Commentary: Neoadjuvant immunotherapy followed by lung cancer resection: Is the future already here?

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Kumar and colleagues\(^1\) performed a retrospective review of an administrative database evaluating the use of immunotherapy for locally advanced lung cancer (cT1-3N2), comparing the use of definitive concurrent chemoradiation followed by immunotherapy (cCRT + IO) with the used of induction chemoinmunotherapy followed by surgery (CT/IO + surgery). They found improved 3-year survival in the surgery group when comparing the groups overall and also after propensity matching. The authors are appropriately measured in their conclusions, with their emphasis that these results should be hypothesis-generating. Immunotherapy will change who we operate on in the future.

There are limited takeaways, however, from this study due to the constraints of the study design, including the use of an administrative database, the fact that most of the surgery patients were likely on a clinical trial, and that patients who were stage IIIB were included.

One cannot use administrative databases to compare different clinical choices, as they lack the ability to understand the decisions on why a treatment choice was made. The National Cancer Database only tracks overall survival, not disease-free survival, and lacks data on performance status, which clearly impacts the choice for surgery as being a part of the treatment paradigm.\(^2\)

Aside from the use of an administrative database for this study, it is clear from the timing of the dataset (2013-2020) that most, if not all, the surgical patients were in clinical trials. This leads to a biased group of patients in the surgical arm, who tend to be younger with fewer comorbidities than those who were not in a clinical trial.\(^3\) A key problem with most clinical trials is that they don’t include patients who are older and frailer. Kumar and colleagues found that the nonsurgery cohort was approximately 4 years older than the surgery cohort in their study, before matching. Even after matching for age and other variables, there was no way to match for performance status, which alone could explain the 3-year survival difference between the cohorts. There is no way to address this bias with the current study design, and the authors acknowledge this is in their discussion.

My last concern was the inclusion of patients who are stage IIIB (T3N2) in this study, and there appears to have been a trend toward more T3 tumors in the nonsurgery group compared with the surgery group \((P = .08)\). Although this wasn’t statistically significant, could this greater rate of patients who are stage IIIB in the nonsurgery arm contribute to the worse outcomes? Surgery is not routine for most patients with stage III lung cancer, let alone stage IIIB.\(^4\) Given this, the inclusion of these patients in the comparison arm of the nonsurgical group will certainly lead to lower survival. Overall, Kumar and colleagues share interesting data that should spark interest in a broader look at the use of immunotherapy in lung cancer. The ability to interpret the comparison arms, however, is limited.

**Conflict of Interest Statement**

Dr Reddy reports Intuitive Surgical (teaching site), Medtronic (Advisory Board), On Target Laboratories (Advisory Board and Grant), Genentech (Advisory Board).

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