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A molecular graded prognostic assessment (molGPA) model specific for estimating survival in lung cancer patients with leptomeningeal metastases

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ABSTRACT

Objectives: Leptomeningeal metastases (LM) had increased in advanced non-small-cell lung cancer (NSCLC) over the last 10 years. The survival outcome remained overall poor, heterogeneous and was reported in association with genotypes in lung cancer patients with LM. Graded prognostic assessment model integrated with molecular alterations (molGPA) might be accurate for outcome prediction of LM patients, but needs to be established.

Materials and methods: We retrospectively screened 8921 consecutive lung cancer patients from January 2011 to March 2018. A total of 301 patients diagnosed as LM were enrolled, and randomly divided into training and validation sets after stratified by gender and age. A molGPA score for each patient was calculated based on the weighted significant parameters including gene mutations.

Result: The median OS for the 301 patients was 9.2 months (95%CI: 7.9–10.5). In the training set, *EGFR/ALK* positivity, Karnofsky performance score (KPS) score ≥ 60 and absence of extracranial metastasis (ECM) independently predicted better OS. We developed a molGPA model based on above significant prognostic factors. This molGPA model classified LM patients into three prognosis groups of high, intermediate and low risk (molGPA score of 0, 0.5–1.0 and 1.5–2.0, respectively. The median OS of high, intermediate and low risk LM patients in the training set was 0.3, 3.5 and 15.9 months, respectively ($p < 0.001$). In the validation set, the median OS was 0.9, 5.8 and 17.7 months in the three molGPA subgroups, accordingly ($p < 0.001$). The C-index of this model in training and validation sets was 0.70 (95%CI: 0.66-0.73) and 0.64 (95%CI: 0.58-0.70) respectively.

Conclusion: The LM molGPA model with integration of gene status, KPS and ECM can accurately classify lung cancer patients with LM into diverse prognosis.

1. Introduction

Leptomeningeal metastases (LM) are a severe complication of systemic cancer usually occurring in advanced stages which affect approximately 1–10% of patients with solid tumors. [1–6] The incidence of LM (3–5%) in advanced NSCLC has increased over the last 10 years, especially in subgroups of patients with targetable mutations [6–8]. Although therapies such as molecular targeted treatments and immunotherapies have been described, standard treatment for LM is yet to be established [6,8–13].The median OS of lung cancer patients with LM is poor though with improvement from a historical 1–3 months to 3–11 months by modern systemic therapies [6,7,9]. This trend suggests that there will be an increase in the prevalence of lung cancer patients with LM in the coming years. Accurate prognosis model for these heterogeneous patients is warranted to appropriately manage patients in the clinical practice.

There were already two classical models used for predicting outcomes in patients with LM of solid tumors. Mostly based on the clinical manifestations like Karnofsky performance score (KPS), extracranial metastasis (ECM) and symptoms, the US National Comprehensive Cancer Network (NCCN) guidelines (version 1, 2018) for patients with LM of solid tumors divided them into two categories: good risk and poor

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risk. [7,14] Good risk patients have a better chance of achieving higher response rate or even longer survival [9]. According to the results of cerebrospinal fluid (CSF) cytology test and brain Magnetic Resonance Imaging (MRI), leptomeningeal tumor spread can be distinguished to diffuse type and nodular type. Moreover, the first is always referred to a good prognosis [1,9].

Our previous study showed that LM were much more frequently seen in *EGFR*- mutated patients. [6] And patients with *EGFR* mutations have a better OS than those with *EGFR* wild types. [13] Due to the existence of blood-brain barrier, many treatments in the past were often considered futile for central nervous system metastasis, especially meningeal metastasis [15]. But, recent molecular therapies have shown high penetration to blood-brain barrier and promising antitumor effects in lung cancer patients with LM [6,7,10–1316–18]. Thus, in the context of targeted therapies, those two models without integration of molecular parameters might not be appropriate for estimating the prognosis of lung cancer patients with LM, especially in the patients with actionable mutations.

We performed this study to establish a lung cancer specific graded prognostic assessment model with integration of molecular alterations (molGPA) to estimate survival in lung cancer patients with LM.

2. Materials and methods

2.1. Study groups

We retrospectively screened 8921 consecutive lung cancer patients at Guangdong Lung Cancer Institute (GLCI) from January 2011 to March 2018. Among these patients, we identified 336 lung cancer patients (3.8%) who were diagnosed as LM in our institute. The diagnostic criteria of LM were CSF positive for tumor cells, or CSF liquid biopsy positive for *EGFR* mutations or *ALK* rearrangements, or typical imaging of brain MRI (linear or micro-nodular pial enhancement in gadolinium-enhanced brain MRI) [7,14,19]. Twenty patients who were lost to follow-up and fifteen patients who had no sufficient electronic medical records in our hospital were excluded from this study. As a result, we analyzed 301 patients who received any kind of anti-cancer treatment in our hospital and had sufficient clinical information (baseline demographics, clinical presentations, and treatment course). They were randomly divided into training set (200 patients) and validation set (101 patients) after stratified by gender and age. This retrospective study was approved by the Hospital's Research Ethic Committee, and complied with the regulations of clinical studies.

2.2. Parameters

The electronic medical records of the enrolled patients were reviewed, including their demographic data, laboratory and imaging examinations, clinical presentations, and major treatment course for LM. Examinations included their histology types, gene profiles of *EGFR* mutation and *ALK* alteration, Thinprep cytologic test (TCT) and brain MRI. Treatments including Tyrosine Kinase Inhibitor (TKI), chemotherapy, radiotherapy such as WBRT and WBI were recorded in this study. Therapeutic regimens for most cases were carried out after multidisciplinary discussions in our institute. Continuous variables were categorized based on clinical reasoning and statistical methods. Age was grouped as >63 years or ≤ 63 years. KPS status was grouped as a score of ≥ 60 or <60.

2.3. Statistical analysis

OS was defined from the date of initial diagnosis of LM to the date of death or censored at the date of last follow-up (November 14, 2018). Variables were compared by the chi-square test and Fisher's exact test. Survival was estimated with the Kaplan-Meier method and compared by the log-rank test between different types. We used multiple Cox proportional hazards regression analysis on the training set to select and weight variables to be included in the novel LM molGPA. All prognostic factors were weighted for significance by statistical significance and hazard ratios (HR). The final index was chosen based on separation of prognostic types and simplicity. Harrell's C index was utilized to estimate the discriminative ability of the various types. Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL.), Stata MP 15.0 and R version 3.5.1. A p-value of < 0.05 in a two-tailed test was considered to indicate statistical significance.

Table 1
Characteristics of the Training and Validation Sets of the 301 Lung Cancer Patients with Leptomeningeal Metastases.

Variables	Training set (N = 200)	Validation Set (N = 101)	*P*-value
Age			0.96
> 63	48(24.0%)	24(23.8%)	
≤63	152(76.0%)	77(76.2%)	
Gender			1
Male	99(49.5%)	50(49.5%)	
Female	101(50.5%)	51(50.5%)	
Histology subtype			0.90
Adenocarcinoma	192(96.0%)	98(97.0%)	
Non-adenocarcinoma	8(4.0%)	3(3.0%)	
KPS at diagnosis of LM			0.97
≥60	156(78.0%)	79(78.2%)	
< 60	44(22.0%)	22(21.8%)	
Gene status			0.71
EGFR/ALK mutation[b]	164(82.0%)	81(80.2%)	
Wild type	27(13.5%)	15(14.9%)	
Unknown	9(4.5%)	5(4.9%)	
TCT[a]			0.30
Positive	74(37.0%)	38(37.6%)	
Negative	61(30.5%)	23(22.8%)	
Unknown	65(32.5%)	40(39.6%)	
MRI			0.89
Positive	143(71.5%)	73(72.3%)	
Negative	57(28.5%)	28(27.7%)	
BM			0.78
Yes	139(69.5%)	73(72.3%)	
No	55(27.5%)	24(23.8%)	
Unknown	6(3.0%)	4(3.9%)	
Neurological symptoms			0.50
Yes	113(56.5%)	57(56.4%)	
No	76(38.0%)	35(34.7%)	
Unknown	11(5.5%)	9(8.9%)	
ECM			0.58
Present	158(79.0%)	77(76.2%)	
Absent	42(21.0%)	24(23.8%)	
Treatments before diagnosis of LM			0.65
TKIs	138(69.0%)	65(64.3%)	
Non-TKI therapy	23(11.5%)	15(14.9%)	
Without treatments	39(19.5%)	21(20.8%)	
Therapy for LM			0.23
TKI	78(39.0%)	42(41.6%)	
Radiotherapy	38(19.0%)	23(22.8%)	
Chemotherapy	40(20.0%)	23(22.8%)	
Supportive care	73(36.5%)	30(29.7%)	
Other	4(2.0%)	3(3.0%)	

[a] Thinprep cytologic test.
[b] EGFR/ALK TKI sensitive mutation.

3. Results

3.1. Baseline characteristics of the study groups

The baseline characteristics of the study groups (301 patients) were presented in Table 1. There was no significant difference in baseline characteristics between the training set (200 patients) and validation set (101 patients). LM were diagnosed at a median age of 56 (range, 26–86) years and 55 (range, 27–77) years respectively in these two sets.

In all groups, there was a preponderance of adenocarcinoma. The majority of these patients were detected with *EGFR/ALK* alteration (245/301, 81.4%) and 67.4% (203/301) received targeted therapy before they were diagnosed as LM. More than three-quarters of these patients presented with younger age (age < 60 years), relatively good performance status (KPS ≥ 60) and ECM. The positive rate of cerebrospinal fluid TCT and brain MRI in the detected patients was 57.1% (112/196) and 71.8% (216/301) respectively. Regarding treatments modalities for LM, 120 (40.0%) patients received TKI therapy, 61 (20.3%) patients received radiotherapy, and 48 (16.0%) patients received chemotherapy. Nearly one third of these patients received supportive care alone after they were diagnosed as LM.

3.2. Validation of lung-molGPA model in lung cancer patients with LM

Previously reported lung-molGPA model was tested in 301 lung cancer patients with LM of this study. Patients with lung-molGPA score of 3.5–4.0 showed a median OS of 17.7 months, which was numerically longer than other groups. (Median OS in months by lung-molGPA: 2.5–3.0, 11.0; 1.5–2.0, 7.0; 0–1.0, 1.3, respectively) However, no statistically significant difference was seen between the median OS of patients with molGPA score of 2.5–3.0 and 3.5–4.0 (p = 0.181). (Supplementary data 1). To optimize the molGPA model for LM of lung cancer, we reanalyzed data from 301 lung cancer patients with LM in this study.

3.3. Survival after leptomeningeal metastases and prognostic factors

For the training set, the median OS was 9.2 (95%CI: 7.7–10.7) months, and the 1- and 2-year OS rates were 38.0% and 15.8% respectively. In the validation set, the median OS was 9.8 (95%CI: 6.7–12.9) months, and the 1- and 2-year OS rates were 40.9% and 19.5% respectively.

We explored the prognostic significance of variables in these patients (Table 2). In the univariate and multivariate analysis, prognostic factors that predicted better OS in the training set were as follows: *EGFR/ALK* positivity (HR: 0.5(0.4–0.8), $p = 0.002$), KPS score ≥60 (HR: 0.2(0.1–0.3), $p < 0.001$) and absence of ECM (HR: 0.6(0.4–0.8), $p = 0.005$).

3.4. Establishment and internal validation of the novel molGPA model for LM of lung cancer

We developed a novel molGPA model for LM of lung cancer using three parameters identified in multivariate analysis: mutation, KPS, ECM. Parameters with larger effect sizes like KPS (HR, 0.2) from 80 to 100 were given a maximum score of 1.0. The remaining two factors, gene status and ECM, had smaller effect sizes (HR, 0.5 and 0.6, respectively) and were given a maximum score of 0.5 (Table 3). LM molGPA score was calculated for each patient and categorized into three groups: 0 (group 1, high risk), 0.5–1.0 (group 2, immediate risk), 1.5–2.0 (group 3, low risk). The median OS for the training set patients with LM molGPA score of 0, 0.5–1.0 and 1.5–2.0 was 0.3, 3.5 and 15.9 months, respectively. In the validation set, the median OS for the three subgroups was 0.9, 5.8 and 17.7 months, respectively (Table 4). Kaplan-Meier curves for OS probability prediction of the training set and validation set were showed in Figs. 1 and 2, which demonstrated significant separations among three groups (In the training set, group1 vs. group 2: $p < 0.001$, group 1 vs. group 3: $p < 0.001$, group 2 vs. group 3: $p < 0.001$. In the validation set, group 1 vs. group 2: $p < 0.001$, group 1 vs. group 3: $p < 0.001$, group 2 vs. group 3: $p = 0.002$.). Kaplan-Meier curves for OS in the training and validation sets were shown in Supplementary Data 2 and Supplementary Data 3. The C-index of this model for the training set and validation sets was 0.70 (95%CI: 0.66–0.73) and 0.64 (95%CI: 0.–0.70) respectively.

Table 2
Univariate and Multivariate Analysis of Overall Survival of the Training Set.

Variables	Univariate		Multivariate	
	HR(95%CI)	*p* value	HR(95%CI)	*p* value
Age(≤63 vs. > 63)	0.9(0.6-1.3)	0.45		
Gender(female vs. male)	1.1(0.8-1.5)	0.78		
Type(non-adeno [a] vs. adeno)	0.8(0.3-2.1)	0.64		
TCT(no vs. yes)	0.9(0.6-1.3)	0.51		
TCT(unknown vs. yes)	0.7(0.4-1.1)	0.13		
MR(no vs. yes)	0.9(0.6-1.5)	0.78		
*Mutation(yes vs. no)	0.4(0.3-0.7)	< 0.01	0.5(0.4-0.80)	< 0.01
KPS(≥60 vs. < 60)	0.2(0.1-0.3)	< 0.01	0.2(0.1-0.3)	< 0.01
BM(no vs. yes)	0.9(0.7-1.3)	0.66		
ECM(no vs. yes)	0.6(0.4-0.9)	< 0.01	0.6(0.4-0.8)	< 0.01
Symptom(no vs. yes)	0.8(0.5-1.2)	0.30		

[a] adenocarcinoma.
* EGFR/ALK TKI sensitive mutation.

Table 3
The Scoring Criteria of the Novel molGPA.

Prognostic Factor	novel molGPA for LM		
	0	0.5	1
KPS	< 60	60-70	80-100
ECM	present	absent	
Gene status	#-	#+	

#-: Absence of EGFR/ALK TKI sensitive mutation.
#+: EGFR/ALK TKI sensitive mutation.

4. Discussion

Lung cancer patients with LM or BM usually had a poor prognosis. Mutations of driver genes were very common in these patients. Notably, our previous study showed LM occurred at a higher frequency in *EGFR*-mutated lung cancer patients (9.4% vs 1.7%). [6] Molecular therapies have shown promising antitumor effects in lung cancer patients with LM. Thus, a prognostic model with the addition of molecular information might be better to stratify these heterogeneous patients into diverse prognosis. On the other hand, the biological and clinical characteristics of lung cancer patients with LM may be different from patients with BM [6,7]. Previously reported lung-molGPA model for lung cancer patients with BM needs further validation or optimization in patients with LM.

To the best of our knowledge, this study was the first and largest study focusing on establishing a molGPA model for lung cancer patients with LM. First, we tested the previously reported lung-molGPA model in 301 LM patients of this study. We found this model could not discriminate the survival outcome between patients with molGPA scores of 2.5–3.0 and 3.5–4.0. Then, according to the significance of each parameter in multivariate Cox model, we optimized a LM molGPA model by weighing in significant clinical and molecular parameters: KPS score, *EGFR/ALK* alteration and ECM. In both the training and validation set, patients with the LM molGPA score of 1.5–2.0 (low risk group) were more likely to have a better OS than the other two groups. Considering that the prognosis of lung cancer patients with LM is improving with molecular therapies, our LM molGPA model integrating driver gene mutations might have potential clinical implications. This model is easy to apply and might help clinicians to accurately classify lung cancer patients with LM into diverse prognosis.

Gene status (*EGFR/ALK* alteration) is of significance for lung cancer patients with LM in the present study (HR: 0.5(0.4–0.8), $p = 0.002$). Consistent with other studies, patient with *EGFR/ALK* alteration, which were routinely tested nowadays, had a better OS than those with wild type [13,20]. Diverse gene status generally means to distinct targeted

Table 4
Grouped Survival of Training Set and Validation Set in Lung Cancer Patients with LM.

Novel molGPA score	Median Survival of Training set (m)	Patient, No. (%)	Median Survival of Validation set (m)	Patient, No. (%)
0.0(group 1)	0.3	7(3.5)	0.9	3(3.0)
0.5-1(group 2)	3.5	86(43.0)	5.8	55(54.5)
1.5-2(group 3)	15.9	107(53.5)	17.7	43(42.5)

group 1: high risk group group 2: immediate risk group group 3: low risk group.

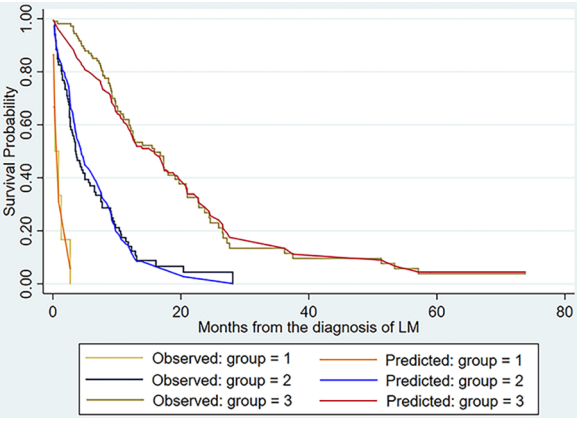

Fig. 1. Kaplan-Meier curves for overall survival probability prediction of the training set: observed versus predicted overall survival. LM, leptomeningeal metastases. group 1: high risk group (molGPA score 0) group 2: immediate risk group (molGPA score 0.5–1.0) group 3: low risk group (molGPA score 1.5–2.0).

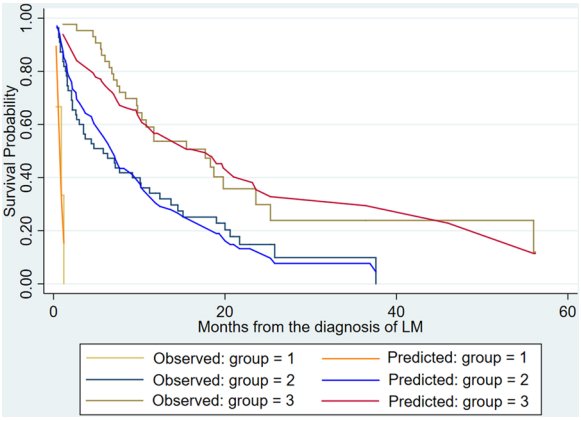

Fig. 2. Kaplan-Meier curves for overall survival probability prediction of the validation set: observed versus Predicted overall survival. LM, leptomeningeal metastases. group 1: high risk group (molGPA score 0) group 2: immediate risk group (molGPA score 0.5–1.0) group 3: low risk group (molGPA score 1.5–2.0).

therapies and clinical outcomes [21]. There were few randomized trials conducted in lung cancer patients with LM who have actionable mutations. However, many retrospective studies revealed that EGFR TKI or ALK TKI had a promising anti-tumor activity for these patients [6–810,11,17,22]. [23,24] Our previous study showed that LM patients who were treated with EGFR TKI had a longer OS compared to those without TKI therapies (10.0 months vs. 3.3 months, P < 0.001), and this findings were consistent with other similar studies. [6,10–12]. With a CSF cytological conversion rate of 64.3%, erlotinib (a first-generation EGFR TKI) showed high penetration rate to blood-brain barrier and promising anti-tumor effect against LM of lung cancer. Besides, the second and third generation EGFR TKIs such as afatinib, osimertinib and AZD3759 also demonstrated an efficacious effect [7,25,26]. When it comes to ALK TKI, studies on the treatment of *ALK*-positive lung cancer patients with LM remained scarce. With an excellent CNS penetration, alectinib (a second-generation *ALK/RET* inhibitor) produced radiological and neurological responses both in the conventional and high dose. [24,27] Overall, *EGFR/ALK* alteration plays an important role in the LM of lung cancer. [28] Lacking of molecular associated parameters, two classical models mentioned above may not be appropriate for lung cancer patients with LM, especially in the patients with actionable mutations.

In our model, the acceptable performance status (KPS score ≥60) was the strongest prognostic factor of better OS for lung cancer patients with LM (HR: 0.17(0.1-0.3), $p < 0.001$). Patients with KPS score 80–100 ha d a better OS than those with KPS 60–70 (Supplementary Data 4). Performance status (PS) was well recognized as the main prognostic factor in lung cancer patients with LM. Several retrospective studies showed that patients with a good Eastern Cooperative Oncology Group PS score (0–1) at the diagnosis of LM had a longer survival than those with a PS score of 2 or more. [6,8,14,16,17,29] KPS score ≥60 was also involved in the NCCN model, to classify LM patients into good risk and poor risk. However, NCCN model did not distinguish the differences between KPS score 60–70 and 80–100, which might weaken the discrimination capacity of the prognostic model.

Absence of ECM is a well-known predictor for better OS in brain metastases (BM) of lung cancer patients. [15,30,31] However, it was rarely mentioned in the prognostic studies on lung cancer patients with LM. In the present study, ECM showed a prognostic significance (HR: 0.6(0.4-0.8), $p = 0.005$). ECM was given a maximum of 0.5 based on its HR and statistical significance. The similar approach was used in the DS-GPA model and Lung molGPA model to predict survival in patients with BM [15,31].

Neurological symptoms, concurrent BM and the result of TCT were not significantly related to OS in our study. However, 105 patients (34.9%) did not perform the CSF TCT in the present study, potentially lead to the negative result of TCT. It is regrettable that CSF TCT was not widely performed in the earlier years. As our previous studies shows, CSF cfDNA is an excellent liquid biopsy medium, which could provide a unique genetic profiles in lung cancer patients with LM and might contribute to the diagnosis and classification of these patients [7,19,32–35]. Further researches are needed to investigate the prognostic significance of CSF cytology test.

Our study has several limitations. The main limitation is its retrospective, single center nature. A prospective and multi-center study would be an ideal validation for this LM molGPA model. Additionally, thirteen patients (13/301, 4.3%) did not conduct gene tests, and clinical information of several outpatients was uncertainty. Both of this may affect the results of the multivariate analysis. Last but not least, therapeutic choices were not included in our prognostic model. Because there was no standard regimen for lung cancer patients with LM and many variables influenced a treatment decision. Several prognostic systems did not include this variable as well [15,36,37].

In conclusion, by combining significant clinical parameters and molecular related parameters: KPS score, *EGFR/ALK* alteration and ECM, we developed and internally validated a novel LM molGPA model. This model could stratify LM patients into high, intermediate and low risk prognosis groups. MolGPA model is easy to apply and may help clinicians to treat LM patients according to their prognosis risk. Thus, this model might contribute to precise management in the era of precision medicine, which needs further extensive validation.

Disclosure

The authors declare no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.03.015.

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