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Young at heart - is that good enough for CT screening?

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When it comes to data, the National Lung Screening Trial (NLST) just keeps on giving. Following the revolutionary results that came from the main trial demonstrating an improvement in lung cancer-specific and all cause mortality of 20% and 6.7% respectively (1), a number of secondary analyses have been carried out by Tanner and colleagues looking various issues such as screening those with racial differences (2) and those who have achieved smoking abstinence (3). The same authors report a study that addresses another important, and as yet unresolved issue - screening the older patient with comorbidities (4). The United States Preventative Services Task Force (USPSTF) statement of 2013 (5) recommends an upper age limit for screening of 80, and recognises that screening may not be appropriate in older individuals with multiple comorbidities. However neither the USPSTF, nor the American College of Chest Physicians (6), or National Comprehensive Cancer Network (7) give more clear guidance on what degree of comorbidity should preclude screening. The paper by Tanner and colleagues brings us one step closer to understanding the complex interplay of factors influencing this sensitive issue.

In this study, Tanner and colleagues compare outcomes of a cohort of 9476 patients from the SEER-Medicare dataset with stage 1 Non Small Cell Lung Cancer (NSCLC) aged 65-74 with NLST participants of the same age. The covariates of age, gender, smoking status, cancer stage and number of comorbidities, using the Deyo-modified Charlson Comorbidity Index (CCI), are examined against the outcomes of post-operative mortality, and 5-year lung cancer-specific and all cause survival. Importantly, they showed that surgical mortality and 5-

year lung cancer-specific survival was similar in the SEER-medicare 'NLST eligible' population (i.e. those with a CCI ≤1) to that reported in NLST. They also showed that surgical mortality and 5-year survival are poorer in those with a CCI of ≥2, and that patients who had radiotherapy had poorer 5-year survival than those who had surgery. They therefore suggest that screening patients with >1 comorbidity, and who would not be eligible for surgical resection may not be of value.

One concern, however, is that it is presumed that patients in the SEER-Medicare database who had radiotherapy, had curative doses of treatment. If some patients had in fact been treated with palliative doses, the outcomes from the SEER database may be underestimated. Furthermore, the authors acknowledge that the impact of stereotactic ablative radiotherapy (SABR) has not been evaluated and SABR may be more suitable than surgery for many patients with co-morbidities. While randomised controlled trials of SABR versus surgery have failed to recruit, a pooled analysis of available randomised patients suggested equivalence (at least) of SABR compared to surgery (8). Other available data are limited by selection bias with fitter patients being allocated surgery, and also the lack of histology in some patients who undergo SABR. (9). Nevertheless (even if surgery were to remain the superior treatment), more widespread availability of SABR would improve survival rates in the non-surgical group, thereby diminishing the differences in survival and potentially making screening patients who may not be surgical candidates, more worthwhile than suggested in the present study.

A second issue is with the use of the CCI. The Deyo-modified CCI, is a score that was developed for its strengths in measurement using available administrative codes, in a cohort of patients undergoing lumbar spinal surgery(10). This patient population and range of

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procedures are however, radically different to those encountered in lung cancer. Furthermore, the dependence on coding, lack of consideration of the severity of the comorbid conditions, and inability to place greater importance on conditions that more greatly impact thoracic surgery morbidity are further limitations associated with use of this score. Current guidance on determining fitness for thoracic surgery(11, 12) are based upon the presence of various cardiac diagnoses (some of which are not present in the CCI such as 'significant arrhythmia') and measuring lung function. More crudely, the ability to climb 1 flight of stairs would eliminate any serious cardiac concern, and 3 flights of stairs would suggest an FEV_1 of at least 1.7L (13). Borderline patients are advised to undergo exercise testing such as 6-minute walk testing or cardio-pulmonary exercise testing. But this is a complex assessment that is not feasible prior to offering LDCT screening. Various surgical scoring systems have also been proposed including 'Thoracoscore' (14) and the 'National Lung Cancer Audit (NLCA) score(15) which present a more structured and effective method of assessing risk if successfully validated, but both may be difficult to assess from heath care records alone and so therefore not feasible prior to invitation to lung cancer screening. More research to determine how best to assess comorbidities in a practical way, and using available data codes is needed.

In addition, it is known that LDCT screening has the potential to cause harm and the rate of these harms has been previously estimated using different entry and exit ages into screening (16). It is possible, that the rate of these harms may be negatively impacted by not screening the older population with comorbidities such as Chronic Obstructive Pulmonary Disease (COPD). Older patients with COPD are acknowledged to have higher lung cancer risk and event rate(17), so excluding this group may result in a higher number needed to screen (NNS) to save one life from lung cancer than suggested by NLST as well as resulting in higher rate

of overdiagnosis. Furthermore, as per data published by Kovalchik et al(18), the false positive rate is reduced if screening is restricted to those patients with higher lung cancer risk, which in turn is largely influenced by age and smoking history, though this is slightly inconsistent with the reports by Pinksy et al (19) that found that older NLST participants had more false positives.

Despite these limitations, this study has addressed an important issue by comparing real-life outcomes with those in the trial setting, and has provided evidence that the results from NLST are generalizable to the older population. The findings around patients with comorbidities have highlighted the need for further research to better establish how we assess surgical risk in this population, as well as the importance of measuring co-morbidities in patients with lung cancer and the potential need for a lung cancer specific co-morbidity tool to be validated (e.g. (20)). It is crucial that a balance is achieved between not inviting individuals who may benefit from screening, versus ensuring that all screened individuals can benefit from lung cancer screening. Unfortunately a randomised controlled trial comparing LDCT screening against a control of no screen specifically in the older population with comorbidities is unlikely to be carried out. Despite the concerns that competing mortality in this group of individuals would reduce the mortality benefit seen compared with that seen when screening the younger, less comorbid population, it is possible that older patients with more than one comorbidity, particularly if mild in severity, will still derive some benefit from screening, particularly as treatments such as SABR are more widely carried out.

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