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Graded Prognostic Assessment (GPA) for Patients With Lung Cancer and Brain Metastases: Initial Report of the Small Cell Lung Cancer GPA and Update of the Non-Small Cell Lung Cancer GPA Including the Effect of Programmed Death Ligand 1 and Other Prognostic Factors

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Abstract

Purpose: Patients with lung cancer and brain metastases represent a markedly heterogeneous population. Accurate prognosis is essential to optimally individualize care. In prior publications, we described the graded prognostic assessment (GPA), but a GPA for patients with small cell lung cancer (SCLC) has never been reported, and in non-small cell lung cancer (NSCLC), the effect of programmed death ligand 1 (PD-L1) was unknown. The 3-fold purpose of this work is to provide the initial report of an SCLC GPA, to evaluate the effect of PD-L1 on survival in patients with NSCLC, and to update the Lung GPA accordingly.

Methods and Materials: A multivariable analysis of prognostic factors and treatments associated with survival was performed on 4183 patients with lung cancer (3002 adenocarcinoma, 611 nonadenocarcinoma, 570 SCLC) with newly diagnosed brain metastases between January 1, 2015, and December 31, 2020, using a multi-institutional retrospective database. Significant variables were used to update the Lung GPA.

Results: Overall median survival for lung adenocarcinoma, SCLC, and nonadenocarcinoma was 17, 10, and 8 months, respectively, but varied widely by GPA from 2 to 52 months. In SCLC, the significant prognostic factors were age, performance status, extracranial metastases, and number of brain metastases. In NSCLC, the distribution of molecular markers among patients with lung adenocarcinoma and known primary tumor molecular status revealed alterations/expression in PD-L1 50% to 100%, PD-L1 1% to 49%, epidermal growth factor receptor, and anaplastic lymphoma kinase in 32%, 31%, 30%, and 7%, respectively. Median survival of patients with lung adenocarcinoma and brain metastases with 0, 1% to 49%, and ≥50% PD-L1 expression was 17, 19, and 24 months, respectively ($P < .01$), confirming PD-L1 is a prognostic factor. Previously identified prognostic factors for NSCLC (epidermal growth factor receptor and anaplastic lymphoma kinase status, performance status, age, number of brain metastases, and extracranial metastases) were reaffirmed. These factors were incorporated into the updated Lung GPA with robust separation between subgroups for all histologies.

Conclusions: Survival for patients with lung cancer and brain metastases has improved but varies widely. The initial report of a GPA for SCLC is presented. For patients with NSCLC-adenocarcinoma and brain metastases, PD-L1 is a newly identified significant prognostic factor, and the previously identified factors were reaffirmed. The updated indices establish unique criteria for SCLC, NSCLC-nonadenocarcinoma, and NSCLC-adenocarcinoma (incorporating PD-L1). The updated Lung GPA, available for free at brainmetgpa.com, provides an accurate tool to estimate survival, individualize treatment, and stratify clinical trials.

Introduction

Lung cancer remains the most common cause of death from cancer, both in the United States and globally.[1,2] Worldwide, in 2020, lung cancer was diagnosed in more than 2.2 million people and nearly 1.8 million died of the disease.[2] In the United States in 2021, lung cancer was diagnosed in an estimated 235,000 patients and an estimated 130,000 died of the disease.[1] Lung cancer represents the most common primary tumor causing brain metastases, accounting for almost 50% of cases. Between 20% and 40% of patients with non-small cell lung cancer (NSCLC) and nearly 50% of patients with small cell lung cancer (SCLC) will develop brain metastases in the course of their disease.[3,4] Including all types of cancer, an estimated 300,000 patients are diagnosed each year with brain metastases in the United States, and the incidence is increasing owing to improved screening efforts, increased sensitivity of newer magnetic resonance imaging (MRI) sequences, and advances in systemic therapies inducing longer survival and hence increasing the temporal risk window for developing brain metastases.[5]

Management of patients with brain metastases is complex for several reasons: the heterogeneity of the patient population; the wide variety of primary malignancies that cause brain metastases; poor drug penetration; genetic clonal selection, which sometimes results in loss of targetable mutations identified in the primary tumor; and exposure to multiple prior therapies resulting in the emergence of resistant phenotypes. After the diagnosis of brain metastases, there are multiple treatment options, including surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), immunotherapy, molecularly targeted therapy, and chemotherapy.

NSCLC

Multiple clinical trials have shown the benefit of immunotherapy in advanced NSCLC. KEYNOTE-024 showed improved survival in patients with programmed death ligand 1 (PD-L1) expression over 50%.[6] This indication was expanded to include patients with PD-L1 expression >1% in 2019 based on data from KEYNOTE-042.[7] Multiple other clinical trials have documented the benefit of additional immunotherapeutic agents, which are now Food and Drug Administration approved, either alone or in combination with chemotherapy, for patients with advanced and metastatic NSCLC.[8–15] These trials, however, either excluded or had very few patients with brain metastases.

Among the trials that included patients with NSCLC and brain metastases, conflicting results have been reported. CheckMate-057,[16] CheckMate-078,[17] and a pooled analysis of KEYNOTE studies 010, 024, and 042[18] showed that patients with baseline asymptomatic or treated brain metastases had similar overall survival (OS) with immunotherapy or chemotherapy, whereas CheckMate 227[19,20] and 9LA[21] as well as a pooled analysis of KEYNOTE studies 021, 189, and 407[22] all showed immunotherapy significantly improved survival compared with chemotherapy. A phase 2 nonrandomized study of 42 patients showed a 29.7% response rate in patients with NSCLC and brain metastases and PD-L1 expression of ≥1% but no response in those with PD-L1 expression <1%.[23]

SCLC

Prophylactic cranial irradiation (PCI) is the standard of care for patients with limited stage SCLC and an option for those with extensive stage disease, based on randomized trials conducted before the era of surveillance MRIs,[24,25] but debate endures because of ongoing concern regarding the neurocognitive toxicity of cranial radiation. More recent prospective randomized trials have shown hippocampal avoidance WBRT provides superior neurocognitive preservation compared with standard WBRT.[26–28] Together, these findings naturally led to randomized trials comparing hippocampal avoidance PCI and standard PCI. These trials[29–31] revealed conflicting results with regards to cognitive outcomes. One possible explanation for these conflicting results is, given the wide heterogeneity of this patient population, the trials were not adequately stratified and thus not comparing patients of similar prognosis.

Prognosis

Evidence-based guidelines based on multiple randomized clinical trials exist for the management of brain metastases.[32–39] These emphasize the importance of understanding prognosis to optimally individualize treatment. There is no accurate contemporary prognostic index for patients with SCLC and brain metastases. There are, however, such indices for NSCLC and many other primary diagnoses. We have previously published a series of articles[40–43] demonstrating that the prognosis for patients with brain metastases varies widely and the factors that determine prognosis vary by primary diagnosis. We developed a prognostic index, the diagnosis-specific graded prognostic assessment (DS-GPA), to estimate survival, guide clinical decision-making, and stratify future clinical trials. The DS-GPA was derived by weighting and normalizing all significant prognostic factors to yield a DS-GPA score, with 0 and 4.0 representing the worst and best prognosis. We also created an online application, available for free at brainmetgpa.com, to facilitate use of this index. Based on this work and our concern that patients with brain metastases were being inappropriately excluded from clinical trials, we developed criteria (the eligibility quotient [EQ]) to guide expansion of clinical trial eligibility for these patients.[43]

The 2016 Lung GPA demonstrated a 15-month median OS for lung adenocarcinoma. Survival varied widely from 5 to 46 months for the worst to best GPA subgroups. Key prognostic factors for the 2016 Lung GPA included molecular profile (epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] mutation status), age, performance status, extracranial metastases, and number of brain metastases.[42,43]

The purpose of this work was 3-fold: (1) to provide the initial report of an SCLC GPA; (2) given the increased use of immunotherapy in NSCLC and the limited data on the prognostic significance of PD-L1 in this clinical setting, we sought to determine the effect of PD-L1 expression and other prognostic factors on survival in patients with NSCLC and brain metastases; and (3) to update the Lung GPA accordingly with this larger contemporary cohort of both patients with SCLC and patients with NSCLC.

Methods and Materials

Patient population

A multi-institutional (20 institutions in 3 countries) investigational review board-approved retrospective database of 4183 patients with lung cancer and newly diagnosed brain metastases diagnosed between January 1, 2015, and December 31, 2020, was created using Research Electronic Data Capture (REDCap) software. Patients with recurrent brain metastases and/or leptomeningeal carcinomatosis were excluded. All other patients who received treatment for brain metastases were included. We do not know how many patients chose supportive care and are not included in the database.

Statistics

Survival was measured from the date of diagnosis of brain metastases to the date of death or last follow-up. The Kaplan-Meier method was used to calculate survival estimates. Multiple Cox regression models were used to estimate hazard ratios (HRs) for OS. Models evaluating treatment included a categorical variable for GPA class and were stratified by institution. Models evaluating treatment exposure after brain metastases used a time-varying covariate to indicate whether treatment had been initiated by time *t*. Analysis was performed using R software, version 4.0.5 (R Foundation for Statistical Computing).

Derivation of the GPA indices

The approach for deriving the updated Lung GPA index was to use multiple Cox regression to identify an initial set of prognostic factors. These factors were then weighted, using half or full point increments, according to the magnitude of effect on survival (ie, HR). The final index was chosen by balancing criteria that included separation of prognostic classes, the percentage of patients in each class, and simplicity of use. Metrics such as the concordance index, R-squared, and log-rank test statistics were used to evaluate model performance. Marginally significant factors were retained only if they afforded nontrivial improvements to the final index. Factors initially considered included those in Table 1. The only other factor considered was tobacco pack-years, which was not prognostic and had missing data for patients known to be tobacco users and was not included in the final model. The number of deaths in the lung adenocarcinoma, nonadenocarcinoma, and SCLC cohorts was 1869, 453, and 409, respectively, which was sufficient for the number of factors modeled.

Results

Characteristics of patients with NSCLC

Table 1 lists patient characteristics, molecular profile, and median OS by histology for the overall data set. The distribution of molecular markers among patients with lung adenocarcinoma and known primary tumor molecular status revealed alterations/expression in PD-L1 50% to 100%, PD-L1 1% to 49%, EGFR, and ALK in 32%, 31%, 30%, and 7%, respectively. Median survival (MS) of patients with lung adenocarcinoma and brain metastases with 0, 1% to 49%, and ≥50% PD-L1 expression was 17, 19, and 24 months, respectively ($P < .01$), confirming PD-L1 is a significant prognostic factor. EGFR, ALK, and

PD-L1 expression were not routinely tested in all patients with lung nonadenocarcinoma or SCLC, and the prognostic significance cannot be determined from the limited numbers.

There was a gradient effect for PD-L1, as shown in Table 1, such that OS increased as PD-L1 increased but not enough to justify further complicating the index. We noticed patients with PD-L1 expression ≥50% were more likely to receive immunotherapy than those with <50% expression; nonetheless, some patients with <50% expression did receive immunotherapy.

Other notable findings include the extent of symptoms and extracranial metastases of these patients. The proportion of patients with adenocarcinoma who were asymptomatic (Karnofsky performance status [KPS] 100) or minimally symptomatic (KPS 90) at the time of diagnosis of the brain metastases was 9% and 33%, respectively. For nonadenocarcinoma, the proportion of patients with KPS 100 and 90 was 6% and 28%, respectively. For SCLC, the proportion of patients with KPS 100 and 90 was 7% and 27%, respectively. Extracranial metastases were present in 62%, 60%, and 58% of patients with SCLC, adenocarcinoma, and nonadenocarcinoma, respectively.

The median time (interquartile range) from diagnosis of the primary tumor to diagnosis of brain metastases (TPDBM) for patients with NSCLC-adenocarcinoma, NSCLC-nonadenocarcinoma, and SCLC was 1 (0–14), 2 (0–10), and 5 (0–10) months, respectively. Based on the nonrandomized utilization of targeted therapies, this appears to delay the development of brain metastases. The median TPDBM for EGFR-mutant patients was 1 (0–19) month, but for those who had received previous targeted therapy, the TPDBM was 22 (11–39) months. Similarly, the median TPDBM for patients with ALK alterations was 5 (0–26) months, but for those who received prior targeted therapy, the TPDBM was 19 (8–41) months. The median TPDBM for patients who expressed PD-L1 was 1 (0–11) month, but for those who received prior immunotherapy the TPDBM was 13 (6–20) months.

Table 1 also shows sex was significant for both adenocarcinoma and nonadenocarcinoma; however, the magnitude of its effect on survival was lower than any of the other factors retained in the GPA, so to include sex, we would have to remove or down-weight other factors. Also, we analyzed sex in previous brain metastases cohorts, and this is the first time we found it to be prognostic. In our 2016 lung cancer study, the HR for male sex was 1.01 for adenocarcinoma (n = 1521) and 1.13 for nonadenocarcinoma (n = 665). It is thus possible that the HRs estimated in the current study could be overestimates of the true effect, further supporting our decision to exclude sex in the current Lung GPA.

Characteristics of patients with SCLC

Table 1 shows the prognostic factors significant ($P < .01$) for survival in patients with SCLC and brain metastases were age, performance status (KPS), extracranial metastases at diagnosis of brain metastases (ECM), and the number of brain metastases. Sex, race, and ethnicity were not significant. EGFR, ALK, and PD-L1 were not routinely tested in these patients with SCLC.

Survival

Figure 1 shows the Kaplan-Meier curves for survival by lung cancer histology and GPA. The median OS for patients with NSCLC-adenocarcinoma, SCLC, or NSCLC-nonadenocarcinoma with brain metastases was 17, 10, and 8 months, respectively. Median follow-up time among patients still alive was 20, 10, and 12 months, respectively. In adenocarcinoma, median OS times for GPA scores of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 6, 15, 30, and 52 months, respectively. In nonadenocarcinoma, median OS times for GPA scores of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 2, 5, 10, and 19 months, respectively. In SCLC, median OS times for GPA scores of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 4, 8, 13, and 23 months, respectively.

A comparison of survival for patients with lung cancer and brain metastases in 2 prior cohorts (1985–2005 and 2006–2014) was published by our group,[42,43] and this current cohort showed continual improvement in survival for lung adenocarcinoma (15 to 17 months from 2006–2014 to 2015–2020, $P < .01$), with no change in survival for patients with nonadenocarcinoma (from 9 to 8 months for the 2006–2014 cohort vs the 2015–2020 cohort, $P = .70$). Survival for patients with lung adenocarcinoma with the best prognosis (GPA 3.5–4.0) improved from 46 months in the 2006 to 2014 cohort to 52 months in the 2015 to 2020 cohort. For patients with nonadenocarcinoma with the best prognosis score, MS improved from 13 to 19 months.

The effect of the molecular profile on survival is shown in Table 1. The risk of death (HR) for patients with negative (wild-type) and unknown EGFR status, relative to positive (mutated), was 1.40 and 2.02, respectively ($P < .01$). The risk of death (HR) for patients with negative (wild-type) and unknown ALK status, relative to positive (altered), was 2.12 and 2.24, respectively ($P < .01$). The risk of death (HR) for patients with PD-L1 expression of 50% to 74%, 25% to 49%, 1% to 24%, 0%, and unknown, relative to 75% to 100% was 1.16, 1.09, 1.29, 1.41, and 1.48, respectively ($P < .01$).

Effect of treatment

Table 2 shows a multivariable analysis of median OS by histology and primary treatment for brain metastases. These data are retrospective, with obvious inherent selection bias, and therefore cannot be used to assess the comparative effectiveness of various treatments. Nonetheless, they are useful for tracking changes in the patterns of care. For example, the use of WBRT alone as the primary treatment for lung adenocarcinoma brain metastases continues to decline from 75% in 1985–2005 to 37% in 2006–2014 to 23% in the current cohort.[43]

Table 3 shows a multivariable analysis of the type and timing of drug therapy for these patients. The aforementioned limitations apply to these data as well. Nonetheless, these data provide some insight into how these drugs are currently being used. PD-L1-positive patients with adenocarcinoma who received immunotherapy after but not before the diagnosis of brain metastases had a slightly lower risk of death (HR, 0.87; $P = .17$) compared with those who did not receive immunotherapy before or after the diagnosis of brain metastases. PD-L1-positive patients with adenocarcinoma who received immunotherapy before the

diagnosis of brain metastases had a slightly higher risk of death (HR, 1.08; $P = .52$) compared with patients who did not receive immunotherapy before the diagnosis of brain metastases.

Patients with mutant EGFR who were naïve to targeted therapy at the time of diagnosis of brain metastases and received EGFR-targeted therapy after the diagnosis of brain metastases subsequently had about half the rate of death (HR, 0.56) as those who did not receive targeted therapy. Patients with mutant EGFR who had received EGFR-targeted therapy (not naïve) before the diagnosis of brain metastases had MS of 15 months (HR, 1.78) compared with 29 months in those who had no EGFR-targeted therapy before diagnosis of brain metastases (Table 1). Patients who initiated EGFR- or ALK-targeted therapy after the diagnosis of brain metastases had a substantially lower subsequent risk of death (HR, 0.56 and 0.54, respectively) compared with those who did not receive such therapy.

Updated Lung GPA

The primary changes in the 2022 Lung GPA from the 2016 Lung GPA are the addition of PD-L1 status to the NSCLC-adenocarcinoma GPA and the creation of unique GPA criteria for each histology (adenocarcinoma, nonadenocarcinoma, and SCLC). The previously identified variables, KPS, ECM, number of brain metastases, age, and EGFR and ALK status, maintained prognostic significance. Table 4 shows the initial report of the SCLC GPA criteria and the updated NSCLC GPA scoring criteria and worksheet. There are 4 common factors (age, performance status, ECM, and the number of brain metastases) in the GPAs for NSCLC-adenocarcinoma, NSCLC-nonadenocarcinoma, and SCLC, although the cutoffs and relative weighting differ in proportion to HRs for each. The criteria also differ in that EGFR, ALK, and PD-L1 are significant for NSCLC-adenocarcinoma only. The updated index is also available in a free online application, available at brainmetgpa.com.

Discussion

These data hold multiple clinical implications but also raise multiple related questions.

How can these prognostic indices best be used by clinicians and in the design of future clinical trials in the immunotherapy era?

With the increasing use of immunotherapy in patients with lung cancer and the increasing incidence of brain metastases, the prognostic significance of PD-L1 status in patients with lung cancer and brain metastases needs to be better clarified. The data presented here quantitate the prognostic significance of PD-L1 status in patients with lung adenocarcinoma and brain metastases and will help clinicians individualize management of patients with this common oncologic problem. In addition, these data illuminate the prognosis and guide management for patients with nonadenocarcinoma NSCLC as well as those with SCLC.

The purpose of prognostic indices is to predict outcomes before treatment, thereby guiding the clinician’s choice of appropriate treatment and providing the patient with perspective to better inform their treatment choices. Predictive tools, in contrast, predict outcomes after treatment. Therefore, the data presented in Table 2 are not intended to show that one particular treatment is superior to another, but they are useful to illustrate patterns of care.

The use of WBRT continues to decline and implementation of SRS alone continues to increase.

Guidelines and molecular profile

Evidence-based multidisciplinary guidelines[33,34] for management of patients with brain metastases emphasize the importance of prognosis to optimally individualize treatment. Those guidelines, however, do not include PD-L1 status and need to be updated to incorporate the data presented here.

Can the SCLC GPA be used to reconcile the conflicting data on PCI, with or without HA, in SCLC?

The randomized trials previously mentioned showing conflicting results[30,31] could undergo secondary analyses with poststratification by the SCLC GPA, as has been done for multiple other trials.[44–47] Such studies could potentially identify which patients would and would not benefit from HA-PCI.

Context with recent and future trials

Many of the landmark trials that confirmed the benefit of immunotherapy in advanced NSCLC excluded patients with brain metastases or had limited eligibility for patients with stable brain metastases.[6–15] The trials that included patients with brain metastases have shown conflicting results regarding the effect of immunotherapy on patients with NSCLC. Some showed a benefit[16–18] whereas others did not.[19–22] Our data, based on a large retrospective sample size, multiple institutions, and real-world clinical practice, show that PD-L1 status is prognostic in patients with NSCLC adenocarcinoma and brain metastases and should be considered in the stratification and design of future clinical trials for this patient population.

Regarding study design for future randomized trials, the data on symptoms presented previously are particularly relevant because of the current debate regarding the proportion of patients who are asymptomatic and whether asymptomatic patients with driver mutations or PD-L1 expression should be randomized to a drug only, SRS only, or drug plus SRS treatment arms. This is both controversial and problematic for several reasons: (1) symptoms can be masked by steroids; (2) to many, deferring local treatment such as SRS for a patient who is symptomatic based on the hope of a prompt response to drug therapy will seem unethical; and (3) if trials randomize patients to a drug-only arm, then the patients show new or progressive brain metastases at the time of the first or second follow-up brain MRI, then crossover from that arm to the SRS arm would be necessary, which would reduce the probability of detecting a difference between the 2 arms. Using the GPA to stratify such trials would mitigate but not eliminate the risk of spending time, limited research funds, and other resources for a large randomized trial only to have that trial be falsely negative for the reasons listed previously. These concerns only amplify the value of large multi-institutional retrospective studies that may illuminate the path forward.

In addition, it is important to note that the GPA also identifies patients with the worst prognosis. Patients with a GPA of 0.0 to 1.0 have poor prognosis, and conservative

management and/or hospice may be appropriate in certain clinical circumstances. Randomized data suggest supportive care is not inferior to WBRT in such patients.[48]

Does targeted therapy delay development of brain metastases?

The TPDBM data presented here suggest but do not prove, because of the nonrandomized utilization of targeted therapies in this retrospective series, that targeted therapy delays the development of brain metastases. These findings are consistent with randomized data on Osimertinib in EGFR-positive patients with NSCLC.[49–51]

Stratification and eligibility for clinical trials

Appropriate stratification of clinical trials is essential to ensure that trial arms are truly comparing similar patients. That is especially true for trials involving patients with brain metastases, given their marked heterogeneity. The GPA is routinely used for this purpose. The clinical trials that have employed the GPA, guidance regarding how the GPA can be used to enhance enrollment of patients with brain metastases in clinical trials, and the definition of the EQ and how it can be used to enroll patients with previously treated brain metastases have been published.[43]

Limitations

Limitations of this study include the retrospective design and inherent selection biases. Because of selection bias, these data cannot be used to conclude the superiority of one treatment over another. Similarly, the data on the type and timing of targeted therapies and immunotherapy (Table 3) should be interpreted with caution. Possible explanations for the apparent lack of benefit of targeted therapies in EGFR-mutant or ALK-rearranged patients who received targeted therapies before the diagnosis of brain metastases include the development of drug resistance or simply that these patients were further along in their disease course.

Furthermore, given the retrospective nature of the data and the relatively small sample size for the patients with NSCLC-nonadenocarcinoma who expressed PD-L1 (191 of 611; Table 3), one should be careful about any conclusions regarding the efficacy of immunotherapy in this subset of patients from these data. Similarly, these data do not provide a reliable way to compare OS in patients who received chemotherapy, immunotherapy, or both before and after the diagnosis of brain metastases. In addition, we do not know how many patients chose supportive care and were not included in this database, hence these data may overestimate survival for the overall population with brain metastases. The lack of a standardized assay for PD-L1 across all institutions is another potential weakness of this study; however, the vast majority, if not all, were performed with Food and Drug Administration-approved assays. Lastly, we did not have data to evaluate the effect of discordance between the molecular profile of the tumor and that of the brain metastases.

Conclusions

This work represents the initial report of an SCLC GPA and an update of the NSCLC-adenocarcinoma and nonadenocarcinoma GPA prognostic indices. PD-L1 status

is prognostic for survival in patients with lung adenocarcinoma and brain metastases and management guidelines should reflect this. Patients with brain metastases are markedly heterogeneous and survival varies widely. The prognostic factors vary not only by primary diagnosis but also by histology. The updated Lung GPA incorporates PD-L1 but also creates unique GPA criteria for each histology (adenocarcinoma, nonadenocarcinoma, and SCLC). Survival and our ability to estimate survival continue to improve. In addition to PD-L1 status, these data reaffirm the significance of previously identified prognostic factors (performance status, extracranial metastases, number of brain metastases, age, EGFR and ALK status) for this patient population. The updated 2022 Lung GPA is useful in clinical decision-making in that more aggressive treatment may be appropriate for patients with good prognosis. The Lung GPA is also useful to stratify clinical trials and to expand eligibility for clinical trials to patients with brain metastases and good prognosis, as defined by the EQ. Including patients with brain metastases in these trials will not only reduce discrimination against those patients but also enhance clinical trial accrual and accelerate scientific progress. Further investigation with both randomized clinical trials and large real-world data sets such as this are needed to optimally individualize care for this heterogeneous population.

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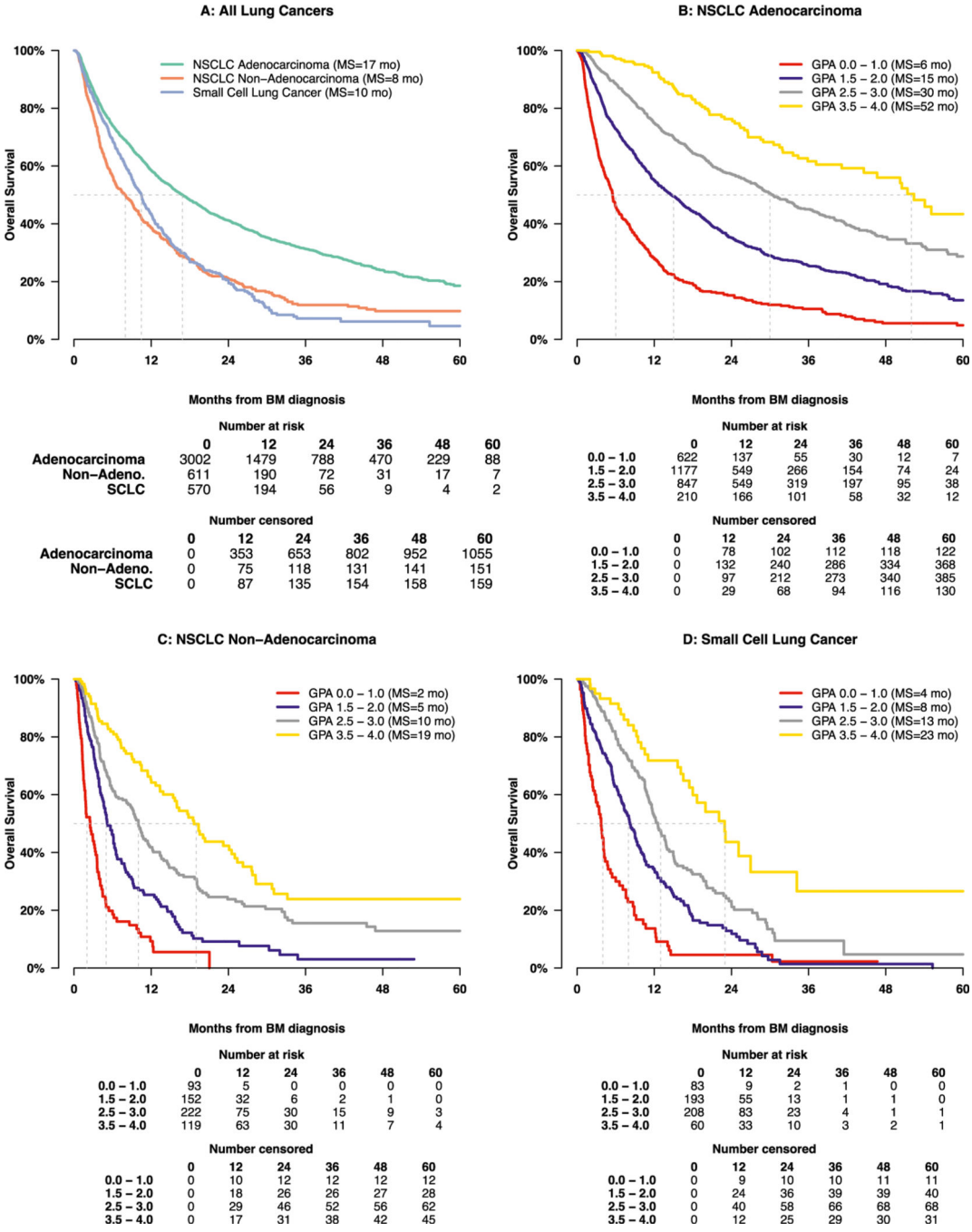

Fig. 1.

Kaplan-Meier curves for survival by Lung GPA class. *Abbreviations:* BM = brain metastases; GPA = graded prognostic assessment; MS = median survival; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

Table 1

Patient characteristics, prognostic factors, and median survival by histology

		NSCLC adenocarcinoma					NSCLC nonadenocarcinoma					Small cell lung cancer				
		n (%)	MS	HR*	95% CI*	*P* value*	n (%)	MS	HR*	95% CI*	*P* value*	n (%)	MS	HR*	95% CI*	*P* value*
Age (y)	<60	886 (30)	25	1.00	Ref	<.01	124 (20)	10	1.00	Ref	<.01	129 (23)	12	1.00	Ref	<.01
	60–64	529 (18)	19	1.13	0.98,1.31		100 (16)	7	0.87	0.62, 1.22		116 (20)	10	1.11	0.80, 1.53	
	65–69	605 (20)	16	1.29	1.13, 1.48		131 (21)	9	1.07	0.77, 1.47		127 (22)	9	1.48	1.07,2.06	
	70–74	454 (15)	14	1.28	1.10, 1.49		114 (19)	9	0.78	0.55, 1.10		128 (22)	11	1.09	0.78, 1.51	
	75–94	528 (18)	11	1.62	1.41, 1.88		142 (23)	4	1.44	1.05, 1.97		70 (12)	9	1.79	1.23,2.61	
Race	White	2088 (70)	16	1.00	Ref	.48	418 (68)	8	1.00	Ref	.49	372 (65)	10	1.00	Ref	.55
	Asian	526 (18)	20	0.96	0.77, 1.21		116 (19)	11	0.73	0.35, 1.52		144 (25)	13	1.21	0.57, 2.54	
	Black	251 (8)	19	0.89	0.75, 1.07		51 (8)	5	1.29	0.86, 1.95		39 (7)	8	0.76	0.51, 1.16	
	Other/unknown	137 (5)	13	1.15	0.90, 1.48		26 (4)	9	1.08	0.64, 1.83		15 (3)	8	1.14	0.57, 2.30	
Ethnicity	Non-Hispanic	2671 (89)	17	1.00	Ref	.37	552 (90)	8	1.00	Ref	.19	524 (92)	11	1.00	Ref	.59
	Hispanic	276 (9)	18	1.06	0.86, 1.30		52 (9)	8	1.25	0.79, 1.98		41 (7)	9	1.24	0.74, 2.08	
	Unknown	55 (2)	9	1.24	0.86, 1.79		7 (1)	6	2.16	0.84, 5.54		5 (1)	9	1.53	0.41, 5.68	
Sex	Female	1615 (54)	20	1.00	Ref	<.01	212 (35)	10	1.00	Ref	.01	282 (49)	9	1.00	Ref	.76
	Male	1385 (46)	14	1.22	1.11, 1.34		399 (65)	7	1.33	1.07, 1.66		288 (51)	11	1.03	0.84, 1.28	
KPS	100	265 (9)	37	1.00	Ref	<.01	39 (6)	15	1.00	Ref	<.01	40 (7)	17	1.00	Ref	<.01
	90	982 (33)	26	1.35	1.10, 1.66		173 (28)	14	1.01	0.64, 1.60		156 (27)	14	1.21	0.73, 2.03	
	80	852 (28)	15	1.93	1.58,2.37		168 (27)	8	1.70	1.08,2.66		159 (28)	10	1.78	1.07,2.96	
	70	485 (16)	9	2.96	2.38, 3.68		109 (18)	5	2.32	1.45, 3.73		121 (21)	6	2.35	1.39, 3.96	
	≤60	344 (11)	4	4.80	3.82, 6.03		107 (18)	3	4.62	2.82, 7.59		78 (14)	4	3.69	2.13,6.40	
	Unknown	74 (2)	32	1.15	0.79, 1.69		15 (2)	21	0.86	0.41, 1.81		16 (3)	25	0.84	0.33,2.11	
ECM	Absent	1132 (38)	27	1.00	Ref	<.01	245 (40)	13	1.00	Ref	<.01	204 (36)	14	1.00	Ref	<.01
	Present	1794 (60)	13	1.71	1.53, 1.90		354 (58)	5	1.85	1.47,2.32		353 (62)	9	1.58	1.25,2.00	
	Unknown	76 (3)	12	1.28	0.94, 1.74		12 (2)	15	1.50	0.75, 2.99		13 (2)	15	0.66	0.28, 1.59	
Number of BM	1	951 (32)	22	1.00	Ref	<.01	252 (41)	12	1.00	Ref	.02	180 (32)	14	1.00	Ref	<.01
	2	452 (15)	21	1.22	1.05, 1.42		92 (15)	7	1.37	1.01, 1.86		68 (12)	12	1.07	0.73, 1.55	
	3	311 (10)	15	1.32	1.12, 1.55		52 (9)	6	1.19	0.80, 1.78		46 (8)	11	1.11	0.72, 1.69	
	4	181 (6)	16	1.40	1.14, 1.72		39 (6)	6	1.47	0.94, 2.31		38 (7)	10	1.30	0.82, 2.04	

		NSCLC adenocarcinoma					NSCLC nonadenocarcinoma					Small cell lung cancer				
		n (%)	MS	HR*	95% CI*	*P* value*	n (%)	MS	HR*	95% CI*	*P* value*	n (%)	MS	HR*	95% CI*	*P* value*
	5	160 (5)	14	1.53	1.23, 1.90		28 (5)	8	1.25	0.77, 2.01		25 (4)	10	1.89	1.14, 3.15	
	6	99 (3)	12	1.59	1.23,2.06		20 (3)	5	1.68	0.97, 2.91		20 (4)	12	1.59	0.88, 2.86	
	7	75 (3)	21	1.03	0.75, 1.41		13 (2)	7	2.60	1.37, 4.94		13 (2)	25	0.98	0.46, 2.09	
	8	74 (2)	16	1.34	0.97, 1.85		17 (3)	7	1.70	0.90, 3.21		11 (2)	4	3.33	1.60, 6.97	
	9	52 (2)	14	1.51	1.06,2.15		6 (1)	3	1.52	0.57, 4.02		10 (2)	15	1.05	0.50, 2.21	
	≥10	640 (21)	12	1.74	1.51,2.00		92 (15)	4	1.66	1.21,2.29		158 (28)	7	2.02	1.51, 2.70	
EGFR	Positive	777 (26)	25	1.00	Ref	<.01	29 (5)	12	1.00	Ref	.43					
	Negative	1813 (60)	16	1.40	1.24, 1.59		253 (41)	9	1.39	0.85, 2.28						
	Unknown	412 (14)	7	2.02	1.59,2.56		329 (54)	6	1.32	0.67, 2.60						
ALK	Positive	161 (5)	44	1.00	Ref	<.01	7 (1)	8	1.00	Ref	.67					
	Negative	2307 (77)	18	2.12	1.66,2.70		271 (44)	10	0.76	0.28, 2.06						
	Unknown	534 (18)	9	2.24	1.63, 3.07		333 (55)	6	0.93	0.31,2.81						
PD-L1	75%–100%	318 (11)	24	1.00	Ref	<.01	51 (8)	7	1.00	Ref	.82					
	50%–74%	273 (9)	23	1.16	0.92, 1.45		38 (6)	8	1.11	0.65, 1.89						
	25%–49%	105 (3)	22	1.09	0.79, 1.50		24 (4)	7	1.05	0.57, 1.95						
	1%–24%	459 (15)	19	1.29	1.05, 1.58		78 (13)	12	0.98	0.62, 1.56						
	0% (negative)	693 (23)	17	1.41	1.17, 1.70		128 (21)	8	1.11	0.74, 1.68						
	Unknown	1154 (38)	13	1.48	1.23, 1.78		292 (48)	6	1.23	0.82, 1.84						

Abbreviations: ALK = anaplastic lymphoma kinase; BM = brain metastases (at initial diagnosis); CI = confidence interval; ECM = extracranial metastases at diagnosis of brain metastases; EGFR = epidermal growth factor receptor; HR = hazard ratio; KPS = Karnofsky performance status at diagnosis of brain metastases; MS = median survival (in months from diagnosis of brain metastases, unadjusted); NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; Ref = reference.

* HR, 95% CI, and P values were estimated by multiple Cox regression of overall survival from time of BM diagnosis, stratified by institution (separate model for each histology).

Table 2

Multivariable analysis of risk of death and median survival by primary treatment for brain metastases

Histology	Overall	WBRT	SRS	WBRT + SRS	Surgery + SRS	Surgery + WBRT	Surgery + WBRT + SRS	Other
NSCLC adenocarcinoma								
n (%)	3002	705 (23)	1357 (45)	35 (1)	380 (13)	71 (2)	5 (0.2)	449 (15)
Mean GPA		1.54	2.05	1.90	2.40	2.19	1.75	1.96
Median survival (mo)	17	9	18	17	28	21	26	18
Risk of death (HR)*		1.00	0.73	0.89	0.62	0.68	0.66	0.81
95% CI*		(Ref)	0.65, 0.83	0.57, 1.39	0.52, 0.74	0.49, 0.94	0.21, 2.06	0.69, 0.95
P value vs WBRT*			<.01	.60	<.01	.02	.47	.01
NSCLC nonadenocarcinoma								
n (%)	611	146 (24)	287 (47)	10 (2)	76 (12)	20 (3)	1 (0.2)	71 (12)
Mean GPA		1.86	2.56	2.65	2.75	2.79	3.00	2.08
Median survival (mo)	8	4	8	14	16	11	NA	9
Risk of death (HR)*		1.00	0.74	0.73	0.47	0.65	NA	0.68
95% CI*		(Ref)	0.58, 0.95	0.32, 1.65	0.33, 0.68	0.35, 1.21	NA	0.47, 0.98
P value vs WBRT*			.02	.44	<.01	.17	NA	.04
Small cell lung cancer								
n (%)	570	314 (55)	108 (19)	4 (1)	10 (2)	19 (3)	1 (0.2)	114 (20)
Mean GPA		1.94	2.62	2.75	2.94	2.40	2.00	2.36
Median survival (mo)	10	9	14	33	14	15	NA	14
Risk of death (HR)*		1.00	0.77	0.82	0.62	0.69	NA	0.72
95% CI*		(Ref)	0.57, 1.02	0.19, 3.45	0.26, 1.48	0.38, 1.25	NA	0.53, 0.96
P value vs WBRT*			.07	.78	.28	.22	NA	.03

Abbreviations: BM = brain metastases; CI = confidence interval; GPA = graded prognostic assessment; HR = hazard ratio; NA = not applicable; NSCLC = non-small cell lung cancer; Ref = reference; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

*Estimates from multiple Cox regression, adjusted for GPA and stratified by institution. HRs are relative to WBRT within each cohort. Median survival estimates are in months and are not adjusted for any other factors. Primary treatment is defined as treatment given within 2 months of BM diagnosis.

Table 3

Survival by type and timing of targeted treatment

Subgroup	n	Median survival (IQR)	HR*	95% CI*	*P* value*	HR†	95% CI†	*P* value†
NSCLC adenocarcinoma	3002	17 (6, 46)						
EGFR-positive	777	25 (11,48)						
Targeted therapy before BM	243	15 (6, 39)	1.78	1.45, 2.18	<.01			
No targeted therapy before BM	534	29 (13, 51)	1.00					
Targeted therapy after BM	376					0.56	0.42, 0.75	<.01
No targeted therapy after BM	158					1.00		
ALK-positive	161	44 (18, NR)						
Targeted therapy before BM	64	35 (12, NR)	1.25	0.74, 2.11	.40			
No targeted therapy before BM	97	46 (28, NR)	1.00					
Targeted therapy after BM	71					0.54	0.21, 1.39	.20
No targeted therapy after BM	26					1.00		
PD-L1 positive	1155	21 (7, 54)						
Immunotherapy before BM	163	15 (5, 38)	1.08	0.86, 1.36	.52			
No immunotherapy before BM	992	23 (7, 58)	1.00					
Immunotherapy after BM	419					0.87	0.72, 1.06	.17
No immunotherapy after BM	573					1.00		
PD-L1 negative/unknown	1847	15 (5, 40)						
Immunotherapy before BM	157	10(4,21)	1.47	1.21, 1.79	<.01			
No immunotherapy before BM	1690	15 (6, 42)	1.00					
Immunotherapy after BM	288					1.13	0.95, 1.34	.16
No immunotherapy after BM	1402					1.00		
Chemotherapy before BM	895	14 (6, 43)	1.11	1.00, 1.23	.04			
No chemotherapy before BM	2107	18 (6, 47)	1.00					
Chemotherapy after BM	781					1.14	1.01, 1.29	.03
No chemotherapy after BM	1326					1.00		
NSCLC nonadenocarcinoma	611	8 (3, 19)						
PD-L1 positive	191	9 (4,21)						
Immunotherapy before BM	49	7 (3, 14)	1.39	0.92, 2.11	.12			

Subgroup	n	Median survival (IQR)	HR*	95% CI*	*P* value*	HR†	95% CI†	*P* value†
No immunotherapy before BM	142	10 (4, 32)	1.00					
Immunotherapy after BM	62					0.74	0.44, 1.22	.23
No immunotherapy after BM	80					1.00		
PD-L1 negative/unknown	420	7 (3, 19)						
Immunotherapy before BM	34	7 (3, 14)	1.12	0.73, 1.72	.61			
No immunotherapy before BM	386	7 (3, 19)	1.00					
Immunotherapy after BM	72					0.72	0.50, 1.02	.06
No immunotherapy after BM	314					1.00		
Chemotherapy before BM	219	8 (3, 19)	1.05	0.85, 1.29	.65			
No chemotherapy before BM	392	8 (3, 20)	1.00					
Chemotherapy after BM	143					0.96	0.73, 1.25	.74
No chemotherapy after BM	249					1.00		
Small cell lung cancer	570	10 (5, 20)						
Immunotherapy before BM	70	9 (3, 15)	1.09	0.79, 1.49	.60			
No immunotherapy before BM	500	11 (5,20)	1.00					
Immunotherapy after BM	112					0.70	0.52, 0.95	.02
No immunotherapy after BM	388					1.00		
Chemotherapy before BM	331	9 (4, 17)	1.46	1.18, 1.80	<.01			
No chemotherapy before BM	239	12 (7, 23)	1.00					
Chemotherapy after BM	170					0.83	0.55, 1.25	.38
No chemotherapy after BM	69					1.00		

Abbreviations: ALK = anaplastic lymphoma kinase; BM = brain metastases; CI = confidence interval; EGFR = epidermal growth factor receptor; GPA = graded prognostic assessment; HR = hazard ratio; IQR = interquartile range; NR = not reached; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1.

*Estimated using multiple Cox regression, adjusted for GPA, and stratified by institution.

†Estimated using multiple Cox regression, adjusted for GPA, and stratified by institution. A time-varying covariate was used to indicate whether a patient had initiated therapy after BM by time *t*. Patients who initiated therapy before diagnosis of BM were excluded from analysis of treatment initiation after BM.

Median survival is in months from date of BM diagnosis.

Table 4

Worksheet for calculation of the 2022 lung graded prognostic assessment (Lung GPA)

NSCLC adenocarcinoma	Prognostic factor	0	0.5	1.0	1.5	2.0	Patient score	Total score	Median survival (IQR)
	KPS at BM dx	≤70	80	90–100	NA	NA		0.0–1.0	6 (2, 13)
	Age at BM dx	≥70	<70	NA	NA	NA		1.5–2.0	15 (5, 38)
	Number BM	≥5	1–4	NA	NA	NA		2.5–3.0	30 (12, NR)
	ECM at BM dx	Present	NA	Absent	NA	NA		3.5–4.0	52 (25, 69)
	EGFR and ALK	Both negative or unknown	EGFR or ALK NA positive	NA	NA	NA			
	PD-L1	Negative or unknown	Positive	NA	NA	NA			
						Sum =			

NSCLC nonadenocarcinoma	Prognostic factor	0	0.5	1.0	1.5	2.0	Patient score	Total score	Median survival (IQR)
	KPS at BM dx	≤60	NA	70	80	90–100		0.0–1.0	2(1,4)
	Age at BM dx	≥70	<70	NA	NA	NA		1.5–2.0	5 (3, 12)
	Number BM	≥5	1–4	NA	NA	NA		2.5–3.0	10 (4,21)
	ECM at BM dx	Present	NA	Absent	NA	NA		3.5–4.0	19 (8, 33)
						Sum =			

Small cell lung cancer	Prognostic factor	0	0.5	1.0	1.5	2.0	Patient score	Total score	Median survival (IQR)
	KPS at BM dx	≤60	70	80	90	100		0.0–1.0	4 (2, 8)
	Age at BM dx	≥75	<75	NA	NA	NA		1.5–2.0	8 (4, 15)
	Number BM	≥8	4–7	1–3	NA	NA		2.5–3.0	13 (7,23)
	ECM at BM dx	Present	Absent	NA	NA	NA		3.5–4.0	23 (11, NR)

Abbreviations: ALK = anaplastic lymphoma kinase; BM = brain metastases; dx = diagnosis; ECM = extracranial metastases; EGFR = epidermal growth factor receptor; GPA = graded prognostic assessment; IQR = interquartile range; KPS = Karnofsky performance status; NA = not available; NR = not reached; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1.

PD-L1 positive is defined as ≥1%.