Disease-specific graded prognostic assessment lung cancer update

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Comment on: Sperduto PW, Yang TJ, Beal K, *et al.* Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). JAMA Oncol 2017;3:827-31.

Lung cancer accounts for almost 30% of cancer deaths. Length of survival after diagnosis of metastatic lung cancer, however, spans a significant range today. While some patients still only survive in the order of a few weeks to months, an increasing percentage are living years due to the recognition of different types of lung cancer genetics and the ability to treat patients in a personalized fashion with targeted therapies. This large span in survival range is particularly noticeable in patients with brain metastases. Only two decades ago, the only treatment available for these patients was whole brain radiation therapy (WBRT) and the accepted survival was 6–8 months at best (1).

Sperduto *et al.* published their first version of the disease-specific graded prognostic assessment (ds-GPA) score for patients with brain metastases in 2010 (2) and were able to demonstrate that independent of treatment strategy, if patients were subdivided by age, Karnofsky Performance Status (KPS), presence or absence of extracranial metastases and number of brain metastases, a better estimate could be made of the patient's possible median survival. This improved ability to predict outcome has allowed physicians to help patients make decisions about whether or not potentially more aggressive but risky or painful treatments were worthwhile trying.

This first publication contained data from patients treated between 1985 and 2005. Erlotinib was Food and Drug Administration (FDA)—approved for treatment of EGFR-mutant lung cancer in the USA in 2004 and since that time multiple second and third line agents have become available commercially. Much data has since been published showing improved progression free survival in patients using tyrosine kinase inhibitors (TKIs) (3) as well

as significant benefit in the treatment of brain metastases (4). Because of this observation, the original lung specific ds-GPA was in need of updating.

Outcome data from 2,186 lung cancer patients across 12 US institutions treated between 2006 and 2014 were therefore collected and re-analyzed for factors that independently predicted survival. Again, the same four original factors were found to be predictive of outcome. In addition, as expected, presence or absence of EGFR-mutations and anaplastic lymphoma kinase (ALK) rearrangement mutations were significant predictors of outcome. In patients with adenocarcinomas—i.e., those more likely to have targetable mutations - median survival ranged from 7 months to almost 4 years (compared with 5 to 12 months in those without a targetable mutation). Re-interpreted, if a patient has a targetable mutation, that same patient would only need one of the additional four factors previously identified by the ds-GPA (age <70 years, KPS 80–100, no extracranial metastases or 1–4 brain metastases) to have an expected median survival greater than any lung cancer patient with non-adenocarcinoma. While these results have been validated in German and Norwegian patients by Nieder *et al.* (5), validation is still required in the Asian countries where the incidence of EGFR-mutations is much higher. In addition, this study does not answer whether or not the use of targeted therapy itself also impacts outcome.

Given the significant impact of having a targetable mutation on survival, however, the question for physicians now is to ask how to best preserve function and quality of life for those whose survival is expected to be in the order of years. In the US, this has translated in many academic

centers into the avoidance of use of focal therapies such as WBRT and even surgery and radiosurgery in order to avoid their toxicities until a time when good pharmacological options no-longer exist. What is not clear however is whether this is the best strategy. A recent multicentered retrospective study showed that further improvement in survival could be obtained using a combination of targeted therapies and radiation compared with using targeted therapy alone as first line treatment of brain metastases without increased toxicity (6). As newer central nervous system-penetrating drugs such as osimertinib become common use, it will become increasingly important to compare single therapies to combination therapy regimens.

Future studies therefore need to be designed specifically for this subpopulation of lung cancer patients in order to determine best sequence of treatments to obtain best outcome for these longer-living patients. For patients with lung cancers with EGFR-mutations, several randomized trials are currently open and attempting to address the question of treatment sequence. These trials include NCT02714010—a phase III study comparing use of any TKI compared with TKI and WBRT for brain metastases—and NCT02338011—a phase II/III study comparing use of gefitinib alone versus gefitinib and WBRT. The results of these studies are likely to become obsolete, however, with the FDA approval of third generation TKI osimertinib for first line treatment of EGFR-mutant lung cancer. Osimertinib has been shown to have unprecedented penetration into the central nervous system in preclinical studies and the study that may help answer treatment sequence then is NCT03497767 which is due to open in August of 2018—a phase II study comparing osimertinib versus osimertinib and stereotactic radiosurgery (SRS) for brain metastases.

For studies that intend to look at treatment of lung cancer patients with and without targetable mutations, however, study design clearly needs to stratify expected outcome estimation using this new Lung-molGPA in order to determine if treatments actually improve upon natural history outcomes.

Acknowledgments

Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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