Editorial

Reconsidering lung cancer screening: is biannual screening possible?

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The results of the National Lung Screening Trial (NLST) (1) have catalyzed an important change in lung cancer detection and management procedures in some countries, particularly the USA. After three screening rounds and an approximately 7-year follow-up, this study was the first to demonstrate that low dose computed tomography (LDCT) could reduce lung cancer mortality by 16% (2) when compared to chest X-rays. No previous studies were able to demonstrate this effectiveness for different screening tests (such as X-rays, or X-rays combined with sputum cytology).

The NLST included smokers and ex-smokers of more than 30 pack-years. In the case of ex-smokers, only those who quit fewer than 15 years ago were included (1). The age range of participants was 55 to 74 and the final number of participants was 53,454, with 26,722 participants in the LDCT arm and 26,732 in the chest X-rays arm. The NLST is a high-powered study which focuses on the detection of statistically significant differences between both screening arms. It has also been criticized for including participants who are on-average younger than average lung cancer patients (only 25% of the NLST participants were older than 65, while 75% of all cases diagnosed in the USA were in patients older than 65) and also because participating centers had lower surgical mortality and morbidity than the national average. So much so, they have been recognized as "excellent" (3,4).

The positive results of the NLST have led many North-American Medical Scientific Societies to recommend screening smokers and ex-smokers who fulfill the inclusion criteria of the NSLT [reviewed in (5)], though unanimous consensus has not yet been established. The American Academy of Family Physicians does not currently support lung cancer screening (6) and many European Medical Societies do not yet recommend lung cancer screening using LDCT. The upper age limit of screenees was increased to 80 years after a report by the United States Preventive Services Task Force regarding lung cancer screening (7).

Since the publication of the NLST many modeling studies have been published analyzing the benefits of screening in different subgroups (particularly, the number of participants needed to screen to detect one lung cancer) (8), the amount of overdiagnosed cancers (9), the cost-effectiveness of screening (10), and other aspects related to lung cancer screening. Nevertheless, no study has been published using NLST patients to ascertain the potential benefits of biannual screening compared to annual screening using LDCT prior to the recent work published by Patz *et al.* (11), which is the topic of this editorial.

This publication analyzes lung cancer incidence and mortality, comparing participants with positive (and negative) findings in baseline screening with participants who have negative baseline screening results. The authors observed that lung cancer incidence in patients negative at baseline screening was a 56% lower than in all patients combined (both positive and negative). Lung cancer mortality was a 67% lower in patients negative at baseline as compared to all patients' incidence (11). The time elapsed between screening and diagnosis for patients with a

negative initial screening was also longer than for all eligible participants at baseline screening (2.2 *vs.* 3.3 years).

Following this description of the main results of the study by Patz *et al.* (11), it is necessary to describe some possible consequences of biannual screening. We must highlight that some of these reflections are not based in the existing literature because there are no studies with the power of the NLST and practically all published studies using LDCT screening have used annual screening rounds.

Overdiagnosis and biannual lung cancer screening

Overdiagnosis can be defined as a screening detected lung cancer that would not have progressed or become life-threatening if left undetected. It has been reported that LC screening with annual LDCT could have an 18% overdiagnosis rate (9). Some authors have even estimated that this figure could be as high as 26% (12). This percentage can be even higher if one considers that the NLST uses chest X-rays as the comparison arm—a technique that the Mayo Lung Action Project has shown to cause overdiagnosis (13). A 2-year screening interval may alter the rate of overdiagnosis. Lung nodules detected with this screening interval may have a higher diameter when detected as they would have 2 years to grow. The diameter and volume of lung nodules are predictive of higher malignancy risk. There could be fewer low-diameter or low-volume nodules in a 2-year screening than in a progressive summation of the percentages of relatively small nodules obtained in annual screenings. This point is supported by the observation that lung cancer incidence in a 2-year screening is not higher than the incidence observed for participants with an initial positive screening (11). The diameter of a nodule deemed positive is also of particular importance with respect to overdiagnosis. The NLST has been criticized for using a 4 mm cut-off point, a threshold commonly considered too low. For a biannual screening, this threshold should be reassessed and possibly increased. Furthermore, the use of a volumetric approach instead of a diametric approach has been demonstrated to reduce the number of false positive outcomes (14) and potentially the overall overdiagnosis rate.

Biannual screening interval and cost-effectiveness of lung cancer screening with LDCT

Lung cancer screening using LDCT is expensive. Even if it is assumed that it is beneficial if the number needed to screen to detect one lung cancer is low, a large amount of resources must be allocated to start and maintain the screening program (15). If screening frequency were to be reduced to a biannual screening, its cost could be reduced approximately by half (excluding infrastructure resources). Assuming no positive result, each screenee should be screened bi-annually using the same structure and resources used for annual screenings. Because we assume that the number of false positives would not be higher with biannual compared to annual screening, the cost of the work-up of positive nodules should be the same for both screening modalities or even lower if the number of false positives is reduced. In fact the paper by Patz *et al.* has observed that the number of positives in the second screening for those participants with negative baseline screening was 11%, compared to 27% of positives in the first and second rounds of the NLST trial (1). Taking into account the availability of LDCT devices, the same device could be used by double the number of patients using biannual screenings. Consequently, if a screening program is to be implemented in a given area, half of the LDCT devices will be needed if biannual screenings are used.

Anxiety and two-year screening interval

A further advantage of a potential biannual screening could be the possibility of reducing anxiety in patients. It has been observed that lung cancer screening may cause anxiety in participants (16). If the screening is performed only every two years, patients may be less anxious due to their involvement in a lung cancer screening program and the possible anticipation of a positive result. Those patients with positive nodules should undergo a tailored follow-up according their respective screening's result—this would also occur in an annual screening.

Biannual screening and radiation exposure

LDCT entails exposure to radiation to the magnitude of 1–1.5 mSv per screening (1). Though this radiation is low compared to standard computed tomography, patients will receive an annual dose if they are going to be screened annually during 25 [55–80] years. Some authors have estimated that the dose of radiation received by screening participants in a LDCT screening program would be even higher than that received by either workers in nuclear power plants or survivors of nuclear explosions (17). Furthermore, approximately 1 in 4 screenings will have a

positive result and a follow-up using computed tomography will be needed in most cases (1). Biannual screening will reduce the amount of radiation received by a half and this is particularly important if we are to consider that the lung is a radiosensitive organ and that there might be an additive effect of tobacco consumption and radiation.

Biannual screening for lung cancer and potential negative effects

A lower screening frequency may have negative side effects even if it is assumed that the screening's yield is similar or even better than annual screenings (in terms of number of false positives, positive predictive value, downstaging, etc.). Perhaps the most important limitation is that current smokers are more likely to forget or give less importance to the need of quitting tobacco. All current recommendations favoring lung cancer screening highlight the need of accompanying screening with subsequent interventions directed at avoidance of tobacco consumption for current smokers (7). If screening frequency is reduced patients may perceive the erroneous message that smoking is not as important in lung cancer development or that its harmful effects might be somewhat attenuated by screening. To avoid this possibility, patients should receive strong and structured tobacco counseling each time they are screened or, at least, current smokers should be approached annually with tobacco counseling. If we are to neglect this approach, part of the benefit achieved through screening will be lost.

More research is needed to recommend biannual screening

While the study by Patz *et al.* (11) supports biannual screening, we need more information before making changes to the current screening recommendations. A thorough risk-benefit analysis comparing advantages and disadvantages of lung cancer screening is needed. A recently published report analyzing SEER registered patients has concluded that lung cancer progression is faster for Caucasians compared to other races. It would take less than one year for a lung cancer to progress from an IA or IB stage to a IIIA or IIIB stage and the authors suggest that an annual screening might not be enough to detect and avoid lung cancer detection in advanced stages (18). These results are partly supported by the findings of the commented study, where 40% of lung cancers were detected in T1 screening while those negative at baseline screening were at stage III or IV (11). This percentage was 37.8% in the first round of the NLST (1). The results of the Nelson study could provide interesting information to compare the results of the current study since they have used screening at years 1, 3 and 5.5 following initial screening, but its final results have not been published yet (19).

The authors recognize that annual LC screening is not based on biological evidence but on organizational criteria and the comments accompanying the paper supports the same affirmation (20). Nevertheless this is not a rigorously defined reason. Researchers and physicians have been using biannual screening for years for cancers with established screening programs, such as breast cancer. This is due to the natural history of the disease, for which it has been demonstrated that biannual screening is feasible and fits better with breast cancer natural progression.

Conclusions

The paper by Patz *et al.* (11) has shown, using a large sample size, that biannual screenings of lung cancer with LDCT might be more beneficial to patients than annual screenings. This screening modality would be also more affordable for healthcare systems. Nevertheless, this study was not primarily designed to compare annual with biannual screening results. A specifically designed study could have different results when biannual screening is maintained over time. A study of this type should have at least 3 or 4 screening rounds to facilitate obtaining robust results. A further question is how to reconcile this screening with tobacco counseling in smokers. More research is also needed to identify which ever-smokers are more prone to develop lung cancer (from a molecular point of view) and this could be useful to perform a tailored screening directed to them. Finally, there are still many doubts regarding the pertinence of lung cancer screening (annual or biannual) if we compare the benefits (16% of reduction of lung cancer mortality) to the possibility of overdiagnosis, high rates of false positive results, deleterious effect of radiation exposure, and overall cost.

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Footnote

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