

## Survival in Untreated Stage I Lung Cancer

**To the Editor:**

The recommended management by Donington et al. 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. 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. 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, overdosed) 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. 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, 

$$D = \frac{\text{cube root of } 2}{1.26} 
\times \log_{1.26} \left( \frac{D_{\text{final}}}{D_{\text{initial}}} \right)
$$

For example, a 1-cm tumor (IA) has undergone 30 TVDs; a 5-cm tumor (IB), 37. With an IA TVD-time of (230 days), 1,610 days (54 months) would be required for a 1-cm tumor to grow to 5 cm. Assuming unchanged TVD-time, the growth rate ratios of diameter and volume are, respectively, D and D³ (eg, fivefold and 25-fold for a 5-cm vs a 1-cm tumor). 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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We refer the reader to the recent consensus statement of the American College of Chest Physicians and the American Society of Clinical Oncology regarding our recent consensus statement and the counterproductive nature 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 and a population-based review from the California Cancer Registry 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.

**References**


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**Response**

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I read with interest the comments of Dr Reich and colleagues regarding our recent consensus statement 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.

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to abstain from treatment, especially if not amenable to less invasive modalities.

Novel cancer treatments are typically introduced in patients with the fewest options. For chemotherapeutics, it is those who have progressed after standard therapy; and for local therapies, it is those who cannot tolerate lobectomy. The prospective American College of Surgeons Oncology Group (ACOSOG) and Radiation Therapy Oncology Group (RTOG) trials demonstrate that in well-selected high-risk patients, novel therapies can be delivered safely, with curative intent and minimal impact on pulmonary function. No one advocates treatment in this population without careful clinical judgment, but the treatments reviewed in our manuscript1 provide new hope for a population that once had very little.

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Financial/nonfinancial disclosures: The author has reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
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REFERENCES