noted that no prior study has investigated the relationship between kidney function and emphysema and that the mechanisms of kidney dysfunction in patients with emphysema need further investigation.

Chandra and colleagues[1] studied 508 cases, assessing the severity of emphysema by CT scan and comparing the results with glomerular filtration rates. However, we note that from Figure 3 of their publication, only 16 patients had an emphysema percentage of ≥ 20%. In this regard, we would like to call to the attention of the authors and the readership of *CHEST* a study published in 1988 that one of us (V. L. R.) participated in.

Pratt et al[2] examined the cause of death in a consecutive series of 1,033 autopsies and observed that chronic renal disease is a much less common cause of death in people with emphysema, as compared with those without emphysema ($P = .0003$). The trend persisted when individuals who died of smoking-related diseases were eliminated from the analysis ($P < .0003$). When only those cases with discernible emphysema were examined (n = 272), the percentage of emphysema in patients dying of chronic renal disease was significantly lower than in all other causes of death ($P < .006$). The percentage of emphysema was assessed by point counting of inflation fixed lung specimens to determine the volume percentage of emphysema.[3]

From a mechanistic perspective, Pratt et al[2] proposed that destruction of the pulmonary vascular bed in emphysema reduces the efficiency of conversion of angiotensin I to angiotensin II. This, in turn, could interrupt, or at least ameliorate, the vicious cycle of renal injury and release of renin leading to production of angiotensin, with a resulting increase in BP and further renal injury. Thus, an individual with emphysema might be less likely to progress to fatal end-stage renal disease. These observations are also consistent with epidemiologic studies that have shown that smokers have, on average, a lower BP than that of nonsmokers.[4] We are in complete agreement with Chandra et al[1] that further studies are necessary to understand the relationship between emphysema and renal function and to explain further the discrepant findings in these authors' study as compared with those of Pratt et al.[2]

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Response

To the Editor:

We welcome the comments on our article by Dr Palvisko and colleagues and thank them for drawing our attention to the large autopsy series published in 1988[1] where the presence of emphysema was predictive of reduced mortality from kidney disease. At first glance, this study may appear to contradict our finding that emphysema is associated with an increased prevalence of mild kidney insufficiency.[2]

However, we believe that this paradox might have a rather uncomplicated explanation. The key difference is that mortality from kidney disease is very different from suffering from mild kidney disease. Epidemiologic studies demonstrate that patients with mild kidney disease do not usually die of end-stage renal disease but, rather, of cardiovascular causes.[3] Therefore, patients with emphysema may have a disproportionately high prevalence of early stage kidney disease but may die preferentially of cardiovascular instead of advanced kidney disease.

What is not contradictory is that in considering the results of each study, one must conclude that further research is required into the development of renal comorbidities in patients with COPD. Both studies suggest that renal disease may be an important contributor to the disproportionate burden of cardiovascular disease and cardiovascular death in patients with COPD.

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Survival in Untreated Stage I Lung Cancer

To the Editor:

The recommended management by Donington et al[1] in a recent issue of *CHEST* (December 2012) of high-risk people with non-small cell, stage I lung cancer (SILC) is premised on a single report evaluating their survival absent intervention. Vrdoljak et al[2] reported that 19 people with SILC (in a case series of 130-people with lung cancer declining all forms of intervention) experienced a 17-month median survival. This assessment of the natural history of untreated SILC is open to question:

1. Vrdoljak et al[2] confined their SILC analysis to stage IB because there were too few cases of untreated stage IA to permit a valid assessment of survival.
2. They did not allocate deaths due to competing lethal morbidities (ie, overdiagnosed) vs those due to SILC.
3. They did not state that all people declining intervention underwent surgical mediastinal exploration (ie, some may have been clinically staged [potentially understaged]).
4. Vrdoljak et al[2] explained the patients' justification for declining intervention:

> Many…had low sociocultural backgrounds with strong opinions about cancer as an incurable disease. Some patients refused therapy because they were afraid that it would drastically change the quality of their "remaining" years. Some patients simply did not accept the presence of lung cancer, denying the disease.

While these explanations are plausible, symptoms attributable to competing morbidities may have influenced the patients' decision.

It is important to appreciate the dependency of growth rates on tumor size. Diameter is a function of the number of tumor volume doublings (TVDs). Tumor diameter in centimeters, $D = \text{cell diameter}(\text{cube root of } 2)^{\text{number of TVDs}}$; $D = 0.001(1.26)^{x}$; log form: $x = \ln 1{,}000D/\ln 1.26$.[3] For example, a 1-cm tumor (IA) has undergone 30 TVDs; a 5-cm tumor (IB), 37. With a IA TVD-time of (230 days), 1,610 days (54 months) would be required for a 1-cm tumor to grow to 5 cm.[3] Assuming unchanging TVD-time, the growth rate ratios of diameter and volume are, respectively, D and D^2 (eg, fivefold and 25-fold for a 5-cm vs a 1-cm tumor).[3] The additional 4.4 years of growth required to achieve a 5-cm (stage B) size increases the likelihood of overdiagnosis (greater in high-risk patients) because of a lengthier exposure to smoking-related, lethal comorbidities. Resectional surgery diminishes life expectancy presumably by accelerating the course of competing, smoking-related, cardiopulmonary morbidities (J. M. Reich, MD, FCCP; J. S. Kim, PhD; J. W. Asaph, MD, unpublished data, 2013).

In conclusion, intervention in high-risk patients with slow-growing SILC is neither urgent nor compelling. Indeed, it may prove counterproductive.

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Response

To the Editor:

I read with interest the comments of Dr Reich and colleagues regarding our recent consensus statement[1] and the counterproductivity of treatment of high-risk patients with stage I non-small cell lung cancer (NSCLC). Their opinion arises from the belief that early-stage NSCLC is a nonfatal disease, the biology of which can be predicted through mathematical models of tumor doubling time. This is a common theme throughout their letters and comments. Because even small NSCLCs have a proclivity for metastasis, and most patients succumb to metastatic disease rather than primary tumors, the relevance of doubling-time models to discussions of the treatment of high-risk patients is unclear.

There are fewer reports on the clinical course of untreated early-stage NSCLC than for other NSCLC populations and significant ethical difficulty in randomizing between treatment and no treatment even among those at high risk, but there is sufficient evidence to define the survival in this group as dismal. In addition to the cited work, three institutional series[2-4] and a population-based review from the California Cancer Registry[5] report on the natural history of untreated early-stage NSCLC. Although retrospective reviews are imperfect, and the subject difficult because of the multifaceted reasons for which patients forgo treatment, three salient points are clearly conveyed across all the series: (1) comorbid pulmonary disease is the primary reason for nontreatment, (2) 5-year overall survival in the untreated is $< 10\%$, and (3) at least one-half of the deaths are attributed to NSCLC. The California Cancer Registry review identified adenocarcinoma in situ as a common histology among the small number of untreated survivors at 5 years, outlining an indolent tumor type that may have an altered risk-benefit ratio related to treatment. The high-risk population is diverse, and for some, but not all, competing comorbidity is a valid reason