Stage of Lung Cancer in Relation to Its Size*

Part 1. Insights

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Abbreviations: CXR = chest radiography; P/G group = Patz and Goodman; RCT = randomized controlled trial

Renewed interest in screening for lung cancer has been sparked by advances in CT technology that now allow for the detection of smaller tumors than previously was possible with chest radiography (CXR). This interest has been addressed by a group led by Patz and Goodman (P/G group), whose fundamental idea has been that:

The fundamental [presumption] on which low-dose CT screening is based predicts and requires that small 5–10-mm lesions observed on CT have not metastasized, and that these lesions are very different from the 1–3-cm lesions detectable on chest radiographs. This reasoning suggests that smaller lesions should have a very different, earlier stage distribution profile compared with larger lesions, which are presumed to have a more advanced stage distribution (i.e., stage shift).

To test this presumption, the P/G group analyzed data from the cancer registry of their hospital. The evidence did not support the stage-shift presumption, and on this basis they cautioned that “the detection of small tumors using screening CT may not result in a shift to an earlier stage distribution.” They went on to assert that a “reduction in mortality needs to be demonstrated by the appropriate clinical trials.” This study followed an earlier one that focused on stage IA cases (<3 cm in diameter), essentially from the same registry. In that earlier study, the P/G group found no correlation between tumor size and 5-year survival, and this already led them to assert the need for a randomized controlled trial (RCT).

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These ideas, studies, and consequent assertions have had a dramatic impact. Most notably, they provided the justification for the National Lung Screening Trial. To quote its principal investigator, “conventional wisdom suggests that the smaller the tumor when it is found, the more likely the chance of survival, but that remains to be proven”; and according to the National Lung Screening Trial protocol:

Simply stated, it is not known whether the detection and treatment of a 5 mm diameter T1 cancer will affect a better outcome than the detection of a 20 mm diameter T1 cancer. A recent retrospective study found no survival advantage among T1 cancers based on size . . . A major impetus to move from chest radiograph screening to CT screening for lung cancer is the promise of detecting smaller lung cancers. Yet, we do not currently know that outcomes are necessarily better when the cancer is 2 mm as opposed to 20 mm. As purveyors of public policy, we are obligated to avoid the premature endorsement of a screening process before its benefit and liabilities have been reconciled.

Given their impact, these two articles by the P/G group call for careful scrutiny. In this article, we critically review them as to their merits. In part 2 of this article, we present data from the Surveillance, Epidemiology and End Results database, compellingly contradicting the evidence and conclusion presented by the P/G group regarding the relationship of stage to size. In another report, we already have given direct evidence that refutes the conjecture of the P/G group that tumor size does not bear on survival with stage I lung cancer.

Use of Registry Data

Let us assume that small tumors documented in a cancer registry indeed have the same stage distribution as do larger tumors. Would this imply similar findings for a screening database? The correct an-
The answer is “No.” In general, cases get to be documented in a registry on diagnosis prompted by symptoms. Lung cancer causes symptoms by two basic mechanisms: by local effects of the tumor (compression or invasion), and by its generally distant metastases. Smaller tumors are less likely to locally cause symptoms and are therefore more likely to be symptomatic because of their distant metastases (Fig 1). This dilutes the size/stage correlation within a registry database relative to that in a screening database, possibly even inverting a positive correlation to a negative one.

This selection bias in registry data were actually acknowledged by the P/G group itself, as they remarked that “the data may not accurately reflect those of a screening program, because both symptomatic and asymptomatic patients were included in the study,” but they dismissed the relevance of this on the grounds of “the similarity between the disease stage distribution in the current study and that published in the prevalence screen data from the CT screening trials.” To us, these databases are seriously incomparable, and any similarity in their stage distributions is merely a matter of chance in the context of how cases got to be documented in the registry of the P/G group (see below) rather than a meaningful scientific finding.

THE TYPE OF REGISTRY USED

In the size category of 2 to 3 cm, approximately 80% of the cases of the P/G group were of stage I, and approximately 90% of the them (all cases) were resected. These proportions are much higher than those in other experiences (including in the Surveillance, Epidemiology and End Results experience addressed in the accompanying second article). This suggests that advanced-stage cancers commonly were not registered, presumably for the reason that the registry was in essence a surgical one. Such a registry does not give a fair picture of the size/stage relationship in a general cancer registry experience.

THE EVIDENCE PRESENTED

The P/G group did not present evidence indicating that a relationship between tumor size and disease stage does not exist. They merely failed to find a statistically significant relationship between size and stage, notably when limiting the data analysis to tumors < 3 cm in diameter. The size restriction limited their ability to detect whatever size/stage relationship might have existed in the downward-biased experience of their registry. That few of the tumors were < 1 cm in diameter was to the same effect.

“Conclusions” and Discussion

From their study on the correlation between size and stage, the P/G group presented as the “conclusion” that the “detection of small tumors using screening CT may not result in a shift to an earlier
stage distribution [emphasis added].” In the same
vein, they asserted that “[evidence] suggests that
tumors that are going to metastasize may do so
before they are visible radiologically or amenable to
intervention. Those tumors that are more clinically
indolent, without evidence of metastatic disease,
may remain so despite their size [emphasis added].”
And subsequently again, the “assumptions that size
correlates with biological behavior and that small
lesions are equivalent to early-stage disease have not
been confirmed for lung cancer. Tumors may already
have demonstrated their potential to remain
localized or to metastasize by the time they are
visible on CT imaging [emphasis added].”

Technically, that conclusion is not even of the
form of a conclusion. Rather, it merely states the
inconclusiveness of their study. What is insinuated is
this: when latent cancers become large enough to be
detected by CT, the ones among them that have not
yet metastasized will remain nonmetastatic until they
reach 3 cm in size, subsequent to which these too are
prone to metastasize. Let us assume that the propor-
tion of early stage cancers among all latent cancers
indeed is constant in that range of size and ask, does
this imply that cancers are not metastasizing in that
range of size? In Figure 2, we show all the possibil-
ities that can occur as tumors grow. Figure 2 dem-
onstrates that it is entirely possible for the propor-
tion of early stage cancers among all latent cancers to
remain constant with increasing cancer size even
when metastases do occur in the size range at issue.
This results from cancers within that size range no
longer remaining latent. Thus, even if the P/G group
had demonstrated absence of size correlation of
stage in that range of size for latent cancer, they
could not have inferred from this finding an absence
of metastasizing in that size range.

**Implications and Credibility**

Let us go even further and assume that the
insinuation stated above is correct (Fig 3). It would
then be appropriate for a patient having a small
CT-detected stage I lung cancer to delay treatment
until the tumor reaches 3 cm in diameter. For, so
long as the tumor is < 3 cm, it is locked into this
stage and therefore there would be no advantage to
early treatment, while there would be an advantage
to delaying life-threatening surgery. We know of
nobody recommending a delay in treatment for small
stage I lung cancers; it is universally accepted among
clinicians that recommending such a delay would be
unacceptable. The idea of no stage progression in
that range of size is patently devoid of credibility.

**The Putative Requirement**

The P/G group posited, as we stated at the onset,
that for CT screening to be beneficial, the smaller,
CT-detected cancers must have an earlier stage
distribution than the larger CXR-detected cancers.
Let us presume, however unrealistically, that there is
no such stage shift and consider a subject enrolled in
a screening trial contrasting CT with CXR in annual
screening. If the subject has a cancer below the size
necessary for detection, he or she is screened again 1
year later. As the size threshold for detection is
significantly smaller for CT than CXR, it is far more
likely that a cancer not detected in the CXR study
arm grows beyond the 3 cm threshold during the
1-year interval between screenings, relative to a
cancer not detected in the CT arm. As an example,
let us consider an adenocarcinoma with a volume
doubling time of 180 days. It would take a 2-cm
cancer < 1 year (315 days) to grow to 3 cm, while for
a 0.5-cm cancer it would take > 4 years (1,400 days)
to grow to 3 cm. Thus, CT screening would still be
beneficial, as a much higher percentage of cancers
would be detected by repeat screening before it
crossed the 3-cm threshold, after which stage pro-
gression occurs even by the admission of the P/G
group.¹
NEED FOR AN RCT

In both of their articles, the P/G group pronounced the need for an RCT to resolve the tenability of their putative presumptions in thinking that CT screening might be superior to CXR screening, these presumptions being that there must be a correlation between tumor size and stage and/or tumor size and 5-year survival within stage I. As they failed to verify those presumptions in both of their articles, they asserted the need for an RCT contrasting the two types of screening. No rationale was given whatsoever as to how this is implied from their work. The need for an RCT is not a logical consequence of their failure to validate their presumption.

THE ARTICLES OVERALL

Even though those two articles by the PG group have had great influence on policy thinking regarding CT screening for lung cancer, notably as to research on the subject, we here present insights of erroneous presumptions, irrelevance of evidence, and unjustifiability and untenability of conclusions. While there may be legitimate discussions as to the type of research necessary to evaluate screening CT, in no way do we find that those articles provide rationale to perform an RCT comparing CT vs CXR.

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REFERENCES