Possible overdiagnosis of early-stage lung adenocarcinoma among never-smokers in Taiwan

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To the Editor:

Overdiagnosis in cancer screening denotes the detection of cancer that does not cause premature mortality [1, 2]. A standard approach to estimate the magnitude of overdiagnosis is through randomised controlled trials and comparing the cancer incidence in the screened group with that in the control group [3]. Recent studies from Asian countries showed that the promotion of computed tomography (CT) screening among individuals who mostly never smoked was associated with a rapidly increased incidence of early-stage lung cancer, whereas a corresponding declined incidence of advanced lung cancer was not observed [4–6]. However, not all of these early-stage cancers were overdiagnosed. Notably, participants with completely resected stage IA lung cancer in the National Lung Screening Trial had a 5-year cumulative incidence of recurrence of 16%, and 81% of the recurrences were distant metastases [7]. As a tumour size of >1 cm is a significant predictive factor of growth in non-solid lung nodules [8], we hypothesised that adenocarcinoma *in situ* (AIS), bronchioloalveolar carcinoma (BAC) and minimally invasive adenocarcinoma (MIA) with tumour sizes >1 cm are unlikely to be overdiagnosed. We attempted to corroborate our hypothesis by comparing the survival of never-smoking patients with that of matched referents.

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EX-107-031). All patients with stage 0/IA lung adenocarcinoma aged 50–80 years and had never smoked were identified from the Taiwan Cancer Registry database (2011–2019). In this database, every lung cancer was pathologically verified and each patient's smoking status was comprehensively recorded, whereas atypical adenomatous hyperplasia was not registered. Each patient with stage 0/IA lung adenocarcinoma was matched with 10 referents randomly selected from the National Health Insurance-reimbursed beneficiaries based on age, sex, calendar year at diagnosis and quintiles of working salaries inferred from insurance premiums. Notably, both patients and referents were free from catastrophic illnesses, including all cancers, end-stage renal disease, organ (*e.g.*, heart) transplantation, autoimmune diseases, schizophrenia, prolonged mechanical ventilation because of end-stage heart failure, *etc.*, cirrhosis of the liver with variceal bleeding, and acute cerebrovascular disease before the year of diagnosis.

Both patients and referents were linked to the National Mortality Registry database and followed up until the end of 2020 for death information. Since a different categorisation of lung adenocarcinoma was proposed in 2011 [9] and the World Health Organization announced the new classification in 2015 [10], the terms AIS, BAC and MIA were used in a mixed manner during the study period. We classified AIS/BAC/MIA and non-BAC/MIA stage IA adenocarcinoma into tumour sizes ⩽1 cm, >1 but ⩽2 cm, and >2 cm but ⩽3 cm in data analyses. We applied the Kaplan–Meier method to estimate survival and compared patient and referents' survival using a log-rank test. Cox proportional hazards regression was performed to identify the predictors of mortality. R software (version 4.2.1) was used to conduct all analyses.

After excluding 1969 individuals with prior catastrophic illnesses, 8990 patients with stage 0/IA lung adenocarcinoma were identified. Irrespective of tumour size, patients with AIS/BAC/MIA did not experience excess mortality compared to the referents up to 10 years of follow-up (figure 1). Patients with AIS/BAC/MIA ⩽1 cm even had a better survival than the referents. The 10-year survival rates of patients with non-BAC/MIA stage IA adenocarcinoma >1 cm but ⩽2 cm and >2 cm but ⩽3 cm were inferior to

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10-year survival for never-smokers with >1 cm but ⩽3 cm AIS/BAC/MIA was not inferior to that of the matched referents, pointing to possible overdiagnosis. Clinicians might consider adhering to Lung-RADS and watchful waiting for these non-solid nodules. https://bit.ly/41U6kxs

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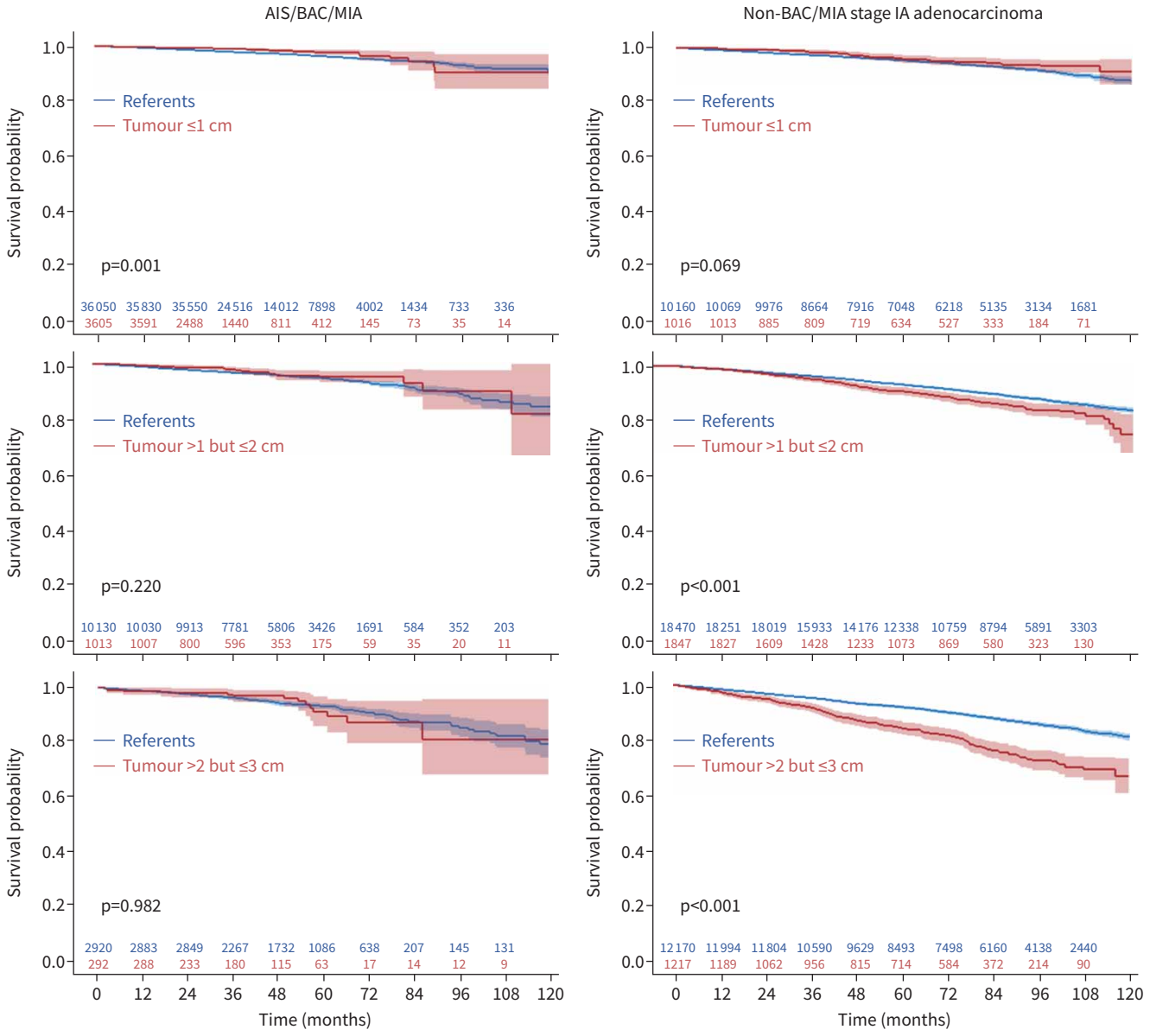

FIGURE 1 Survival of never-smoking patients (red) and age-, sex-, calendar year-, income- and catastrophic illness-matched non-cancer referents (blue). The coloured shadows illustrate the 95% confidence intervals. Numbers at the bottom of each diagram represent the numbers of individuals at risk. AIS: adenocarcinoma *in situ*; BAC: bronchioloalveolar carcinoma; MIA: minimally invasive adenocarcinoma.

those of the referents (log-rank tests, p <0.001). After adjustments for age, sex, calendar year, working salary and comorbidities (myocardial infarction, stroke, dementia, diabetes mellitus), the adjusted hazard ratios of patients *versus* referents were 0.64 (95% confidence intervals (CI): 0.44–0.92) and 0.76 (95% CI: 0.45–1.29) for patients with >1 cm but ⩽2 cm and >2 cm but ⩽3 cm AIS/BAC/MIA, respectively.

This study explored the progression of early-stage lung adenocarcinoma among never-smokers in Taiwan. After controlling for confounding by age, sex, calendar year at diagnosis, income and comorbidities, our study did not find inferior 10-year survival for never-smokers with >1 cm but ⩽3 cm AIS/BAC/MIA as compared to the referents, pointing to a possible overdiagnosis. Clinicians might consider adhering to Lung CT Screening Reporting & Data System (Lung-RADS) and watchful waiting for these tumours, which most often present as non-solid nodules [11]. In contrast, patients with non-BAC/MIA stage IA adenocarcinoma >1 cm but ⩽3 cm survived for a shorter time than the referents, indicating a solid nodule this size usually enlarges exponentially and is unlikely to be overdiagnosed [12].

Our study had limitations. First, although these cancers were not necessarily screening-detected, nearly all the patients underwent curative surgery. Whether the indolent tumour itself or curative surgery leads to non-inferior survival is unknown. It is almost impossible to randomise patients with lung cancer into an observational arm without therapy to determine their natural progression. Second, elderly patients with non-BAC/MIA stage IA adenocarcinoma >1 cm but ⩽3 cm could still be overdiagnosed owing to competing risks of mortality. Their inferior survival might result from a diminution in pulmonary function after surgery. Nevertheless, we excluded individuals with catastrophic illnesses from both the patient and reference groups. Most chest surgeons also assessed the post-operative pulmonary function before lung resection to avoid post-operative functional disability.

In conclusion, we failed to prove that AIS/BAC/MIA detected in never-smokers with a tumour size >1 cm is unlikely to be overdiagnosed. However, data from non-BAC/MIA stage IA adenocarcinomas with tumour sizes of >1 cm seem to corroborate this hypothesis.

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