. Four of 22 subjects (18%) were given a diagnosis of radiologically occult lung cancer following bronchoscopy. In McWilliams et al,[21] the purpose of bronchoscopy appears to have been inspection of the central airways in about 45% (320 of 711) of cases, whereas in the other cases, cytology or histology specimens were obtained. It is unclear to what extent the ACCP guidelines were followed. In both studies, no nodule criteria were specified in the decision to perform bronchoscopy.

So far, lung cancer screening trials do not carry specific recommendations with respect to the role of bronchoscopy in the workup of suspicious nodules after a positive test result,[2,18,19,22] and a significant number of bronchoscopies have been performed.[20] Screening detects more early-stage lung cancers, whereas advanced-stage lung cancers that are present as interval cancers amenable to bronchoscopy are excluded from analyses.[1] Our hypothesis was that the diagnostic value of bronchoscopy in this workup process might be low because suspicious nodules are usually small and often peripherally located.[1,18,19] If this is true, bronchoscopic evaluation could be eliminated from the standard workup of suspicious CT scan-detected nodules, which would enhance the cost-effectiveness of a lung cancer screening program and avoid the harms of bronchoscopy. Therefore, our objective was to investigate prospectively the diagnostic value of bronchoscopy in the NELSON trial and to evaluate the diagnostic yield of the various diagnostic techniques used during bronchoscopy.

Materials and Methods

Study Population

The nodule management strategy of the NELSON trial has been described earlier.[16,23] In short, 15,822 individuals with a high risk for lung cancer were randomized either to a low-dose CT scan (n = 7,915) during baseline screening (first round), 1 year later (second round), and 3 years later (third round, 2 years after the second round) or to no screening (n = 7,907). All consecutive participants with a positive test result during baseline screening and the second and third rounds between April 2004 and the end of December 2008 were included in this study. A test result was considered positive when a pulmonary nodule >500 mm^3 (>9.8 mm in diameter) was detected or when the nodule was growing with a VDT of <400 days.[1,16,21] If the solid component of the nodule was 50 to 500 mm^3, the test result was undeterminable, and a repeat scan was done to assess the VDT. When the VDT was <400 days on the repeat scan, the test was considered positive; otherwise, it was negative.[1,16] The NELSON trial was approved by the ethics committees of all participating centers, and all participants provided written informed consent (approval number IRB00001838).

Bronchoscopy

Conventional bronchoscopies were performed by experienced pulmonologists working at the four screening sites in The Netherlands (Utrecht, Groningen, and Haarlem) and Belgium (Leuven).[16] During white-light bronchoscopy, bronchial washings were performed for cytology and culture, whereas bronchial brushings and biopsy specimens were taken (52C-1 forceps) in the case of central lesions. In $<1\%$ of cases, biopsy was performed under fluoroscopic guidance. The bronchoscopists did not use CT scan fluoroscopic guidance or ultrathin bronchoscopes. A flexible

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