Commentary: Known unknowns and unknown unknowns: The case of the indeterminate margin

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Joanna Sesti, MD (left), and Subroto Paul, MD, MPH (right).

Central Message

Indeterminate margins are rare after lung cancer resection, and adjuvant therapy provides no survival benefit.

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There are known unknowns and unknown unknowns. Unknown unknowns are always more difficult to assess.¹ In the issue of the *Journal*, Raman and colleagues² use the National Cancer Database to assess the unknown of the indeterminate margin after lung cancer surgery. How can a lung resection margin, bronchial and otherwise, be neither positive nor negative? As Raman and colleagues² note, both technical and biologic factors, such as poor sectioning or staining, or the morphology of the cells at the margin, can lead to an equivocal margin status. Indeterminate margins are rare, and there is therefore no consensus on what to do with them. Because of their rarity, no single institution can comprehensively study them with sufficient power. Only large national databases, such as the National Cancer Database, can shed some light on such a rare phenomenon.

Raman and colleagues² examined the frequency of indeterminate margins after lung cancer surgery, its effect on survival, and the impact of adjuvant therapy on those patients with indeterminate margins. They found that indeterminate margins adversely affect overall survival and that adjuvant therapy (chemotherapy, chemoradiation, etc) does not improve survival. As expected, anatomic resections were less likely to be associated with indeterminate margins.² The results are intriguing as to why adjuvant therapy provides no benefit. Multiple possibilities exist, which range from that there is truly no benefit to that the study is underpowered to find one to the possibility that the group is so heterogeneous that patients who benefit are lost in the overall group. Unfortunately, the National Cancer

Database, like other large databases, is limited by the lack of granularity required to tease out the probable cause. Because of the rarity of the problem, only another database can attempt to answer it. Future studies involving large sets of artificial intelligence-analyzed electronic health record data that include pathology and survival data may provide more definitive answers.

So, what do we do? The study suggests that we pause and assess the patient and the risks and benefits of the adjuvant therapy for that patient. We go with that is known about the patient and what known therapy can do for that patient.

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