sarcoidosis patients with pulmonary hypertension had a higher risk of death on the wait list than those with normal pulmonary artery pressures. Sarcoidosis patients with normal pulmonary artery pressures have an unpredictable natural history, which is a vexing problem for lung transplant surgeons trying to decide whether to perform a transplant in someone who is stable or to use the organ for someone who is more ill.

Thomas M. Egan, MD, MSc
University of North Carolina
Chapel Hill, NC

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Correspondence to: Thomas M. Egan, MD, MSc, Division of Cardiothoracic Surgery, Department of Surgery, 108 Burnett-Womack Building, CB No. 7065, University of North Carolina, Chapel Hill, NC, 27599-7065.

REFERENCES

To the Editor:

We appreciate the comments of Dr. Egan regarding our study1 of outcomes for patients with sarcoidosis awaiting lung transplantation. He raises two issues with our analysis.

First, he suggests that size bias might explain some of the differences we noted in waiting times. Because more lung donors are male but most sarcoidosis patients listed for lung transplant are female, there may be too few organs that would be appropriate for smaller, female patients. This certainly is a possibility. Thus, we have subsequently conducted a multivariate analysis to control for this potential source of confounding. In so doing, we find that gender does not correlate with probability of undergoing lung transplantation in patients with either sarcoidosis or idiopathic pulmonary fibrosis. Nonetheless, race remains a significant predictor of transplantation. These results underscore our concerns about the potential for racial bias in the allocation of lungs for transplantation and make size bias a less likely explanation for our observations.

Second, we only meant our data to suggest that perhaps the waiting time credit for patients with idiopathic pulmonary fibrosis be re-evaluated. The issue of the most appropriate allocation system for scarce organs is a complicated, multifaceted question, with significant social and ethical implications. Rather, we intended for our findings to spur discussion over this topic in the transplant community. Any algorithm for the distribution of lungs for transplantation cannot be based purely on numerical probabilities of benefit—such models cannot capture many factors, particularly when the disease studied is rare. Similarly, scoring systems that include severity of illness to the exclusion of prior waiting time may be open to gaming and abuse, as noted with the older allocation system for liver transplants.

Andrew F. Shorr, MD, MPH, FCCP
Walter Reed Army Medical Center
Washington, DC

Steven Nathan, MD, FCCP
Inova Fairfax Hospital
Fairfax, VA

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Correspondence to: Andrew F. Shorr, MD, MPH, FCCP 9005 Cherbourg Dr, Potomac, MD 20854; e-mail: afshorr@duanmail.com

REFERENCE

Lung Cancer Screening

Contumacy vs Mendacity

To the Editor:

Integrity is the currency of scientific discourse; mendacity and attempts to discredit findings by impeaching their author are its counterfeit. Contumacy (obstinate resistance to authority) is irrelevant in this context, for, since 1632, when Galileo was incarcerated by the Inquisition for publishing his Dialogo sopra i due massimi sistemi del mondo, tolemaico e copernicano, appeals to authority to resolve scientific disputes have been held in small regard.

The author’s editorial2 intentionally misrepresents the content of my article2 in order to repudiate it, stating that I “postulated” that 33% of lung cancers were overdiagnosed, that 33% were nonaggressive, and that death occurs when the FEV1 falls to 1 L. I preceded figures provided for overdiagnosis (cancers that prove nonlethal due to either tissue overinterpretation or death from a comorbidity), clinical behavior, and lethal FEV1 values in my model with the statement: “Consider the following hypothetical scenario.” My intent was to provide a conceptual model that might resolve the seeming paradox of higher mortality despite increased survival in screenees. I posited that it could be accounted for if the increased long-term mortality consequent to loss of pulmonary reserve in persons with overdiagnosed lung cancers was not offset by a reduction in mortality afforded screenees with nonaggressive (those that might be cured if identified early) lung cancers. The author’s misrepresentation is not attributable to a misreading or oversight. He raised this issue when he reviewed the article, and I furnished (unneced, since the article was unambiguous) clarification. In an ad hominem argument, he further implies that, because of my prior association with the Kaiser Permanente system, my conclusions were motivated by an effort to spare the health plan the expense of membership screening. I am not currently associated with that organization, I was not influenced by the association, and I received no monetary or other consideration for authoring the...
article. In contrast, as head of thoracic surgery for City of Hope Medical Center, the author stands to financially benefit from the proposed screening. He owes the readership of CHEST an apology.

The 15% 5-year lung cancer survival the author cites in arguing against the existence of overdiagnosis and nonaggressive lung cancers applies to clinically diagnosed lung cancer; there is no plausible justification for ascribing equal lethality to the biological behavior of screen-diagnosed lung cancer. On the contrary, the Mayo study reported a 5-year survival in the screened cohort of 35% vs 15% in the unscreened cohort, but the number of “advanced” lung cancers was identical in the two cohorts (and the screened cohort experienced a higher lung cancer mortality than the unscreened cohort). He contends that overdiagnosed lung cancer is an “ephemeral entity,” citing in support of this dictum the studies of Flehinger et al and Sobue et al. The former is a Monte Carlo mathematical simulation of screening outcome employing four model parameters based on the Mayo Clinic data. It clearly did not address overdiagnosis, which is an empirical observation. Sobue et al reported on 42 persons with screen-identified stage IA lung cancer who did not undergo surgery either because of refusal (65%) or medical contraindication (35%). Only 14% underwent either mediastinoscopy or CT (ie, they were most likely understaged). The majority had squamous carcinomas; only 12 patients (29%) had adenocarcinomas (peripheral adenocarcinomas, which have the most favorable prognosis, constituted 78% of the cases in the Early Lung Cancer Action Project [ELCAP] prevalence screen). Radiation therapy or chemotherapy, or a combination, was provided to 34 of the 42 persons. After 10 years of follow-up since diagnosis, all had died, 20% of causes other than lung cancer. Whether this outcome provides definitive evidence of the efficacy of nonsurgical therapy, or plausible evidence of overdiagnosis, I leave the reader to decide. The high prevalence of autopsy-detectable lung cancer in individuals who died of other causes, which McFarlane and his colleagues (cited in my initial article) provided in abundance, constitutes definitive evidence that lung cancer is not invariably the cause of death in individuals with this condition. Corroborative evidence for overdiagnosis bias is provided in my article and by Woloshin et al. In a recently published article originating in the Mayo Clinic, Swensen et al state, “The morbidity and mortality associated with radiation, biopsy and surgical procedures must be considered. Mortality and morbidity considerations are particularly disconcerting in cases of benign lesions and overdiagnosed cancers. Clinicians currently lack the ability to determine which cancers will be lethal and which ones are the result of overdiagnosis” [italics added]. The dictum that overdiagnosis bias does not exist entails its corollary: that a diagnosis of lung cancer confers immunity to death from all other causes. That screening results in overdiagnosis is ineludible; the issue is how often it occurs. Precise estimates would be contingent on the sensitivity of the screening method, the duration of follow-up of both cohorts, and the accuracy of tissue interpretation. Upper-limit estimates are constrained by the proportion of “missing cases” in the control group and, assuming equal cohort size, are given by the following formula: (No. of cancers in the screened group – No. of cancers in the control group)/(No. of cancers in the screened group). The figures are 22% in the Mayo Clinic study and 32% in the Czech study. Low-dose CT screening will necessarily increase overdiagnosis (and its adverse consequences) because earlier diagnosis will provide a greater duration of exposure to comorbidities. That the benefit of earlier diagnosis in individuals with nonaggressive lung cancer will offset this detrimental effect remains to be demonstrated.

The author disingenuously advocates radiation therapy as a potential alternative to surgery to circumvent the long-term consequences of lobectomy modeled in my article. It has a lower success rate than surgery; it incurs a substantial loss of pulmonary function; it incites pleural fibrosis resulting in further pulmonary compromise; it devitalizes the irradiated lung, predisposing it to infection; and it forfeits the sampling of hilar and mediastinal lymph nodes, followed by lymphadenectomy, which may be necessary for cure or for guiding postoperative therapy. For these several reasons, none of the patients in the ELCAP study was offered radiation therapy as the preferred intervention.

The unexpected and counterintuitive findings of recent randomized control trials of hormone replacement therapy, arthroscopic knee surgery, autologous bone marrow transplantation (to permit intensified therapy in metastatic breast cancer, and flecainide (to prevent sudden death in persons with ventricular arrhythmias) are cogent and persuasive reminders of the limitations of case-control and single-cohort studies, which, in each instance, supported these interventions. Had the Mayo and Czech studies employed survival rather than mortality as the main outcome measurement, each would have been regarded as an outstandingly successful demonstration of the efficacy of lung cancer screening. It is evident that identification of increased numbers of persons with stage IA lung cancer by means of low-dose CT will improve survival in comparison with historical controls, for both the Mayo Clinic and the Czech studies, which employed the less sensitive diagnostic method of plain radiography, found this to be the case. That improvement in mortality can be inferred from improvement in survival is not self-evident; furthermore, a stage shift cannot be confirmed absent demonstration of a reduction in the number of individuals identified with advanced lung cancer in comparison with a concurrent control cohort. As Woloshin et al recently observed, all that can be accomplished by further single-cohort studies of screening will be to “...generate precise estimates of how often spiral CT scans detect abnormalities that could be associated with cancer, how often patients with these abnormalities undergo various follow-up tests, and how often LC is detected.” Swensen et al reported that approximately one half of individuals undergoing surgical biopsy of an indeterminate nodule in the United States and Europe have benign disease, and that among 1,520 individuals screened with low-dose CT at the Mayo Clinic, 51% had a positive study, 13% had indeterminate nodules, and an estimated 98% of these were false-positive.

It is time to replace certitude with certainty, which can be accomplished only by a prospective randomized controlled study, as is being undertaken by the National Cancer Institute.

Human experience, which is constantly contradicting theory, is the great test of truth.