Stage IA Lung Cancer Size and Survival

To the Editor:

I read the provocative article by Port et al1 (November 2003) with great interest, and I congratulate the authors on achieving the favorable outcome reported. The article demonstrated an association between stage IA lung cancer (LC) size, the predictor variable, and improved survival, the outcome variable. To correctly infer that the association is causal requires the elimination of potentially confounding variables—extrinsic factors that are associated with the predictor variable and a cause of the outcome variable. The means of ascertainment is a potential confounder, for if screening was found to be both causally related to survival and associated with ascertainment at a smaller size, it would account for this association.

Patients with screening-ascertained LC survive longer than patients with LC ascertained by other means because screening unavoidably entrains three biases: lead-time bias (earlier diagnosis prolongs survival); length-biased sampling (identification of a favorable spectrum of cases—those with slower growth. This bias has the greatest impact in prevalence screens); and overdiagnosis bias (identification of cancers that are not destined to be lethal, ie “pseudodisease”). Additionally, persons selected for LC screening are often, appropriately, pre-evaluated to exclude individuals with clinically significant comorbidities. For these reasons, a comparison of survival according to tumor diameter is valid only under the assumption that cases have been matched according to the means of ascertainment. They should, as well, be matched by other covariants—age and gender (which you corrected for in the Cox proportional hazards regression model) and comorbidity. The article did not describe by what means the LCs in 222 patients not identified by an ongoing CT screening program were ascertained. Participation in nonstudy screenings might account for the accrual of half of the patients during the last quarter of the study.

In the analysis of the cost-effectiveness of low-dose CT (LDCT) screening, based on the Early Lung Cancer Action Project prevalence study from which were drawn 22 LDCT-identified patients, the authors estimated that their median size was 10 mm (vs 20 mm for symptom-detected tumors).2 Three tumor volume doublings are required to double the diameter of a spherical tumor. Aoki et al3 reported that, among resectable adenocarcinomas < 3 cm in diameter, tumor volume doubling time (TVDT) ranged from 42 to 1,486 days, and half the tumors had tumor TVDTs > 1 year. For this reason, the expected lead-time bias imparted by LDCT screening would be approximately 3 years. The cost-effectiveness article2 employed a TVDT of 180 days, the doubling time of the “average adenocarcinoma,” most of which grow faster than stage IA adenocarcinomas. The improvement in survival produced by LDCT length-biased sampling and overdiagnosis are not quantifiable. Conflating the (smaller) LDCT-ascertained stage IA LCs (with their 3-year lead-time bias) with cases ascertained by other means undoubtedly contributed substantially to the difference in survival in patients with LCs ≤ 2 cm vs > 2 cm.

Of the 244 cases in the series, how many were ascertained by means of plain radiographic screening? How many by CT screening? How were these screening-ascertained cases distributed between LCs ≤ 2 cm vs > 2 cm? If you find that screening-ascertained cases were disproportionately associated with LCs ≤ 2 cm, you can correct for the confounding by stratification of the Cox proportional hazards regression model and survival plots according to whether or not the subjects had LCs that were screening ascertained (comorbidities can be assumed to be about equal in nonscreened individuals). If the survival advantage of smaller size persists after stratification, it would provide justification for substaging IA cases by size, as suggested.

If, however, survival after stratification is not significantly influenced by size, one could derive a crude estimate of the magnitude of LC survival improvement attributable to the biases introduced by screening by comparing the time required to achieve comparable survival levels in the screening-ascertained vs otherwise-ascertained cases. A comparison of LDCT-screened vs unscreened survival would be of particular interest. For example, if one found that LC survival was 80% at 5 years in patients with LDCT-identified stage IA LC vs 80% at 2 years in patients with stage IA LC identified without screening, it would imply that the aggregate effect of the biases imparted by LDCT screening was 3 years.

Apparently due to a transcription error, reference 9 in the article by Port et al1 was incorrectly cited as “in press.” The article by Marcus et al was published in the Journal of the National Cancer Institute in 2000 (volume 92; pages 1308 to 1316).

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References
2 Wisnivesky JP, Mushlin AI, Sicherman N, et al. The cost-

To the Editor:

We read with interest Dr. Reich’s comments regarding our recently published work that correlates tumor size with survival in patients with stage IA non-small cell lung cancer.1 His principal point is that the survival advantage we observed for tumors ≤ 2 cm in size was essentially due to the lead-time benefit conferred by the 22 low-dose CT screen-detected cases and other nonstudy screening cases. In our own view, our conclusions that size predicts outcome within stage IA is an indisputable fact that is consonant with the bulk of published clinical evidence.2–4 A single study5 proposed the contrary and highly unlikely proposition that size alone had no bearing on stage distribution and long-term outcome. The limitations of that study and its other design flaws have been carefully reviewed.1 In our study, we re-emphasize the primacy of tumor size as an independent predictor of outcome. Lead-time or not, the relevance of this observation to the practicing lung cancer clinician is immeasurable in an era of adjuvant, neoadjuvant, and targeted therapies. We obviously did not set out to disentangle the multiple and complex biases that shroud the issue of screening for lung cancer or any other malignancy. However, if one carefully examines the Kaplan-Meier disease-free survival estimates shown in Figure 2 of our article, one observes that the slope of the two curves approaches zero after 6 years for larger tumors (> 2 cm) and after 7.5 years for smaller tumors. The parallel orientation of the curves suggests to us that the survival advantage for smaller tumors represents a genuine effect of tumor size on long-term outcome beyond that imparted by lead-time alone. However, we submit that a definitive conclusion on the magnitude of lead-time effect can only be reached after sufficiently long follow-up (preferably > 10 years) in a controlled study design.

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Hydroxyethyl Starch-Induced Postoperative Bleeding in Cardiac Surgery Patients

More Trials Needed?

To the Editor:

Avorn et al8 (October 2003) report the results of a retrospective study among 238 coronary artery bypass graft patients at Brigham and Women’s Hospital showing hydroxyethyl starch (HES) exposure to be an independent dose-related risk factor for postoperative bleeding. Their study confirms the findings of five previous retrospective studies4–6 with a total of 1,812 patients, as well as our metaanalysis7 of 16 randomized controlled trials with 653 total patients. Based on previous retrospective studies and the metaanalysis, the Blood Products Advisory Committee of the US Food and Drug Administration voted overwhelmingly in 2002 to support a warning statement on the product labeling of HES regarding the evidence for excessive bleeding in cardiac surgery patients receiving HES. In 2003, a warning was added to the product labeling, recommending against the use of HES in cardiac surgery (package insert, Hospal; B. Braun Medical; Irvine, CA; revised March 2003; 6% hetastarch in 0.9% sodium chloride injection).

The copious evidence and recent regulatory action notwithstanding, Avorn et al advocate not the avoidance of HES in cardiac surgery but rather another randomized trial. Additionally, it continues to be the institutional policy of Brigham and Women’s Hospital that HES be used in preference to albumin for diverse fluid management indications including cardiac surgery.8 Avorn et al adumbrate, without substantiation, that the prior 16 randomized trials were of unsatisfactory quality. Yet, the randomization method was found to be inadequate in only 2 of the 16 trials, and exclusion of patients after study entry was reported in only 4 trials.9 Furthermore, the results were remarkably consistent, with higher postoperative bleeding among cardiac surgery patients receiving HES than albumin in 58% of randomized comparisons, including all three blinded trials.8

Avorn et al incorrectly state that in our metaanalysis we “may have omitted some studies that would have been appropriate for consideration.” This was not the case. After an exhaustive search using multiple methods, we included all 16 existing randomized trials of HES vs albumin with available postoperative bleeding data. There were no omissions or exclusions whatever. Indeed, the methodology of the metaanalysis was characterized in a companion editorial as “a model for such studies.”10 They also erroneously cite a letter to the editor as suggesting our metaanalysis was biased.11 That letter pertained to a different metaanalysis of ours,13 and we have elsewhere rebutted the letter.12

Substantial uncertainty no longer persists as to the effects of HES on bleeding after cardiac surgery. We question the value of devoting limited clinical research resources to a seventeenth randomized trial. Resources might more fruitfully be allocated to re-evaluating institutional fluid management policies in light of the evidence outlined above and current HES product labeling.

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REFERENCES


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