Editorial

Inequivalence of non-aggressiveness in clinically diagnosed lung cancers and overdiagnosis in lung cancer screening trials

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Overdiagnosis (OD) designates the screen-identification of cancers which would not have become manifest within the lifetime of an individual due to some combination of indolent growth, immunological editing, limited metastatic potential, loss of vascular supply, and competing lethal morbidities. Of these variables, the existence and duration of exposure to competing morbidities is critical; it is most influenced by the subjects' age and the cancer's dimension and growth rate. Persons with OD lung cancer can only be harmed: they experience a circa 3% operative mortality (1), severe disability in many survivors (2), and a substantial reduction in longer-term disease-free survival, due to loss of pulmonary reserve (3). Accurate estimation of the magnitude of OD is therefore of great importance in assessing the benefit of screening.

OD can also occur when incidental lung cancer is identified in a chest radiograph (CR) taken for some reason other than lung cancer screening, which the authors designate as "clinically diagnosed" (4). There are a number of reasons to question the equivalence of the estimate of clinically diagnosed "non-aggressive lung cancer" (NLC) with estimates of OD in lung cancer screening trials. The most obvious are the far smaller dimensions of actionable nodules evident in computed tomography (CT) trials, which lead to lengthier exposure of detected cases to competing lethal comorbidities. Due to their lepidic architecture, CRs (*vs.* CT) are insensitive for detecting bronchioloalveolar carcinomas (adenocarcinoma *in situ*), which, because of their indolent growth, are far more likely to be OD. For example, Patz *et al.* estimated their CT OD at 79% (5). Other critical differences are clinical staging (c-stage) in the NLC study *vs.* pathological staging (p-stage) in intervention trials. Because c-staged stage I lung cancers (c-SILC) contain more understaged cases, their overall survival is expected to be less than p-staged stage I lung cancers (p-SILC), with a corresponding lower rate of OD.

Twenty six percent of all the patients were dropped from the NLC analysis because of undocumented tumor size, which might influence the NLC estimate. Additionally, of the 74% NLC with Surveillance, Epidemiology and End Results (SEER)-reported dimension, only 26% were ≤24 mm and only 4% <15 mm. In contrast, approximately 80% of CT identified lung cancers in the Early Lung Cancer Action Project were stage IA (≤30 mm) (6).

The Mayo program (MP) resembles the NLC study in that the cancers in both were CR-detected (7). The MP subjects differed in being healthy volunteers, youthful (≥45 *vs.* ≥65 years old), and comprised all stages and histologies, each of which diminishes expected OD. There were 206 *vs.* 160 identified cases in the MP screened *vs.* controls, an excess of 46; 46/206=22%. This percent OD is nearly 10-fold the 2.4% figure cited in the NLC analysis whose subjects were (presumably) less healthy, older, and confined to c-stage I non-small cell lung cancer (SINSCLC), prognostically the most favorable stage and histology.

Methodological differences employed in this analysis put

in question the putative comparability of non-aggressive and overdiagnosed lung cancer:

(I) Although a number of methods for ascertaining the magnitude of OD have been advanced, the prevailing method is case differential in screened *vs.* control cohorts after sufficient time has elapsed to permit the clinical appearance of most subclinical cases in the latter (8);

(II) The NLC series was confined to persons with untreated SINSCLC. The decision to decline resection for potentially curable disease often reflects inoperability due to known, competing, lethal morbidities. It may have been influenced by the population's age—67% were ≥75 years old. An explanation for why persons who ultimately declined surgery underwent invasive biopsy and staging procedures was not provided in the SEER database. This anomalous and unaccounted-for feature challenges the representativeness of their survival experience *vs.* persons in screening trials who chose to undergo resection;

(III) Smaller tumor dimension, by increasing the duration of exposure to competing lethal morbidities, increases the likelihood of OD. For example, six tumor volumes doubling times (circa 4 years) are needed to increase tumor size from 5 (actionable diameter in CT trials) to 20 mm (9). Approximately one-third of healthy white male smokers in their late 60s would be expected to succumb to all causes within 4 years during which interval a 5 mm lung cancer might remain clinically silent (10). Length biased sampling further favors the identification of slower growing lung cancer;

(IV) OD, measured as the excess cancers in screened *vs.* control cohorts after completion of follow-up, will be far higher in CT than in CR trials. In the large CR trials, the excess was 22–24% (11); in the NLST (*vs.* CR controls) it was 18% (5). The sum of the excess in CR *vs.* unscreened plus the CT *vs.* CR controls, 23% + (≥18%) ≥41%. In the three reporting European trials of CT *vs.* unscreened controls, the pooled excess was 48% (12-14).

Additional considerations

(I) Apparent screening OD is inversely related to the duration of follow-up, as more incidental cases are found, diluting true OD, which occurs only during screening;

(II) Contamination (CR or CT imaging) in the control cohort reduces the computed apparent OD;

(III) The comment, "*These results are useful for the management of clinically detected, early stage cancers and suggest that most cases should be considered for curative resection*" (4) is not entirely germane, for detection of any resectable lung cancer in an operable candidate is a compelling indication for intervention.

Conclusions

Estimation of non-aggressiveness in clinically diagnosed lung cancer does not provide a valid estimate of OD in lung cancer screening trials.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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