TARGETED VERSUS SYSTEMATIC NODAL STAGING IN EARLY-STAGE LUNG CANCER

To the Editor:

With interest, we read the article by Sullivan and colleagues.¹ In a noninferiority trial, they compared targeted versus systematic sampling using endobronchial ultrasound–guided transbronchial fine-needle aspiration for the detection of mediastinal nodal metastases in patients with suspected early-stage (cN0-N1) lung cancer. We compliment the authors’ effort to gain more insights into this important topic but believe the study suffers from important design issues. We disagree with the authors’ conclusions, which, in our opinion, are invalid based on the presented data.

The primary outcome is the proportion of missed nodal metastases. This unit of analysis (lymph nodes instead of patients) is suboptimal, as treatment decisions based on endobronchial ultrasound–guided transbronchial fine-needle aspiration outcomes are made at the patient level. Overall, 256 lymph nodes (from 91 patients) underwent both targeted and systematic sampling. The final pathologic result served as the reference standard, which resulted in an overestimated and systematic sampling. The remaining 2 nodal metastases were subsequently diagnosed by surgery. Hence, missed nodal metastases occurred in 3.12% (8/256) for targeted sampling and 7.78% (2/256) for systematic sampling, with an absolute difference of 4.64% (6/256). However, the authors report an absolute difference of 1.56% (4/256).

This apparent error in the primary outcome is unfortunate but not critical for the interpretation of the data. More problematic is the fact that the authors set the noninferiority margin at 6%, which is larger than the overall incidence of nodal metastases in this study (ie, 3.51%). This means that, by definition, targeted sampling cannot be inferior to systematic sampling in this population, because the difference in missed nodal metastases between the strategies can obviously not be larger than the overall incidence. In fact, for the same reason, not doing any tissue staging is also noninferior to systematic sampling using this 6% noninferiority margin. Based on their pilot study, which showed an overall incidence of 5.45% (ie, also less than 6%),² the authors could have anticipated that it would be statistically impossible not to show noninferiority.

Therefore, the authors’ conclusion that the study shows noninferiority of targeted sampling was already established before study initiation and is fully driven by the low incidence of nodal metastases in this population and not by the actual diagnostic performance of both strategies. Only 1 of 9 nodal metastases was identified by targeted sampling, resulting in a diagnostic sensitivity (at nodal level) of only 11.1%. For systematic sampling, this was 77.8%. It seems difficult to claim noninferiority based on this.

The authors report: “this study proves that targeted sampling is a viable alternative to systematic sampling.” In our opinion, the presented data do not support this statement. On the contrary, our interpretation is that also in a low-incidence setting, if mediastinal nodal sampling is considered, a systematic approach is preferred, and targeted sampling seems to have limited value.

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Conflict of Interest Statement

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References

