Overdiagnosis Bias in Squamous Cell Cancer Clarifying Definitions

To the Editor:

I read with interest the article by Dr. Sato et al1 regarding the issue of overdiagnosis bias in radiographically occult squamous cell cancer published in a recent issue of CHEST (July 2004). There are, however, some details that we may learn from them, given their vast experience regarding this controversial matter.

In the Objective section of the abstract, the authors defined overdiagnosis bias as "a disease that does not produce signs or symptoms before the patient dies from other causes." However, in Figure 1, the survival curve of the resected patients seems misleading. In contrast to the natural course survival curve, the curve of the resected cohort does not match the data presented on page 110: "Of the 207 surgically treated patients, 125 (60%) died within 10 years (from primary lung cancer, 14 [11%]; from metachronous secondary lung cancer, 28 [22%]) [Table 2]. Thus, among treated patients who died, the rate of lung cancer death, including the first primary and metachronous second primary lung cancer, was 33.6% (42 of 125 patients)." Based on their definition, dying from other causes must also include all other causes, be it subsequent metachronous primaries and non-lung cancer-related causes.

In the "Results" section the authors stated that "The overall survival rates of the 44 untreated patients were 53.2% at 5 years and 33.5% at 10 years (Fig 1). Among the 44 untreated patients, 15 (34%) remained asymptomatic. Nine of the 15, however, died due to the following conditions: cardiovascular disease (4 patients); extrapulmonary malignancy (2 patients); emphysema (1 patient); and unknown causes (2 patients)."

Death rate at 10 years of the natural course in the untreated patients is thus 66.5%, as is shown in Figure 1. “Two thirds of the patients with such tumors in our study died from primary lung cancer within 10 years” is based on detailed analyses from the cancer registry showing clearly that all untreated individuals indeed died because of the untreated, early detected primary diseases (ie, disease-specific mortality). This remains unclear in the text. From our longitudinal data from 2 to 10 years of follow-up, still 22% of patients with bronchoscopically occult squamous cancers treated locally with proven cure at the initial site died due to non-lung cancer-related causes, having already the highest risk for acquiring subsequent primaries at the relative end of their field carcinogenesis period.2

One also reads in the “Results” section, “In the 10 patients with normal radiograph findings, there were no lung cancer deaths. However, patients who had abnormal shadows at the time of treatment had worse prognoses (Fig 2).” This seems to indicate lead-time bias, as one cannot easily compare the > 1-cm lesion already at the 30th volume doubling time to those sputum-positive radiographically occult cancers representing much earlier stage cases that may be in the severe dysplasia and carcinoma in situ stages.

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Figure 1. Survival curves of patients with radiographically occult squamous cell carcinoma who underwent resection.
To the Editor:

In my article, I focused on the natural course of patients who do not receive any treatment. I believe, however, that the treatment results may shed some light on this disease. So I also examined a group who had undergone complete resection. This group was not the same as the nontreated group.

In Figure 1, the end point was primary lung cancer death. As you know, some articles deal with such death as the end point. But in other reports, lung cancer death including primary and secondary lung cancer death is often considered to be the end point. In my personal communications, I asked Dr. G. M. Strauss (February 2002), a famous doctor dealing with the results of mass screening in the United States, which is better or which is most common: primary lung cancer death alone or all lung cancer death including primary and secondary lung cancer? He told me that in the United States, primary lung cancer death is commonly used. Therefore, in my article I used primary lung cancer death as the end point. Please see Figure 1 for the curves calculated by primary lung cancer death and all lung cancer death.

The algorithm of the Kaplan-Meier method is sometimes confusing and puzzling; therefore, I used Statview software (SAS Institute; Cary, NC). As you know, for calculating the estimated survival rate, we must know the follow-up period and the cause of death in each case. Because the duration of follow-up is different in each patient, simple calculation at 10 years is not the same as that of the value calculated by the software. I hope you are familiar with this software program and the Kaplan-Meier algorithm.

To understand the behavior of this type of lung cancer, we sometimes use lead-time bias and length bias, as you pointed out. Melamed et al\(^1\) mentioned that squamous cell carcinomas detected by cytologic examination alone are very slow growing and tend to remain localized until being detected by radiograph examination. As far as I know, the understanding of this type of early lung cancer is still unclear; therefore, I wanted to show our data.

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