JAMA Oncology | Brief Report

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)

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IMPORTANCE Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. As systemic therapies improve, patients with lung cancer live longer and thus are at increased risk for brain metastases. Understanding how prognosis varies across this heterogeneous patient population is essential to individualize care and design future clinical trials.

OBJECTIVE To update the current Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) for patients with non–small-cell lung cancer (NSCLC) and brain metastases. The DS-GPA is based on data from patients diagnosed between 1985 and 2005, and we set out to update it by incorporating more recently reported gene and molecular alteration data for patients with NSCLC and brain metastases. This new index is called the Lung-molGPA.

DESIGN, SETTING, AND PARTICIPANTS This is a multi-institutional retrospective database analysis of 2186 patients diagnosed between 2006 and 2014 with NSCLC and newly diagnosed brain metastases. The multivariable analyses took place between December 2015 and May 2016, and all prognostic factors were weighted for significance by hazard ratios. Significant factors were included in the updated Lung-molGPA prognostic index.

MAIN OUTCOMES AND MEASURES The main outcome was survival. Multiple Cox regression was used to select and weight prognostic factors in proportion to their hazard ratios. Log rank tests were used to compare adjacent classes and to compare overall survival for adenocarcinoma vs nonadenocarcinoma groups.

RESULTS The original DS-GPA was based on 4 factors found in 1833 patients with NSCLC and brain metastases diagnosed between 1985 and 2005: patient age, Karnofsky Performance Status, extracranial metastases, and number of brain metastases. The patients studied for the creation of the DS-GPA had a median survival of 7 months from the time of initial treatment of brain metastases. To design the updated Lung-molGPA, we analyzed data from 2186 patients from 2006 through 2014 with NSCLC and newly diagnosed brain metastases (1521 adenocarcinoma and 665 nonadenocarcinoma). Significant prognostic factors included the original 4 factors used in the DS-GPA index plus 2 new factors: *EGFR* and *ALK* alterations in patients with adenocarcinoma (mutation status was not routinely tested for nonadenocarcinoma). The overall median survival for the cohort in the present study was 12 months, and those with NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5 to 4.0 had a median survival of nearly 4 years.

CONCLUSIONS AND RELEVANCE In recent years, patient survival and physicians' ability to predict survival in NSCLC with brain metastases has improved significantly. The updated Lung-molGPA incorporating gene alteration data into the DS-GPA is a user-friendly tool that may facilitate clinical decision making and appropriate stratification of future clinical trials.

JAMA Oncol. 2017;3(6):827-831. doi:10.1001/jamaoncol.2016.3834
Published online November 17, 2016.

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Supplemental content

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Worldwide, in 2012, there were an estimated 1.24 million new lung cancers and 1.1 million lung cancer-related deaths.[1] In 2016, in the United States alone, an estimated 224 000 new patients will be diagnosed with lung cancer, and over 158 000 will die from the disease.[2] One of the most frequent and serious complications of this ubiquitous disease is metastasis to the brain, for which lung cancer remains the most common cause. Although there are no global or national population-based estimates on the true incidence of brain metastases, conservative estimates are that 10% to 30% of patients with lung cancer will develop brain metastases.[3] In the past, survival after the development of brain metastases was poor and treatment often considered futile.[4] With the recent advent of molecularly targeted therapies[5,6] and immunotherapies,[7,8] survival from lung cancer continues to improve. Patients are thus at greater risk for developing late sequelae of the disease, such as brain metastases. These trends coupled with the wide availability of magnetic resonance imaging suggest there will be an increasing number of patients diagnosed with brain metastases in coming years.

Extensive efforts have focused on predicting outcomes for the extremely heterogeneous population of patients who develop brain metastases. Data from 1200 patients in 3 clinical trials performed by the Radiation Therapy Oncology Group (RTOG) were used to generate the Recursive Partitioning Analysis (RPA).[9] The RPA is a prognostic index using patient age, Karnofsky Performance Status (KPS), control of primary tumor, and extracranial metastases to define 3 classes of disease with median survival ranging from 2.3 to 7.1 months.[9] More recently, data from a retrospective database of 3940 patients was used to design the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) (available free at BrainMetGPA.com).[10] A series of GPA studies have shown that survival and the factors that predict survival vary widely by diagnosis. For lung cancer with brain metastases, the prognostic factors significant for survival were age, KPS, extracranial metastases, and the number of brain metastases. Four classes of disease were defined, with median survival ranging from 3.0 to 14.8 months.[10]

Our group has recently published a study on the effect of gene alterations on survival in patients with lung cancer and brain metastases that was based on a multi-institutional retrospective database.[11] That study showed that patients with *EGFR* and *ALK* alterations have a markedly improved survival vs those without the alterations. The purpose of the present study was to update the original DS-GPA with these molecular data to create the new Lung-molGPA.

Key Points

Question What is the effect of molecular alterations on survival of patients with non–small-cell lung cancer and brain metastases?

Findings In this database analysis, in addition to previously known prognostic factors, *EGFR* and *ALK* gene alterations of the original primary lung tumor were found to be associated with survival. This association has been incorporated into an updated prognostic index (Lung-molGPA).

Meaning Survival and the ability to predict survival for this population has improved significantly, and the Lung-molGPA may help facilitate clinical decision making and appropriate stratification of future clinical trials.

Methods

This study was approved by the institutional review board of each participating institution. All participants provided their written informed consent.

A multi-institutional retrospective database was created, including 2186 patients with NSCLC (1521 adenocarcinoma and 665 nonadenocarcinoma) and newly diagnosed brain metastases between 2006 and 2014. Variables considered included the 4 used by the existing DS-GPA (patient age, KPS, extracranial metastases, and the number of brain metastases) plus gene mutation status (*EGFR*, *ALK*, or *KRAS* positive), pack-years of tobacco use, sex, race, histopathologic grade, and total volume of brain metastases. Type of treatment was not considered because the purpose of a prognostic index is to estimate survival prior to treatment. Nonetheless, the treatment breakdown for the 1521 patients with lung adenocarcinoma was 50% stereotactic radiosurgery (SRS) alone; 22% whole-brain radiotherapy (WBRT); 9% WBRT + SRS; 7% surgery + SRS; 5% surgery + WBRT; and 1% surgery + WBRT + SRS.

Multiple Cox regression was used to initially select and weight variables to be included in the new Lung-molGPA. The primary end point was overall survival measured from start of brain metastasis treatment. Continuous variables were categorized to assess potential nonlinear effects. Both effect magnitude (hazard ratio [HR]) and statistical significance were used to select variables. The final index was chosen on the basis of separation of prognostic classes with respect to overall survival, distribution of patients, and simplicity. Log-rank tests were used to compare adjacent classes as well as to compare overall survival for adenocarcinoma vs nonadenocarcinoma groups.

Results

The participant characteristics have been previously published.[11] The multivariable model used to select and weight factors in the Lung-molGPA is summarized in eTable 1 in the Supplement. **Table 1** details the median survival by DS-GPA score in the original study (1985-2005) and in the current study (2006-2014) for patients with NSCLC and brain metastases. In the current study, the overall median survival rates for adenocarcinoma (15.2 months) and nonadenocarcinoma (9.2 months) were significantly different ($P < .001$).

Adenocarcinoma

Patient age, KPS, presence of extracranial metastases, and number of brain metastases were again confirmed to be prognostic. Positive findings for *EGFR* and *ALK* were also independently prognostic and were added to the Lung-molGPA. Factors with larger effect sizes were given a maximum score of 1.0, with

Table 1. Comparison of Historical and Recent Survival in Patients With NSCLC and Brain Metastases

	1985-2005		2006-2014			
	All NSCLC, DS-GPA		Nonadenocarcinoma NSCLC Lung-molGPA[a]		Adenocarcinoma NSCLC Lung-molGPA[a]	
Lung GPA Score	MS, mo	Patients, No. (%)	MS, mo	Patients, No. (%)	MS, mo	Patients, No. (%)
0.0-1.0	3.0	254 (14)	5.3	175 (26)	6.9	337 (22)
1.5-2.5	5.5	705 (38)	9.8	324 (49)	13.7	664 (44)
2.5-3.5	9.4	713 (40)	12.8	166 (25)	26.5	455 (30)
3.5-4.0	14.8	161 (9)		0	46.8	65 (4)
Overall	7.0	1833 (100)	9.2	665 (100)	15.2	1521 (100)

Abbreviations: DS, diagnosis-specific; GPA, graded prognostic assessment; MS, median survival; NSCLC, non–small-cell lung cancer.

[a] The Lung-molGPA is the updated DS-GPA designed from the data in the present study.

Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

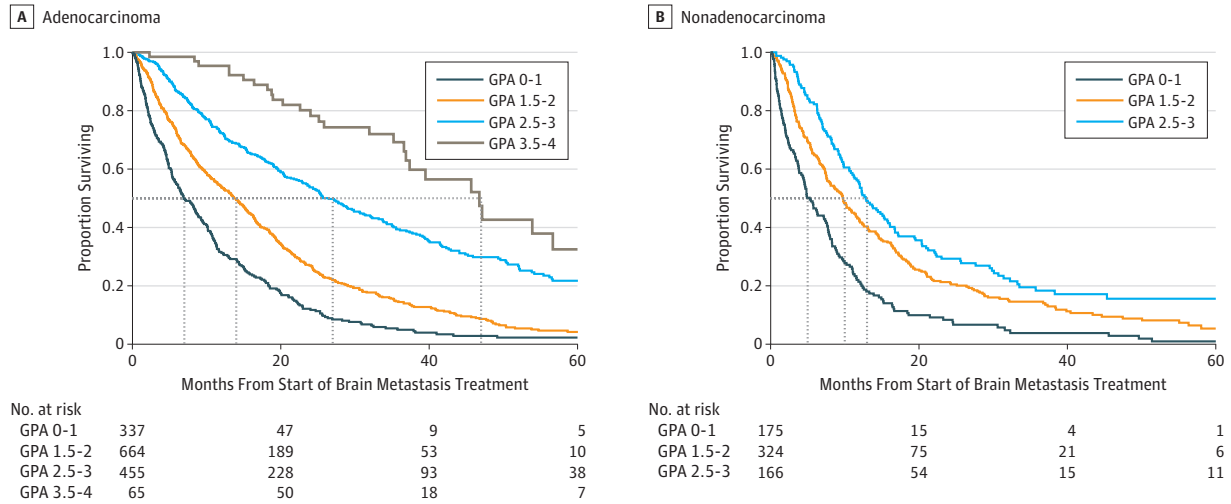
	GPA Scoring Criteria[a]			
Prognostic Factor	0	0.5	1.0	Patient Score[b]
Age, y	≥70	<70	NA	___
KPS	<70	80	90-100	___
ECM	Present		Absent	___
Brain metastases, No.	>4	1-4	NA	___
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos	___
Total	NA	NA	NA	___

Abbreviations: DS, diagnosis-specific; ECM, extracranial metastases; GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; MS, median survival; NA, not applicable; neg/unk, negative or unknown; NSCLC, non–small-cell lung cancer; pos, positive.

[a] Adenocarcinoma MS in months by GPA: 0-1.0 6.9; 1.5-2.0, 13.7; 2.5-3.0 ,26.5; and 3.5-4.0, 46.8; nonadenocarcinoma MS in months by GPA: 0-1.0, 5.3; 1.5-2.0, 9.8; 2.5-3.0, 12.8.

[b] Evaluating clinician completes this column.

Figure. Kaplan-Meier Curves Showing Survival by the Lung-molGPA for Non–Small-Cell Lung Cancer



GPA indicates graded prognostic assessment.

higher scores corresponding to better prognosis. These included KPS from 90 to 100 (HR, 0.6 vs KPS ≤70), no extracranial metastases (HR, 0.5), and *EGFR* or *ALK* positivity (HR, 0.5 vs *EGFR* and *ALK* negativity or unknown). The remaining 2 factors, age and number of brain metastases, had smaller effect sizes (HR, 0.7 and 0.8, respectively) and were given a maximum score of 0.5. Thus, the maximum score remained 4.0; the parameters of the new Lung-molGPA are detailed in **Table 2.**

Survival rates by the 4 prognostic classes are detailed in Table 1 and illustrated in the **Figure.** Only 4% of participants had Lung-molGPA scores of 3.5 to 4.0 (n = 65); however, this group had median survival of nearly 4 years. All adjacent classes had

significantly different hazard functions (unadjusted $P = .03$ for 1 vs 2; $P < .001$ for 2 vs 3; and $P < .001$ for 3 vs 4).

Nonadenocarcinoma

The 4 original variables were confirmed to be prognostic in the nonadenocarcinoma cohort. Mutation status was not routinely tested in this cohort and therefore not a part of this analysis. Although HRs suggested slightly different optimal cutoffs for age and number of brain metastases compared with adenocarcinoma, these differences did not produce a substantially better prognostic index. Therefore, we retained the same variable weighting for the 2 cohorts, although nonadenocarcinoma had a maximum score of 3.0, since patients could not receive a point for *EGFR* or *ALK* positivity. Overall survival was lower for the 3 classes relative to adenocarcinoma, as detailed in Table 1. All adjacent classes had significantly different hazard functions (unadjusted $P < .001$ for 1 vs 2; and $P = .04$ for 2 vs 3).

Discussion

Survival for patients with brain metastases has improved over the past 2 decades. In our updated Lung-molGPA, median survival now ranges from 3.0 to 46.8 months. The DS-GPA has unveiled nuances in management not previously appreciated: (1) recent secondary analyses applying the DS-GPA to landmark randomized trials showed that patients with good DS-PGA prognosis (score >3) achieved a survival benefit with the addition of WBRT to SRS[12,13] contrary to the current clinical trend to avoid WBRT; (2) The survival benefit of *ALK* alterations found by the Lung-molGPA has been reported by others[14]; and (3) contrary to the findings of a study that did not use the DS-GPA,[15] the number of brain metastases is a prognostic factor in terms of survival. Accurate prognosis is a vital factor to inform patients, their families, and their physicians when making often difficult cancer treatment decisions.

Limitations

the study has some limitations. The data are retrospective with inherent selection bias, so they cannot be used to conclude that one treatment is better than another. Also, the type, timing, combination, and sequence of chemotherapy and targeted therapies, both before and after the diagnosis of brain metastases, varied widely thus precluding the ability to assess the effect of these agents on the study patients.

Conclusions

The updated Lung-molGPA defined in the present study was associated with improved prognostic ability over the RTOG RPA and the original DS-GPA by incorporating the effect of *EGFR* and *ALK* gene alterations on survival in patients with NSCLC and brain metastases. The Lung-molGPA is a user-friendly tool that may facilitate clinical decision making and better design and stratification for future clinical trials in this heterogeneous patient population.

ARTICLE INFORMATION

Accepted for Publication: July 18, 2016.

Published Online: November 17, 2016. doi:10.1001/jamaoncol.2016.3834

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Conflict of Interest Disclosures: The following authors have served as consultants on other topics unrelated to the present work: Dr Kirkpatrick (Varian), Dr Shih (Genentech), Dr Roberge (Varian, Siemens, Accuray, BrainLab, Elekta), Dr Alexander (Abbvie, Precision Health Economics, Amgen), and Dr Mehta (Abbott, Novelos, Phillips, BMS, Celldex, Roche, Elekta, Novocure, Novartis, Cavion, Pharmacyclics). No other conflicts are reported.

Funding/Support: Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Minnesota; database support and management was provided by Susan Lowry, database programmer and analyst and REDCap Administrator, Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota. Funding was provided by National Institutes of Health (NIH) grant UL1TR000114 from the National Center for Advancing Translational Sciences (NCATS) and NIH grant P30 CA77598 utilizing the Biostatistics and Bioinformatics Core shared resource of the Masonic Cancer Center, University of Minnesota and the NCATS.

Role of the Funder/Sponsor: The funders and sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Invited Commentary

Association of Molecular Marker Status With Graded Prognostic Assessment of Lung Cancer With Brain Metastases

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Historically, the prognosis for patients with brain metastases was thought to be uniformly poor, which led to a purely palliative approach to treating the many patients diagnosed with this very common neurologic complication of cancer. In addition, brain metastases were previously considered a homogeneous disease, despite the myriad of tumors that could potentially spread to the brain and the observed variability in response to local and systemic therapies. Because physicians believed that the vast majority of patients with brain metastases would have uniformly poor outcomes, they adopted whole-brain radiation therapy (WBRT) as the standard of care: it is easy to administer, widely available, and effective at providing palliation.

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As our understanding of brain metastases has evolved, however, interest in clinical trials has intensified; focus on optimizing care has sharpened; acceptance of treatment options such as stereotactic radiosurgery (SRS) has increased; and the need for robust prognostic indices has become evident. One of the first prognostic indices was the Recursive Partitioning Analysis, a system that was based on data from Radiation Therapy Oncology Group (RTOG) trials[1] and that stratified brain metastases into 3 distinct groups using patient age, Karnofsky Performance Status (KPS), primary tumor status, and extracranial disease. The Graded Prognostic Assessment (GPA),[2] which incorporated the number of brain metastases rather than primary tumor status and further subdivided age into 3 categories, allowed for a less subjective and more quantitative prognostic index than the RTOG Recursive Partitioning Analysis. In a later refinement, the Disease-Specific GPA (DS-GPA)[3] further stratified patients with brain metastases by primary site and highlighted the differences among the various tumors that metastasize to the brain.[3] Nonetheless, the need for even better prognostic tools was highlighted by Kondziolka et al,[4] who estimated survival using prognostic scores in combination with clinical, radiologic, and primary tumor data in 150 patients with brain metastases. The researchers then surveyed a group of expert neurosurgeons, radiation oncologists, and medical neuro-oncologists regarding prognosis and found considerable inaccuracy among the predictions: 45% and 18% of surveyed clinician predictions inaccurately estimated patient survival by more than 6 months and more than 12 months, respectively.

In this issue of *JAMA Oncology*, Sperduto and colleagues[5] report on an updated DS-GPA for lung cancer with brain metastases by incorporating genetic and molecular information, the Lung-molGPA. Unlike the previous DS-GPA for lung cancer, which included patient data from 1985 through 2005, this study incorporates data from a contemporary, retrospective multi-institutional database of 2186 patients from 2006 through 2014. Two new factors (*EGFR* mutation and *ALK* rearrangement in adenocarcinoma) combined with the 4 known significant factors (patient age, number of brain metastases, extracranial disease, and KPS) from the previous Lung DS-GPA further stratified patients into 4 groups with median survival times now ranging from 3.0 to 46.8 months. The most favorable prognostic factors were KPS scores between 90 and 100, absence of extracranial metastases, and *EGFR* or *ALK* positivity in adenocarcinoma. Patients with the highest GPA scores of 3.5 to 4.0 represented only 4% of all patients. The overall median survival for the group increased from 7 months at the time of the DS-GPA design to 12 months in the contemporary data.