Commentary

Estimated risks of recurrence and mortality in lung cancer: comprehensive analysis by a population-based study

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Lung cancer remains the leading cause of cancer-related mortality worldwide in spite of recent advances in treatment. Prognosis varies from patient to patient according to a variety of factors such as disease stage and treatment modality. Compared with those enrolled in clinical trials, which tend to be restrictive in their eligibility criteria, a greater variety of lung cancer patients is encountered in daily clinical practice. It would therefore be helpful for oncologists to be able to estimate the risks of disease recurrence as well as survival for patients in such a general population.

A recent study by Consonni and colleagues has provided a comprehensive analysis of recurrence and survival based on a population of more than 2,000 patients with lung cancer at stages IA to IV who received either surgical or nonsurgical treatment (1). As is generally recognized, mortality increased as disease stage at diagnosis became more advanced. Similarly, the rate of local or distant recurrence also increased with stage from ~34% (stage IA) to 63% (stage IIIA) among surgically treated patients at stage I to IIIA. The recurrence hazard rate for patients at stage IIIB or IV not treated with surgery was about double that for those at stages I to IIIA treated with surgery (0.32 and 0.17, respectively), despite the overall recurrence rate being only 26.6% in the former group as a result of the competing risk of mortality. The absolute risk of first distant recurrence (that is, metastasis) exceeded that of first local recurrence, regardless of stage. Recurrence at any site increases mortality, but the effect of distant recurrence is greater than that of local recurrence. Furthermore, the absolute risk of any recurrence increased markedly in the first 2 years after diagnosis and more gradually thereafter.

Whereas many previous population-based studies of lung cancer focused on the association between candidate prognostic factors and outcome (2-5), Consonni *et al*. provide data for recurrence risk and survival after recurrence. These data suggest that lung cancer should be thought of as a systemic disease even at the localized early stages, given that the absolute risk of distant recurrence exceeds that of local recurrence even at stage I. In addition, recurrence rates in patients who underwent surgery and received adjuvant treatment were higher than those in patients treated with surgery alone, suggestive of an insufficient efficacy of the adjuvant therapy and the need for further improvement. Indeed, there have been few changes to adjuvant treatment regimens for decades. One potential change worth considering is the introduction of immunotherapy to perioperative settings. The fact that tumor bulk appears to influence the tumor-specific immune response (6) provides a rationale for the application of immunotherapy either at the early stages of cancer, when tumor volume is minimal, or after complete tumor resection. A recent study revealed that both progression-free and overall survival was prolonged in melanoma patients receiving ipilimumab as an adjuvant treatment (7,8). Neoadjuvant and adjuvant immunotherapy are under evaluation for lung cancer, with the results of these studies being awaited with interest (9,10).

The prognosis of patients with lung cancer positive for

activating mutations of the epidermal growth factor receptor gene (*EGFR*) or for the *EML4-ALK* translocation differs from that of patients without such driver gene alterations as a result of the availability of effective targeted therapies. The study by Consonni *et al*. included only 104 patients who received molecularly targeted treatments out of the total study population of 2,098 patients, and it provides no details regarding the recurrence risks specifically for these individuals. A population-based evaluation of subsets of patients receiving molecularly targeted therapies would also be of use. On the other hand, in contrast to the limited numbers of patients who benefit from targeted therapy, immunotherapy has now been approved as a standard treatment for patients with advanced or metastatic lung cancer (11-14). Given the limited amount of time that has been available for observation to date, the significance of the late plateau or "tail" apparent in the survival curve for lung cancer patients treated with immune checkpoint inhibitors remains unclear. Nevertheless, the introduction of immunotherapy for lung cancer patients is certain to affect prognosis to some extent, and population-based studies that include such patients treated with immunotherapy are warranted.

Performance status, which is also considered a useful prognostic factor, was not included as a separate category in the study by Consonni *et al*. The provision of such data would add more detailed information regarding recurrence and mortality, given that performance status often has a large impact on the choice of treatment modality. On the other hand, the study also does not present findings related to other traditional prognostic factors such as sex and age, the impact of which on outcome for lung cancer patients appears to be inconclusive (3,15-19).

As a final thought, the findings of population-based studies can help to identify specific subgroups of patients for whom an improvement in therapy is needed. Although it is not always easy to notice such subpopulations in individual studies, the more such studies that are undertaken the easier it becomes.

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Footnote

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