Editorial

Measures of outcome in lung cancer screening: maximising the benefits

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In their article, Miller and colleagues report on the survival results of smokers enrolled in their community-based multicentre computed tomography (CT) screening program for lung cancer (1). In a cohort of 1,267 primarily moderate to high risk smokers, followed with annual CT screening for 5 years, 36 subjects underwent biopsy, 30 were confirmed to have lung cancer of which 28 were primary lung cancers. Overall 5-year survival was 64% and 5-year lung cancer specific survival was 71% in the screened patients, where the overall-survival compared favourably to the 5-year survival in a group of non-screened lung cancer patients (64% *vs.* 19% respectively, P<0.001) (1).

While these investigators are to be congratulated for successfully conducting a CT-based screening program for lung cancer, their results do not in themselves provide convincing evidence that CT screening for lung cancer is beneficial (2,3). The single most important aspect of this study is that survival is an unreliable statistic to use to measure success from screening (2,3), especially in a single arm study (1,4). As set out below, this is particularly the case for CT screening for lung cancer where a number of specific performance-related issues have remained relatively poorly appreciated (2,3,5-7).

First, the National Lung Screening Trial (NLST) reported a 20% reduction in lung cancer specific mortality in the CT arm compared to the chest X-ray (CXR) arm (8). This correlated with an absolute reduction in lung cancer mortality in the CT arm of approximately 0.33% compared to the CXR arm (about 3 less lung cancer deaths per 1,000 people screened). However, reduction in mortality correlates poorly with survival as survival takes no account of biases such as lead time and length time bias (2,3). Survival makes no consideration of over-diagnosis, histology shift masquerading as stage shift and competing cause of death (see below). Survival statistics are also very sensitive to whether the lung cancer cases reported include all lung cancer cases in the screening cohort or just those detected by the screening process. The uncertainty surrounding survival benefit is further exacerbated when the control group has not been randomized so that the risk of getting lung cancer, and dying from lung cancer, are at least comparable prior to starting the screening intervention. Over-diagnosis, which describes the treatment of otherwise indolent lung cancers, was estimated to be 18% in the CT arm of the NLST relative to the CXR arm (9). However based on the European CT screening studies, where outcomes from CT screening are compared to no screening, the real rate of over-diagnosis appears to be closer to 30–40% if estimated from excess cancers in the CT arms of these studies (10,11). The inclusion of over-diagnosed lung cancer cases in survival statistics creates an artificial elevation in the survival rates for lung cancer (2,3,6). This is because survival rates include lung cancer cases, with clinically indolent behaviour, for whom dying over the duration of the study would not have occurred in the absence of screening (termed lead time bias). This is why randomization of comparably eligible smokers into a control arm is so important to establishing beneficial outcomes from screening (8).

Second, it is now clear that stage shift differences do not always translate into survival benefit because the lung cancers identified during CT screening are biologically different to those that are identified during no screening (termed length time bias) (12,13). We have shown this in

a post-hoc analysis of the NLST where a favourable stage shift in the CT arm of "healthy smokers" (with no airflow limitation and higher percentage of early stage cancers) could be almost entirely attributed to histology shift favouring indolent cancers (14). This may be even more evident in the European CT screening trials where much higher numbers of adenocarcinomas, and cancers formerly described as bronchioloalveolar carcinomas (BAC), have been consistently identified in the CT screening arms compared to no screening (15). In another post-hoc analysis of the NLST up to 80% of the over-diagnosed cancers were BAC in histology (9). In other words, the diagnosis of BAC is a useful marker for the tendency to over-diagnosis and overtreatment. These BACs make up to 60% of all lung cancers identified in CT screening studies of Japanese non-smokers (16). On this basis we suggest that combining this group of cancers into the adenocarcinoma group will potentially disguise (under-represent) the proportion of over-diagnosed lung cancers and thus unnecessary treatment in a CT screening program. It will also spuriously improve survival statistics (2,3). That said in the study by Miller and colleagues (1), there were no lung cancers of the BAC histological subtype although about 4 would be expected based on the NLST results (12% were BAC in the CT arm of the NLST) (14). We suggest that over-diagnosis and histology shift may underlie an apparent advantageous stage shift and serve to overestimate survival in those undergoing CT screening (2,3). In stark contrast, in a randomized study this over-diagnosis group may potentially be shown to contribute to increased morbidity (from unnecessary surgery with post-operative complications), yet contributing nothing to any reduction in mortality. In this regard, it has been reported that the mortality and morbidity associated with work up of benign nodules was 3- to 4-fold higher in the CT arm compared to the CXR arm of the NLST (11).

Third, probably the least discussed aspect of CT screening for lung cancer to date is the issue of competing causes of death (6,7). Smokers who are eligible for lung cancer screening are in general older and have smoked for many years (15). We have reported that about 35% of NLST participants have underlying COPD based on pre-bronchodilator spirometry although 70% are unaware of this (14). Other relevant lung cancer risk factors include low body mass index, family history of lung cancer or past history of another cancer (17-19). While this group of smokers are undoubtedly at greater risk of lung cancer in absolute terms, they are also at risk of dying from other causes (6,7). In a post-hoc analysis of the NLST (N=18,475), we have reported that having COPD (pre-bronchodilator FEV_1/FVC <0.70) was associated with a 2-fold greater risk of developing lung cancer, a 2.3-fold increase risk of dying of lung cancer and a 1.9-fold increase risk of dying of other causes, when compared to those with no COPD (7). Interestingly in those with COPD, the lung cancer specific mortality reduction from CT screening *vs.* CXR, was only half that achieved in those with no COPD (reduction in lung cancer specific mortality was 15% in COPD *vs.* 28% in "healthy smokers") (7). We suggest that the reduced mortality reduction in those with COPD may result in part from early deaths from causes other than lung cancer eroding the value of screening (7,20). In unpublished results of a subgroup of the NLST, we recently found that only 23% of all deaths in the CT arm were from lung cancer, while 26% were from cardiovascular disease, 6% from respiratory disease, 19% from other cancers and 26% for the remainder. This means the over-all survival and lung cancer specific survival is also a function of the underlying risk in the group being screened. Smokers of lower risk in one screening study might survive better just because they have a lower overall risk of death and lower risk of dying of their lung cancer (15). This might be the case for screening studies including younger lighter smokers, and explain in part the apparent superior survival statistics described by IELCAP-based studies (1,21). The overall survival and lung cancer specific survival in our sub-analysis of the NLST (N=10,054 subjects), where there were 216 lung cancers identified in the CT arm, was 60% for overall survival and 65% for lung cancer specific survival. In regards to the former, this is slightly less than the 64% reported in the CT screening program of Miller and colleagues potentially reflecting the lower overall risk in their study of younger lighter smokers (1). With regards to the latter, our lung cancer specific survival of 65% is slightly lower than the 71% reported by Miller and colleagues which again may reflect the lower risk of the group being screened in their study, where only 54% of the lung cancer cases would be eligible for the NLST (1). These results fall far short of the 88% 10-year survival reported by the IELCAP investigators from their single arm study and cannot be easily reconciled with the study by Miller and colleagues using a similar protocol (1,4,21). We propose that a lower risk population in the IELCAP study was contributory. One important issue though is the IELCAP study only reported results on screen-detected lung cancers and did not include interval cancers (lung cancers not identified by the screening process) that have very poor survival. This means survival

rates is very dependent on just which lung cancer cases are being reported. In a post-hoc analysis comparing the IELCAP outcomes in only screen-detected lung cancers, with those from NLST, better survival in the former was attributed to a greater proportion of smaller cancers with stage 1 disease (21). However, the IELCAP participants were younger with lower pack year exposures, and likely less comorbid diseases like COPD, yet the effect of these differences on survival were not described in this study.

In conclusion, outcome measures that best reflect the benefits of screening are derived from mortality rather than survival statistics, in particular mortality rates compared to an identical group randomized to a different ("non-screening") intervention arm. Moreover, not only is a clinically significant reduction in lung cancer specific mortality important to achieve [e.g., 20% in the NLST, (8)], but also a reduction in overall mortality from screening is desirable (22,23). It is only with the latter that a screening intervention can be said to "save lives". It is interesting to note that despite a 20% reduction in lung cancer specific mortality in the NLST (8), an overall mortality reduction of only 7% was achieved and this difference has not been fully explained. As set out above, screening for lung cancer is unique among most screening programs in that participants are older with long smoking histories. This means comorbid disease is common and competing causes of death highly relevant to outcomes. We concur with those suggesting that there exists a "sweet spot" among smokers otherwise eligible for screening where the benefits clearly outweigh the harms and where mortality reductions, or number need to screen to avert one lung cancer death, are maximized relative to other causes of death (24,25).

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Footnote

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