Identification of a High-Risk Group for Brain Metastases in Non-Small Cell Lung Cancer Patients.

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Abstract

Purpose: Identification of a truly high-risk group of brain metastases (BM) in patients with non-small cell lung cancer (NSCLC) could lead to early interventions and probably better prognosis. The objective of the study was to identify this group by generating a multivariable model with recognized and accessible risk factors.

Methods: A retrospective cohort from patients seen at a single center during 2010-2020, was divided into a training (TD) and validation (VD) datasets, associations with BM were measured in the TD with logit, variables significantly associated were used to generate a multivariate model. Model's performance was measured by 10-Fold cross validation of the TD and in the VD with the AUC/C-statistic, Akaike information index, and Press's Q precision test.

Results: From 570 patients with NSCLC with complete records a TD and VD were formed, no significant differences were found amid both datasets. Variables associated with BM in the multivariate logit analyses were age [P 0.021, OR 0.97 (95%CI 0.94-0.99)]; male gender [P 0.010, OR 2.44 (95%CI 1.24-4.82)]; mutational status [P 0.03, OR 2.1 (95%CI 1.07-4.12)]; and carcinoembryonic antigen levels [P 0.002, OR 1.002 (95%CI 1.001 – 1.003)]. BM were diagnosed in 23% of the whole cohort. Stratification into low, medium, or high-risk groups after simplification of the model, displayed a frequency of BM in the VD of 8%, 16% and 40% respectively (P 0.027).

Conclusion: A multivariate model comprising age, gender, CEA, and mutation status allowed the identification of a truly high-risk group of BM in NSCLC patients.

Introduction

Lung cancer (LC) is the most common malignancy and a leading cause of cancer-related death(1). Up to 25–50% of non-small cell lung cancer (NSCLC) patients will develop brain metastases (BM) during their disease course(2), and LC is the most frequent primary tumor to metastasize to the brain(3). BM contribute substantially to the overall cancer mortality because patients with BM usually have a poor prognosis despite multimodal treatments and advances in systemic therapies(3). The identification of a high-risk group of BM in NSCLC could lead to earlier interventions including prophylactic cranial irradiation (PCI). PCI has been examined for several decades as a fraught gauge to prevent BM in NSCLC(4), probably because of the absence of a truly identified high-risk group.

Some authors have reported individual risk factors associated with a higher risk of BM such as age, gender, performance status, levels of tumor markers – including carcinoembryonic antigen (CEA) –, epidermal growth factor receptor (EGFR) mutation status, anaplastic lymphoma kinase (ALK) rearrangement(5); however, until now, there is no universal definition of an accurate high-risk group of BM.

The study aimed to identify a high-risk group of BM from recognized and accessible BM risk factors at diagnosis of NSCLC by building a multivariable model.

Methods

A retrospective cohort – using the following eligibility criteria: confirmed pathologic diagnosis of non-small cell lung cancer (NSCLC), age ≥ 18 years, oncologic follow-up by the thoracic oncology unit (TOU) from January 2020 to July 2020 – was equally randomized into a training (TD) and a validation (VD) dataset. In the TD, associations between variables and the diagnosis of BM were measured with a bivariate logistic regression test, those variables considered as significantly associated with BM ($P < 0.05$) were considered to build a multivariate model, and a logistic regression test was used to measure associations with BM. Variables that – after multivariate logistic test – were still considered significantly associated with BM ($p < 0.05$), were tested for correlations among each other, those variables with a significant correlation were considered for exclusion.

Patients with initial treatment started at the TOU and having all variables associated with BM described in their clinical records (selection criteria) were included in the statistical analyses of the predictor model. Supplemental Fig. 1 (online) describes the sources and methods of selection and inclusion.

The area under the curve (AUC) was measured for the proposed models in the TD to identify the most accurate. Model's performance was measured by a 10-Fold cross-validation of the TD, and in the VD by determining the C-statistic, Akaike information criterion (AIC), and Press's Q precision test.

Predictor variables had to be either studied or present in at least 10% of the studied population for inclusion in the model. Missing data occurred in tumor grade (15%), tumor size (18%), CEA (58%) and NLR (52%), imputation of such large amount of missing data was considered unreliable, and the missing values were included in a separate category as previously done (6); therefore, regarding parameters missing for some of the cohort, statistical tests were calculated for the available data similar to previous reports(7), after these adjustments, complete information used for analysis is reported for 277 patients in the TD and 293 patients in the VD.

For a better clinical understanding of the model, continuous predictor variables were graphed through a receiver operating curve (ROC) to measure sensitivity and 1-specificity for each value, the Youden index (YI) was then calculated and the value with the highest YI rate was used for categorization of the predictor variable. In the TD, the categorization for age ≤ 65 vs > 65 years had the highest YI (YI = 0.191 S = .47 E = 0.71). The cutoff value for CEA was determined as < 20 vs ≥ 20 as we have done previously(8).

Results

General characteristics were described in Supplemental table (online), there were no significant differences between initial TD and VD. Mean age at lung cancer diagnosis was 61.1 years, female gender was more frequent, half of the patients had a smoking history, the most frequent histology was

adenocarcinoma (88%), poorly differentiated NSLC was seen in 50%, mutational status [EGFR mutation (EGFRm) or ALK rearrangement (ALKr)] was positive in 47%, most patients had clinical stage IV at diagnosis (87%), mean CEA levels was 120 pg/mL (Min-Max 0.28–3416), mean initial tumor size was 5.2 cm (Min-Max 1.1–16 cm). Mediastinal (49%), bone (36%), contralateral lung metastases (32%), suprarenal (11%) and liver (10%) were the most frequent non-BM distant anatomic sites.

Univariate and multivariate logistic regression analysis to determine associations between variables and BM in the TD are described in Table 1. Univariate associations was quantified as significant for the following variables: Age [Odds ratio (OR) 0.96, 95% confidence interval (CI) 0.95–0.98, $P < 0.0001$], Male gender [OR 1.6 (95%CI 1.18–2.16) $P = 0.002$], smoking history [OR 0.69 (95%CI 0.51–0.93) $P = 0.017$], adenocarcinoma [OR 0.45 (95%CI 0.27–0.74) $P = 0.002$], Moderate or High histologic grade [OR 3.13 (95%CI 1.13–7.41), $P = 0.009$ and OR 2.2 (95%CI 1.19–6.65) $P = 0.018$], CEA levels [$P = 0.01$, OR 1.002 (95%CI 1.001–1.003)]. Mutational status positive [OR 1.96 (95%CI 1.44–2.66) $p < 0.0001$], clinical stage IV [OR 3.61 (95%CI 2.21–5.88) $P < 0.0001$], pleural disease [OR 0.7 (95%CI 0.51–0.96) $P = 0.02$] and having extrathoracic (non-BM) metastases [OR 1.94 (95%CI 1.42–2.64) $P < 0.0001$], particularly bone metastases [OR 1.93 (95%CI 1.39–2.66) $P < 0.0001$]. After a multivariate conditional analysis test, variables that remained statistically significant were age [OR 0.97 (95%CI 0.94–0.99) $P = 0.021$], male gender [OR 2.44 (95%CI 1.24–4.82) $P = 0.010$], mutational status positive [OR 2.1 (95%CI 1.07–4.12) $P = 0.03$], CEA [OR 1.002 (95%CI 1.001–1.003) $P = 0.002$], no substantial correlation was seen between prediction variables.

Table 1

Univariate and multivariate logistic regression analysis to determine associations between characteristics and the diagnosis of brain metastases in the training dataset (n = 277).

Characteristic	Univariate		Multivariate Intro		Multivariate Conditional (forward)	
	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)
Age	< 0.0001	0.96 (0.95–0.98)	0.026	0.97 (0.94–0.99)	0.021	0.97 (0.94–0.99)
Male vs Female	0.002	1.6 (1.18–2.16)	0.015	2.53 (1.19–5.35)	0.010	2.44 (1.24–4.82)
Smoking +	0.017	0.69 (0.51–0.93)	0.793	0.90 (0.43–1.89)	-	-
Adenocarcinoma vs Non-adenocarcinoma	0.002	0.45 (0.27–0.74)	0.956	0.96 (0.27–3.37)	-	-
Histologic grade	0.034	Ref	0.826	Ref	-	-
Well	0.009	3.13 (1.13–7.41)	0.650	1.50 (0.25–8.78)		
Moderate	0.018	2.82 (1.19–6.65)	0.561	1.67 (0.29–9.59)		
Poor						
Mutational status +	< 0.0001	1.96 (1.44–2.66)	0.069	1.98 (0.94–4.15)	0.030	2.10 (1.07–4.12)
Clinical stage IV vs ≤ III	< 0.0001	3.61 (2.21–5.88)	0.951	1.03 (0.34–3.07)	-	-
ACE	0.001	1.00 (1.00–1.00)	0.033	1.00 (1.00–1.00)	0.010	1.00 (1.00–1.00)
Tumor size	0.09	0.94 (0.89–1.01)	0.043	0.86 (0.75–0.99)	-	-
NLR	0.11	0.93 (0.85–1.01)	-	-	-	-
Pleural disease	0.028	0.70 (0.51–0.96)	0.431	0.86 (0.75–0.99)	-	-
Node positive	0.75	1.05 (0.77–1.42)	-	-	-	-
Hilar adenopathy	0.83	0.95 (0.60–1.50)	-	-	-	-

*Not included

	Univariate		Multivariate Intro		Multivariate Conditional (forward)	
Mediastinal adenopathy	0.72	1.05 (0.78–1.42)	-	-	-	-
Lymphovascular invasion	0.83	1.04 (0.67–1.62)	-	-	-	-
Contralateral lung disease	0.18	1.24 (0.90–1.71)	-	-	-	-
Any extra-thoracic non-BM	< 0.0001	1.94 (1.42–2.64)	0.161	1.70 (0.80–3.59)	-	-
Liver metastases	0.027	1.81 (1.06–3.06)	-	-	-	-
Bone metastases	< 0.0001	1.93 (1.39–2.66)	-	-	-	-
Suprarrenal metastases	0.48	1.18 (0.73–1.91)	-	-	-	-
*Not included						

The AUC in the TD with the proposed model showed a predictive sensibility of 74%, the same value was obtained in the 10-fold cross-validation, and 72% in the VD, the AIC remained stable in both TD and VD, 289 and 274 respectively; and finally, the precision was shown to be statistically significant in both datasets (P = 0.001) as presented in Table 2.

Table 2
Model's performance in the training, 10-fold cross-validation, and validation data sets

Proposed model			
	Training dataset	10-fold cross-validation (95%CI)	Validation dataset (95%CI)
AUC	0.74 (0.67–0.80)	0.74 (0.72–0.76)	0.72 (0.65–0.79)
C-statistic (P)	< 0.0001	< 0.0001	< 0.001
AIC	289	3097	274
Press's Q**	52	581 (P = 0.001)	89.8
*Akaike Information Criterion			
**Critical value determined at 6.63 for a P = 0.001			

After simplification of the model (categorization), Kaplan-Meier curves were built to measure the cumulative risk of BM according to the three groups: low risk = 0 prognostic values, medium risk 1 or 2 positive risk factors, or high-risk ≥ 3 ; a significant difference was shown in both datasets (VD P = 0.027 and TD P = 0.045), as shown in Table 3.

Table 3. Simplified model: prevalence of brain metastases according to categories

(Low = no risk factors, Medium 1-2, or High Risk ≥ 3).

Dataset	Category	Patients with BM %(n)	P
Training (n 277)	Low	11% (2/18)	0.003
	Medium	24% (45/191)	
	High	43% (29/68)	
Validation (n 293)	Low	8% (2/25)	<0.0001
	Medium	16% (32/206)	
	High	40% (25/62)	
Total (n 570)		24% (135/570)	

Discussion

In a retrospective cohort of patients with NSCLC divided into a TD and VD a multivariate model to predict the presence of brain metastases was built. Model's performance was adequate in the TD, in the 10-Fold TD cross-validation and in the VD; calibration, adjustments and precision test were used to confirm the predictive capacity.

Risk factors for BM in NSCLC reported previously comprise: Age(9)(10)(11), gender(11), non-squamous cell carcinoma/ adenocarcinoma(9)(12)(13)(11), clinical stage(13), number of extracranial metastases(10), malignant pleural effusion(10), nodal involvement(12), EGFRm or ALKr(13)(14), high CEA(8), neutrophil-lymphocyte ratio(15), elevated neuro-specific enolase(9), and high CA125(9), with the exception of the latest two, all were analyzed in the present study. Although several clinical markers have been explored, no adequate model has a proven capability of predicting which patients with NSCLC will have BM(5) or failing to identify a group who would benefit from prophylactic cranial irradiation as a measure of extending overall survival(16), there is a window of opportunity exploring molecular markers(7). Previous authors have defined a high-risk group for BM according to particular characteristics, to mention some: a) Age < 70 years, adenocarcinoma or large cell histology, tumor size > 3 cm, tumor grade $\geq$ II, and node positive disease(6), b) Adenocarcinoma, EGFRm + or ALKr + and CEA > 20 pg/mL(8). Other studies have proposed nomograms to predict BM in resected NSCLC(17)(18) with limited

resonance. We believe that the performance of our model shows enough evidence to be considered for a prospectively and/or external validation.

The following bias should be considered, including a referral bias, for all patients were seen at a single cancer center, and most had an advanced clinical stage at presentation. The selection bias should also be considered, to minimize this bias the whole cohort was randomly divided into a TD and VD and associations were determined only in the TD, it should be noted that analyses of the model were done only in those patients initially treated at the TCU and had complete information. This was a retrospective study; therefore, interventions were not permissible, all patients had the same medical attention as determined by the thoracic oncology unit. We included patients with all clinical stages and with BM or not at LC diagnosis or during follow-up to have a better possibility for generalization of the model.

Conclusion

A multivariate model comprising age, gender, CEA, and mutation status allowed the identification of a truly high-risk group of BM in NSCLC patients. External and prospective validation of the model is encouraged.

Declarations

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* [Internet]. 2021 Jan 1 [cited 2021 Mar 26];71(1):7–33.
2. Wang M, Wu Q, Zhang J, Qin G, Yang T, Liu Y, et al. Prognostic impacts of extracranial metastasis on non-small cell lung cancer with brain metastasis: A retrospective study based on surveillance, epidemiology, and end results database. *Cancer Med*. 2021 Jan;10(2):471–82.
3. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. *Nat Rev Dis Primer*. 2019 Jan 17;5(1):5.
4. Russell AH, Pajak TE, Selim HM, Paradelo JC, Murray K, Bansal P, et al. Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: Results of a prospective randomized trial conducted by the radiation therapy oncology group. *Int J Radiat Oncol* [Internet]. 1991 Aug 1;21(3):637–43.
5. An N, Jing W, Wang H, Li J, Liu Y, Yu J, et al. Risk factors for brain metastases in patients with non-small-cell lung cancer. *Cancer Med*. 2018 Dec;7(12):6357–64.
6. Waqar SN, Samson PP, Robinson CG, Bradley J, Devarakonda S, Du L, et al. Non-small-cell Lung Cancer With Brain Metastasis at Presentation. *Clin Lung Cancer*. 2018 Jul;19(4):e373–9.
7. Kamer I, Steuerman Y, Daniel-Meshulam I, Perry G, Izraeli S, Perelman M, et al. Predicting brain metastasis in early stage non-small cell lung cancer patients by gene expression profiling. *Transl Lung Cancer Res*. 2020 Jun;9(3):682–92.
8. Maldonado F, Gonzalez-Ling A, Oñate-Ocaña LF, Cabrera-Miranda LA, Zatarain-Barrón ZL, Turcott JG, et al. Prophylactic Cranial Irradiation in Patients With High-Risk Metastatic Non-Small Cell Lung Cancer: Quality of Life and Neurocognitive Analysis of a Randomized Phase II Study. *Int J Radiat Oncol Biol Phys*. 2021 Apr 26;
9. Ji Z, Bi N, Wang J, Hui Z, Xiao Z, Feng Q, et al. Risk Factors for Brain Metastases in Locally Advanced Non-Small Cell Lung Cancer With Definitive Chest Radiation. *Int J Radiat Oncol* [Internet]. 2014 Jun 1;89(2):330–7.
10. Ouyang W, Yu J, Zhou Y, Hu J, Huang Z, Zhang J, et al. Risk factors of metachronous brain metastasis in patients with EGFR-mutated advanced non-small cell lung cancer. *BMC Cancer*. 2020 Jul 28;20(1):699.
11. Hsiao S-H, Chung C-L, Chou Y-T, Lee H-L, Lin S-E, Liu HE. Identification of subgroup patients with stage IIIB/IV non-small cell lung cancer at higher risk for brain metastases. *Lung Cancer Amst Neth*. 2013 Nov;82(2):319–23.

12. Zhang Q, Cai X-W, Feng W, Yu W, Fu X-L. Risk factors of brain metastases as initial failure in completely resected stage IIIA(N2) non-small cell lung cancer. *Ann Transl Med*. 2020 Mar;8(6):374.
13. Yang B, Lee H, Um S-W, Kim K, Zo JI, Shim YM, et al. Incidence of brain metastasis in lung adenocarcinoma at initial diagnosis on the basis of stage and genetic alterations. *Lung Cancer Amst Neth*. 2019 Mar;129:28–34.
14. Mitra D, Chen Y-H, Li R, Hermann G, Atkins K, Kozono D, et al. EGFR mutant locally advanced non-small cell lung cancer is at increased risk of brain metastasis. *Clin Transl Radiat Oncol*. 2019 Sep;18:32–8.
15. Koh YW, Choi J-H, Ahn MS, Choi YW, Lee HW. Baseline neutrophil-lymphocyte ratio is associated with baseline and subsequent presence of brain metastases in advanced non-small-cell lung cancer. *Sci Rep*. 2016 Dec 7;6:38585.
16. Park HS, Decker RH, Wilson LD, Yu JB. Prophylactic Cranial Irradiation for Patients With Locally Advanced Non–Small-Cell Lung Cancer at High Risk for Brain Metastases. *Clin Lung Cancer [Internet]*. 2015 Jul 1;16(4):292–7.
17. Zhang F, Zheng W, Ying L, Wu J, Wu S, Ma S, et al. A Nomogram to Predict Brain Metastases of Resected Non-Small Cell Lung Cancer Patients. *Ann Surg Oncol*. 2016 Sep 1;23(9):3033–9.
18. Won Y-W, Joo J, Yun T, Lee G-K, Han J-Y, Kim HT, et al. A nomogram to predict brain metastasis as the first relapse in curatively resected non-small cell lung cancer patients. *Lung Cancer Amst Neth*. 2015 May;88(2):201–7.

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