PLOS ONE

RESEARCH ARTICLE

A Survival Scoring System for Non-Small Cell Lung Cancer Patients with *De Novo* Bone Metastases

Yu-Mu Chen[1☯], Ying-Tang Fang[1☯], Chien-Hao Lai[1], Kun-Ming Rau[2], Cheng-Hua Huang[2], Huang-Chih Chang[1], Tung-Ying Chao[1], Chia-Cheng Tseng[1], Wen-Feng Fang[1,3], Chin-Chou Wang[1,3], Yung-Che Chen[1,4], Yu-Hsiu Chung[1], Yi-Hsi Wang[1], Mao-Chang Su[1], Shih-Feng Liu[1], Kuo-Tung Huang[1], Hung-Chen Chen[1], Ya-Chun Chang[1], Yu-Ping Chang[1], Meng-Chih Lin[1]*

1 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan, **2** Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, **3** Department of Respiratory Care, Chang Gung University of Science and Technology, Chiayi Campus, Chiayi, Taiwan, **4** Graduate Institute of Clinical Medical Sciences, Chang Gung University College of Medicine, Kaohsiung, Taiwan

☯ These authors contributed equally to this work.
* linmengchih@hotmail.com

Citation: Chen Y-M, Fang Y-T, Lai C-H, Rau K-M, Huang C-H, Chang H-C, et al. (2016) A Survival Scoring System for Non-Small Cell Lung Cancer Patients with *De Novo* Bone Metastases. PLoS ONE 11(12): e0167923. doi:10.1371/journal.pone.0167923

Editor: Ramon Andrade de Mello, Western General Hospital, UNITED KINGDOM

Received: June 9, 2016

Accepted: November 22, 2016

Published: December 8, 2016

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The author(s) received no specific funding for this work.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

In the pre-tyrosine kinase inhibitors (TKIs) era, non-small cell lung cancer (NSCLC) patients with *de novo* bone metastases had a worse prognosis than those without. However, whether epidermal growth factor receptor (EGFR)-TKIs affect the outcomes of *EGFR* mutant NSCLC patients with *de novo* bone metastases has not been well studied thus far. We retrospectively studied the effect of *EGFR* mutation status and first-line EGFR-TKIs on patient outcomes and created a survival scoring system for NSCLC patients with *de novo* bone metastases. This retrospective study evaluated 1510 NSCLC patients diagnosed between November 2010 and March 2014. Among these patients, 234 patients had *de novo* bone metastases. We found that 121 of these 234 patients (51.7%) had positive *EGFR* mutation tests, and a positive *EGFR* mutation test significantly affected overall survival (OS) (*EGFR* mutant: 15.2 months, *EGFR* wild type: 6.5 months; $p < 0.001$). Other prognostic factors significant in the multivariable analysis for NSCLC with *de novo* bone metastases included Eastern Cooperative Oncology Group performance status (PS) (OS; PS 0–2: 11.2 months, PS 3–4: 4.9 months; $p = 0.002$), presence of extraosseous metastases (OS; with extraosseous metastases: 8.8 months, without extraosseous metastases: 14.0 months; $p = 0.008$), blood lymphocyte-to-monocyte ratio (LMR) (OS; LMR > 3.1: 17.1months, LMR $\leq$ 3.1: 6.9months; $p < 0.001$). A positive *EGFR* mutation status reversed the poor outcomes of NSCLC patients with *de novo* bone metastases. A simple and useful survival scoring system including the above clinical parameters was thus created for NSCLC patients with *de novo* bone metastases.

Introduction

Lung cancer is the leading cause of cancer death worldwide and in Taiwan.[1, 2] Today, a further understanding of the molecular mechanisms underlying non-small cell lung cancer (NSCLC) has resulted in the development of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs). Previous studies showed that EGFR-TKIs improved quality of life, progression-free survival (PFS), and even overall survival (OS) in advanced NSCLC patients harboring *EGFR* mutations.[3–5]

However, as the most common cause of cancer-related pain, bone metastases significantly reduce quality of life.[6] Bone metastases occur in 24.0–39.8% of NSCLC patients, most commonly involving the weight bearing skeleton and proximal long bones.[7, 8] Bone metastases also lead to skeletal-related events (SREs), which can negatively affect quality of life and survival duration.[9] The median survival duration for patients with bone metastases is often less than 1 year.[10–12]

The lung has been demonstrated to be the primary cancer site in more than 50% of cases of unknown primary cancer with bone metastases at autopsy.[13] Among patients with metastatic spinal cord compression (MSCC) secondary to cancer with bone metastases, lung cancer has a worse prognosis than MSCC related to other solid tumors.[14–16] Although several bone-directed targeted therapies have been introduced, these patients' prognosis is still poor.[10]

The aim of this study was to determine if patients positive for *EGFR* mutations who were taking first-line EGFR-TKIs experienced a reversal of the poor outcomes of NSCLC patients with *de novo* bone metastases. We also investigated other clinical factors affecting outcomes in these patients, and created a simple and useful survival scoring system.

Materials and Methods

Patient and clinical characteristics

This retrospective study evaluated patients with NSCLC who were diagnosed between November 2010 and March 2014 at Kaohsiung Chang Gung Memorial Hospital in Taiwan. All patients were subsequently followed-up until November 2015. The inclusion criteria were age >18 years, histologically or cytologically confirmed advanced-stage NSCLC with *de novo* bone metastases, and having undergone an *EGFR* mutation test.

We used Tc99–bone scans with chest radiography and computed tomography for initial evaluation of the presence of bone metastases. If the results were conflicting between the clinical physicians and nuclear medicine physicians, we held a joint meeting for consensus. If bone was the only possible distant metastasis site, and it was feasible to perform curative surgery after excluding bone metastasis, a positron emission tomography scan was performed for further evaluation. Sometimes, bone metastases were the initial presentation of advanced NSCLC and were diagnosed via bone biopsy samples.

Patients were excluded if they had previously received any targeted therapy, chemotherapy, or immunotherapy. Patients were excluded if they refused to take EGFR-TKIs when they were positive for *EGFR* mutations. This study's design was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital, and the requirement for informed consent was waived due to the retrospective design.

Baseline assessments were performed within 4 weeks of treatment initiation, including clinical characteristics and findings from chest radiography, chest computed tomography, bone scan, and brain magnetic resonance imaging. The clinical characteristics included age, body mass index (BMI), sex, smoking status, blood lymphocyte-to-monocyte ratio, Eastern

Cooperative Oncology Group performance status (PS), diabetes mellitus, *EGFR* mutations, tumor histology, and sites and symptoms of distant metastases.

EGFR mutation testing

Tumor specimens were obtained from biopsy samples that were obtained via bronchoscopy, computed tomography-guided biopsy, or surgical procedures. Tumor specimens from pleural effusion cytology were also considered acceptable. The genetic analyses were performed using Scorpion primers and genomic DNA that was extracted from the paraffin-embedded tissues (QIAGEN EGFR RGQ PCR Kit), which were subjected to amplification refractory mutation system-polymerase chain reaction.[17]

Evaluating response to EGFR-TKI treatment

To evaluate the tumor response, patients underwent chest radiography every 2–4 weeks and chest computed tomography every 2–3 months. Disease status was determined by the attending clinician according to Response Evaluation Criteria in Solid Tumors guidelines (version 1.1).[18] Overall survival (OS) was defined as the period from the first day of EGFR-TKI treatment until death, loss to follow-up, or the last follow-up.

Statistical analyses

Statistical analyses were performed using MedCalc software (version 14.10.2). The OS analyses were performed using the Kaplan-Meier method and the log-rank test. A Cox proportional hazards regression model was used to evaluate independent factors that affected the survival outcomes. Receiver operating characteristic (ROC) curves were drawn and Youden's index was used to determine the best cut-off value for LMR, the area under the curve, sensitivity and specificity of the survival scoring system. A p value of <0.05 was considered statistically significant.

Results

Patient characteristics

Among 1510 patients who were diagnosed with lung cancer between November 2010 and March 2014, we identified 234 NSCLC patients with *de novo* bone metastases (Fig 1). Among these patients, 51.7% (121/234) patients had positive *EGFR* mutation tests. The mean patient age was 61.9 ± 13.0 years and 43.6% (102/234) of the patients were men. At the last follow-up, 13.2% (31/234) of the patients were alive. The median OS was 10.5 ± 1.0 months, the longest follow-up was 54.8 months. The best cut-off point of LMR determined by ROC curve and Youden's Index was 3.1. Patients were divided into high or low LMR based on above cut-off value. The first-line therapy for study patients were listed in S1 Table.

Survival analysis

Survival analysis according to distant metastatic sites. Besides 87 patients had bone metastases only, 147 patients had other concomitant distant metastases at diagnosis. (Fig 2) Of the 147 patients, 38 patients had concomitant brain metastases, 46 patients had concomitant pleura metastases, 19 patients had concomitant brain metastases, and 44 patients had more than 2 concomitant distant metastases. Patients with bone metastases only had longer OS duration than those concomitant with other metastatic sites.

Survival analysis for patients with *de novo* bone metastases. In the univariable analysis, prolonged OS was significantly associated with female sex (p = 0.001), absence of diabetes

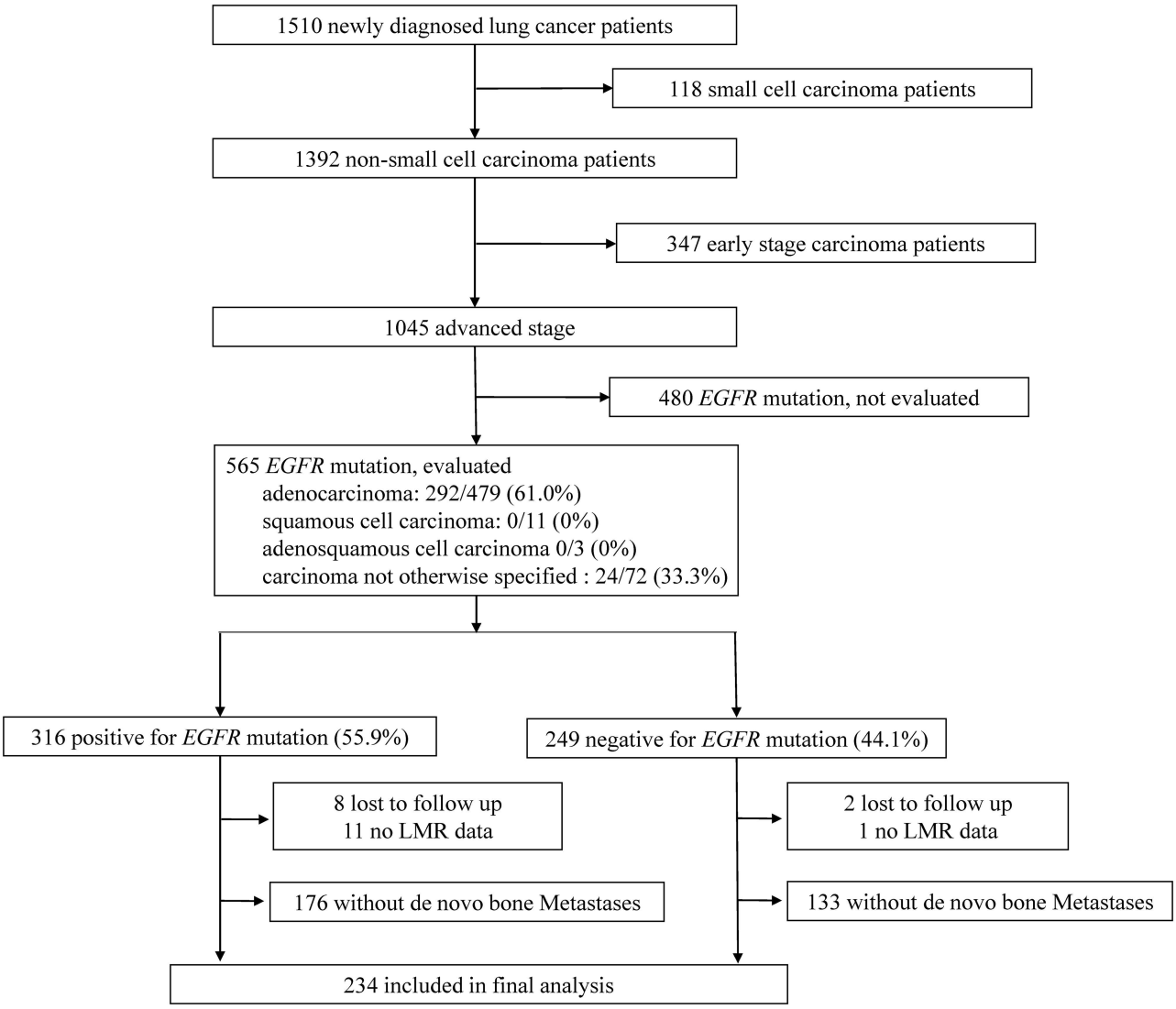


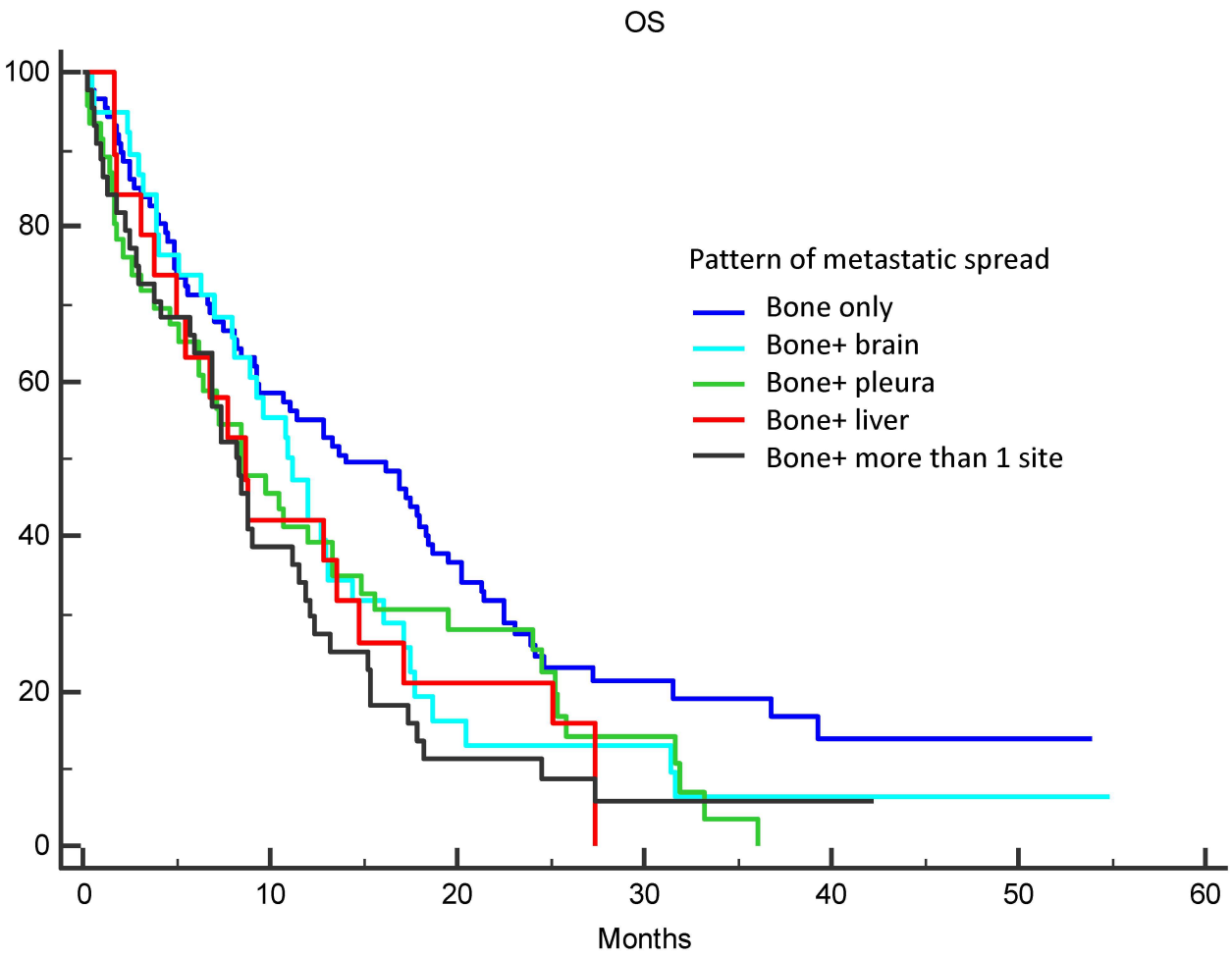
Fig 1. The inclusion and screening for this study. Among 1,510 patients who were diagnosed with non-small-cell lung cancer between November 2010 and March 2014, 234 patients with *de novo* bone metastases were included in the final analysis.

doi:10.1371/journal.pone.0167923.g001

mellitus ($p = 0.007$), never smoker ($p = 0.007$), a PS of ≤ 2 ($p < 0.001$), a positive *EGFR* mutation test result ($p < 0.001$), no extraosseous metastasis ($p = 0.003$), and LMR > 3.1 ($p < 0.001$) (Table 1). Age, body mass index, and tumor histology were not significantly associated with OS. In the multivariable analysis, prolonged OS was independently associated with a PS of ≤ 2 ($p = 0.002$), positive *EGFR* mutation test results ($p = 0.004$), no extraosseous metastasis ($p = 0.008$), and LMR > 3.1 ($p < 0.001$) (Table 1). These Four prognostic factors were included in the scoring system (Table 2).

Survival scoring system

The scoring system ranged from 0 to 4. The distribution of survival scores over the 234 patients is shown in Fig 3A The median OS duration was 20.2 months for patients with 0 points, 15.2 months for patients with 1 point, 9.2 months for patients with 2 points, 5.1 months for patients with 3 points, and 2.6 months for patients with 4 points (Fig 3B). Three prognostic groups



Metastatic Sites	n	OS	p
Bone only	87	14.0	0.028
Bone + brain	38	10.9	
Bone + pleura	46	8.5	
Bone+ liver	19	8.7	
Bone+ more than 1 site	44	8.2	

Fig 2. Kaplan-Meier curve for overall survival according to patterns of metastatic spread. Patients with bone metastases only had longer OS duration than those concomitant with other metastatic sites. (p = 0.028)

doi:10.1371/journal.pone.0167923.g002

were identified according to the total score: 0–1 points (group A), 2 points (group B), and 3–4 points (group C). The median OS was 17.9 month in group A, 9.2 month in group B, and 4.9 month in group C ($p < 0.001$) (Fig 4).

Discussion

Previous studies revealed patients with adenocarcinoma were more likely to have bone metastases than those with small cell lung cancer, and those with squamous cell carcinoma were less

Table 1. Impact of baseline clinical parameters on overall survival of NSCLC patients with *de novo* bone metastases.

	Univariate analysis			Multivariate analysis		
	n	OS (months)	P value	Hazard ratio	P value	95% CI
Age, years			0.135		0.102	
>60	127	8.8		1.29		0.951–1.753
≤60	107	12.1		1.00		
BMI			0.173		0.795	
>22	122	12.4		1.00		0.764–1.421
≤22	112	9.0		1.04		
Sex			0.001		0.337	
Male	102	8.4		1.24		0.802–1.902
Female	132	12.0		1.00		
DM			0.007		0.120	
YES	22	5.5		1.49		0.902–2.455
NO	212	10.9		1.00		
Smoking history			0.007		0.449	
Never	155	12.0		1.00		0.753–1.897
Former / current	79	8.2		1.12		
Performance status			<0.001		0.002	
ECOG 0–2	203	11.2		1.00		1.313–3.352
ECOG 3–4	31	4.9		2.10		
EGFR Mutation			<0.001		0.004	
Yes	121	15.2		1.00		1.161–2.212
No	113	6.5		1.60		
Tumor type			0.248		0.923	
Adenocarcinoma	194	10.8		1.00		0.685–1.518
Non-adenocarcinoma	40	9.3		1.02		
Extraosseous metastasis			0.003		0.008	
Yes	147	8.8		1.59		1.131–2.245
No	87	14.0		1.00		
LMR			<0.001		<0.001	
>3.1	112	17.1		1.00		1.404–2.679
≤3.1	122	6.9		1.94		

BMI, body mass index; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LMR, lymphocyte-to-monocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival

doi:10.1371/journal.pone.0167923.t001

likely to have bone metastases.[19, 20] Fortunately, adenocarcinoma was more likely to have *EGFR* mutations than other histologic types.[21] In a previous study, among NSCLC patients, more than 35.3% of patients with bone metastases exhibited bone involvement at the time the lung cancer was diagnosed.[10] Our study revealed 43.8% (243/555) patients had *de novo* bone metastases, and we included only patients with *de novo* bone metastases to decrease confounding factors. In patients receiving platinum-based chemotherapy, the outcomes of NSCLC patients with bone metastases is poor, with a median survival of less than a year.[22–24] Our study revealed EGFR-TKIs had prolonged the median survival duration from 6.5 months to 15.4 months.

In pre-TKIs era, young advanced NSCLC patients had better prognosis than older patients.[25] However, in TKIs era, previous study showed that young lung cancer patients with positive EGFR mutant test had only 3.3 months PFS when receiving first-line EGFR-TKIs. [26]

Table 2. Scoring system for NSCLC with bone metastasis.

	Score
Performance status	
ECOG 0–2	0
ECOG 3–4	1
EGFR Mutation	
Yes	0
No	1
Extraosseous metastasis	
Yes	1
No	0
LMR	
>3.1	0
≤3.1	1

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; LMR, lymphocyte-to-monocyte ratio; NSCLC, non-small cell lung cancer

doi:10.1371/journal.pone.0167923.t002

Regardless of EGFR mutation status, our study revealed younger or older than 60 years old NSCLC patients with de novo bone metastases had equivalent OS length. Higher BMI were found prognostic factor in advanced NSCLC patients receiving chemotherapies.[27] Although our study revealed *de novo* bone metastases patients with BMI > 22 had a 3.4 months OS

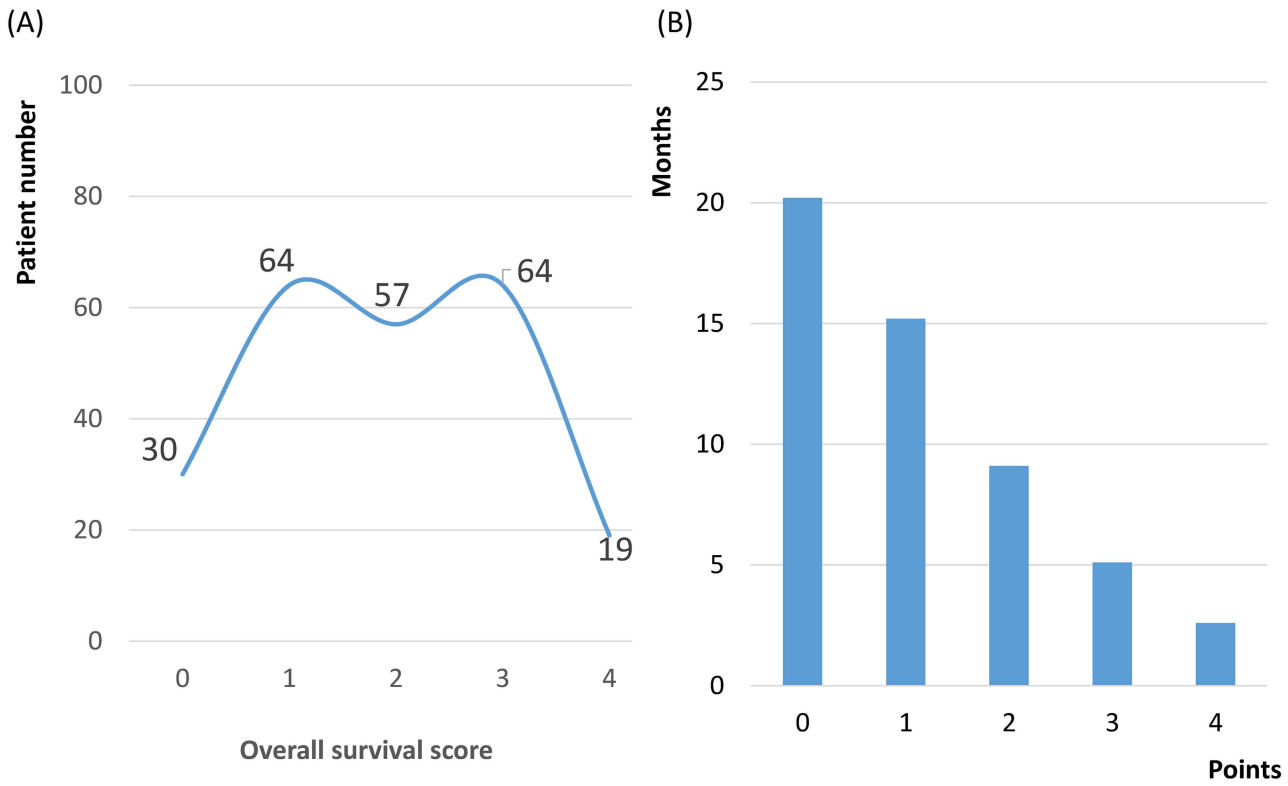
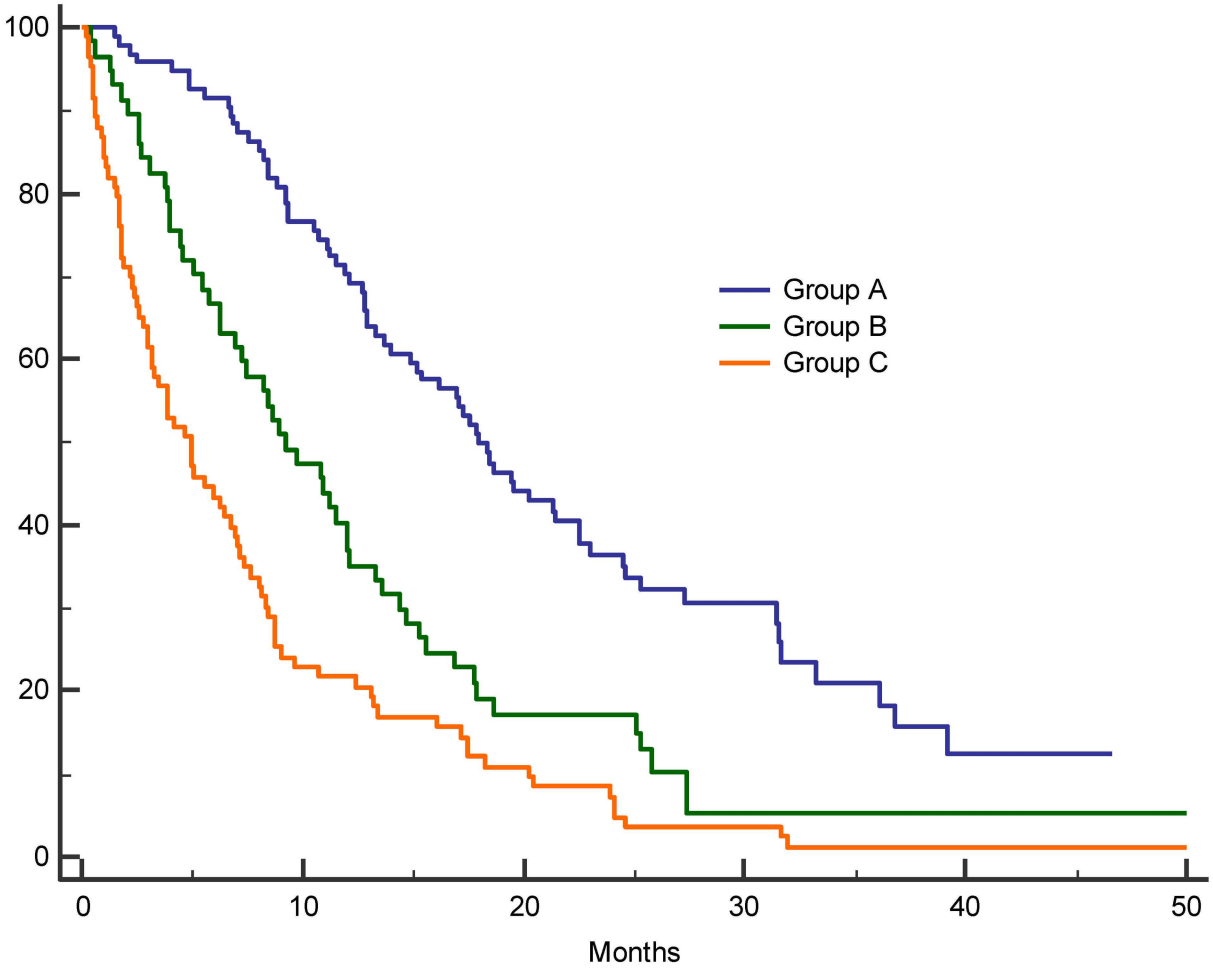


Fig 3. (A) Distribution of survival scores over the 234 patients; (B) Median overall survival related to the corresponding scores.

doi:10.1371/journal.pone.0167923.g003



Number at risk/events					
Group A 94/0	72/22	38/52	13/62	4/69	0/69
Group B 57/0	27/30	9/47	2/52	1/52	1/52
Group C 83/0	19/64	9/74	3/80	1/82	1/82

Survival score	n	Event	OS	p
Group A	94	69	17.9	<0.001
Group B	57	52	9.2	
Group C	83	82	4.9	
Total	234	203	10.5	

Fig 4. Kaplan-Meier curve for overall survival of the three prognostic groups A, B, and C. OS among NSCLC patients with *de novo* metastases according to three prognostic groups A, B, and C.

doi:10.1371/journal.pone.0167923.g004

prolongation than those with BMI $\leq$ 22, the result did not meet statistical significance. Female, non-smoker and adenocarcinoma histology were predictor of having positive EGFR mutation. [28–31] However, our study revealed they were not prognostic factors in NSCLC patients with *de novo* bone metastases.

Previous studies revealed lung cancer patients with good PS had better outcomes when receiving chemotherapies or first-line EGFR-TKIs.[26, 32, 33] Consistent with previous studies, our study revealed patients with bone metastases had better survival if they had a good PS. [22] We assume patients with poor PS are not appropriate for chemotherapies, radiotherapies, or palliative surgery; experience more myelosuppression; are more likely to succumb to non-cancer death; and consequently have dismal outcomes.[34]

Previous studies have shown that the presence and number of distant metastases are prognostic factors for NSCLC patients treated with chemotherapy or EGFR-TKIs.[26, 35–37] Our study revealed that patients with bone metastases only had better outcomes than those who had distant metastasis at sites other than bone.

Previous revealed LMR was prognostic factor in early-stage malignancies including lung cancer[38], and nasopharyngeal carcinoma [39]; in advanced-stage malignancies including diffuse large B-cell lymphoma [40, 41], lung cancer patients receiving chemotherapies[42], and breast cancer patients receiving neo-adjuvant chemotherapies.[43] Our study revealed that patients with *de novo* bone metastases had better prognosis if they had higher baseline blood LMR ratio. To the best of our knowledge, this is the first study demonstrating that LMR is a prognostic factor in NSCLC patients with *de novo* bone metastases.

The present study had several limitations. First, we did not have access to the use of bone-directed targeted therapies. Whether these agents have a synergic effect with EGFR-TKIs cannot be explored. However, most patients started receiving bone-directed agents when they had first time SREs in our institute and a first SRE often heralds subsequent SREs. Thus, we decided not to evaluate the impact of bone-directed agents on survival outcome to prevent bias. Second, our study used a retrospective design with a small patient population, and prospective studies are needed to validate our findings.

Conclusion

Positive *EGFR* mutation status reversed the poor outcomes of NSCLC patients with *de novo* bone metastases. A simple and useful survival scoring system was thus created for NSCLC patients with *de novo* bone metastases.

Supporting Information

S1 Table. First-line therapy of study patients.
(DOC)

S1 Data. Raw data file.
(SAV)

Acknowledgments

We thank Tsui-Ping Tang and I-Chun Lin for data collection.

Author Contributions

Conceptualization: YMC CHL YHW TYC CCT MCL.

Data curation: Y. C. Chen Y. C. Chang YPC.

Formal analysis: YMC YTF YHC MCL.

Investigation: YMC YTF KMR CHH.

Methodology: YMC WFF CCW SFL H. C. Chen.

Resources: MCS MCL.

Software: YMC KTH H. C. Chang.

Supervision: MCL.

Validation: YMC YTF.

Visualization: YMC MCL.

Writing – original draft: YMC YTF CHL.

Writing – review & editing: MCL.

References

1. Henley SJ, Richards TB, Underwood JM, Eheman CR, Plescia M, McAfee TA, et al. Lung cancer incidence trends among men and women—United States, 2005–2009. MMWR Morbidity and mortality weekly report. 2014; 63(1):1–5. PMID: 24402465
2. Wang BY, Huang JY, Cheng CY, Lin CH, Ko J, Liaw YP. Lung cancer and prognosis in taiwan: a population-based cancer registry. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2013; 8(9):1128–35.
3. Chen G, Feng J, Zhou C, Wu YL, Liu XQ, Wang C, et al. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. 2013; 24(6):1615–22.
4. Thongprasert S, Duffield E, Saijo N, Wu YL, Yang JC, Chu DT, et al. Health-related quality-of-life in a randomized phase III first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients from Asia with advanced NSCLC (IPASS). Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2011; 6(11):1872–80.
5. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. The Lancet Oncology. 2015; 16(2):141–51. doi: 10.1016/S1470-2045(14)71173-8 PMID: 25589191
6. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain. 1997; 69(1–2):1–18. PMID: 9060007
7. Kosteva J, Langer C. The changing landscape of the medical management of skeletal metastases in nonsmall cell lung cancer. Current opinion in oncology. 2008; 20(2):155–61. doi: 10.1097/CCO.0b013e3282f54cf2 PMID: 18300765
8. Kakhki VR, Anvari K, Sadeghi R, Mahmoudian AS, Torabian-Kakhki M. Pattern and distribution of bone metastases in common malignant tumors. Nucl Med Rev Cent East Eur. 2013; 16(2):66–9. doi: 10.5603/NMR.2013.0037 PMID: 24068635
9. Coleman RE. Skeletal complications of malignancy. Cancer. 1997; 80(8 Suppl):1588–94. PMID: 9362426
10. Oliveira MB, Mello FC, Paschoal ME. The relationship between lung cancer histology and the clinicopathological characteristics of bone metastases. Lung cancer. 2016; 96:19–24. doi: 10.1016/j.lungcan.2016.03.014 PMID: 27133744
11. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer treatment reviews. 2001; 27(3):165–76. doi: 10.1053/ctrv.2000.0210 PMID: 11417967
12. Cha YK, Lee HY, Ahn MJ, Choi YL, Lee JH, Park K, et al. Survival outcome assessed according to tumor burden and progression patterns in patients with epidermal growth factor receptor mutant lung adenocarcinoma undergoing epidermal growth factor receptor tyrosine kinase inhibitor therapy. Clinical lung cancer. 2015; 16(3):228–36. doi: 10.1016/j.cllc.2014.11.002 PMID: 25499173
13. Nottebaert M, Exner GU, von Hochstetter AR, Schreiber A. Metastatic bone disease from occult carcinoma: a profile. International orthopaedics. 1989; 13(2):119–23. PMID: 2744913

14. Tabouret E, Cauvin C, Fuentes S, Esterni B, Adetchessi T, Salem N, et al. Reassessment of scoring systems and prognostic factors for metastatic spinal cord compression. The spine journal: official journal of the North American Spine Society. 2015; 15(5):944–50.
15. Rades D, Weber A, Karstens JH, Schild SE, Bartscht T. Prognostic role of the number of involved extraspinal organs in patients with metastatic spinal cord compression. Clin Neurol Neurosurg. 2014; 118:12–5. doi: 10.1016/j.clineuro.2013.12.007 PMID: 24529222
16. Quraishi NA, Manoharan SR, Arealis G, Khurana A, Elsayed S, Edwards KL, et al. Accuracy of the revised Tokuhashi score in predicting survival in patients with metastatic spinal cord compression (MSCC). Eur Spine J. 2013; 22 Suppl 1:S21–6.
17. Horiike A, Kimura H, Nishio K, Ohyanagi F, Satoh Y, Okumura S, et al. Detection of epidermal growth factor receptor mutation in transbronchial needle aspirates of non-small cell lung cancer. Chest. 2007; 131(6):1628–34. doi: 10.1378/chest.06-1673 PMID: 17565015
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009; 45(2):228–47. doi: 10.1016/j.ejca.2008.10.026 PMID: 19097774
19. Janssen-Heijnen ML, Coebergh JW. The changing epidemiology of lung cancer in Europe. Lung cancer. 2003; 41(3):245–58. PMID: 12928116
20. Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. International journal of epidemiology. 1997; 26(1):14–23. PMID: 9126499
21. Yang JC, Wu YL, Chan V, Kurnianda J, Nakagawa K, Saijo N, et al. Epidermal growth factor receptor mutation analysis in previously unanalyzed histology samples and cytology samples from the phase III Iressa Pan-ASia Study (IPASS). Lung cancer. 2014; 83(2):174–81. doi: 10.1016/j.lungcan.2013.11.021 PMID: 24361280
22. Sugiura H, Yamada K, Sugiura T, Hida T, Mitsudomi T. Predictors of survival in patients with bone metastasis of lung cancer. Clin Orthop Relat Res. 2008; 466(3):729–36. doi: 10.1007/s11999-007-0051-0 PMID: 18196360
23. Hansen BH, Keller J, Laitinen M, Berg P, Skjeldal S, Trovik C, et al. The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop Scand Suppl. 2004; 75(311):11–5. PMID: 15188660
24. Decroisette C, Monnet I, Berard H, Quere G, Le Caer H, Bota S, et al. Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2011; 6(3):576–82.
25. Kuo CW, Chen YM, Chao JY, Tsai CM, Perng RP. Non-small cell lung cancer in very young and very old patients. Chest. 2000; 117(2):354–7. PMID: 10669674
26. Chen YM, Lai CH, Chang HC, Chao TY, Tseng CC, Fang WF, et al. The impact of clinical parameters on progression-free survival of non-small cell lung cancer patients harboring EGFR-mutations receiving first-line EGFR-tyrosine kinase inhibitors. Lung cancer. 2016; 93:47–54. doi: 10.1016/j.lungcan.2016.01.001 PMID: 26898614
27. Dahlberg SE, Schiller JH, Bonomi PB, Sandler AB, Brahmer JR, Ramalingam SS, et al. Body mass index and its association with clinical outcomes for advanced non-small-cell lung cancer patients enrolled on Eastern Cooperative Oncology Group clinical trials. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2013; 8(9):1121–7.
28. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(36):13306–11. doi: 10.1073/pnas.0405220101 PMID: 15329413
29. Tokumo M, Toyooka S, Kiura K, Shigematsu H, Tomii K, Aoe M, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. Clinical cancer research: an official journal of the American Association for Cancer Research. 2005; 11 (3):1167–73.
30. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer research. 2004; 64(24):8919–23. doi: 10.1158/0008-5472.CAN-04-2818 PMID: 15604253
31. Lie CH, Chang HC, Chao TY, Chung YH, Wang JL, Wang CC, et al. First- or second-line gefitinib therapy in unknown epidermal growth factor receptor mutants of non-small-cell lung cancer patients treated in Taiwan. Clinical lung cancer. 2011; 12(2):116–24. doi: 10.1016/j.cllc.2011.03.006 PMID: 21550558
32. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without

indication for chemotherapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009; 27(9):1394–400.

33. Langer C, Lilenbaum R. Role of chemotherapy in patients with poor performance status and advanced non-small cell lung cancer. Seminars in oncology. 2004; 31(6 Suppl 11):8–15. PMID: 15599829

34. Oshita F, Shinkai T, Miya T, Kojima A, Ohe Y, Tamura T, et al. [The relation between myelotoxicity and performance status or aging in chemotherapy of non-small cell lung cancer]. Nihon Kyobu Shikkan Gakkai zasshi. 1991; 29(2):231–8. PMID: 1851904

35. Park JH, Kim TM, Keam B, Jeon YK, Lee SH, Kim DW, et al. Tumor burden is predictive of survival in patients with non-small-cell lung cancer and with activating epidermal growth factor receptor mutations who receive gefitinib. Clinical lung cancer. 2013; 14(4):383–9. doi: 10.1016/j.cllc.2012.10.007 PMID: 23313171

36. Chen YM, Lai CH, Chang HC, Chao TY, Tseng CC, Fang WF, et al. Baseline and Trend of Lymphocyte-to-Monocyte Ratio as Prognostic Factors in Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer Patients Treated with First-Line Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. PloS one. 2015; 10(8):e0136252. doi: 10.1371/journal.pone.0136252 PMID: 26313661

37. Chen YM, Lai CH, Chang HC, Chao TY, Tseng CC, Fang WF, et al. Antacid Use and De Novo Brain Metastases in Patients with Epidermal Growth Factor Receptor-Mutant Non-Small Cell Lung Cancer Who Were Treated Using First-Line First-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. PloS one. 2016; 11(2):e0149722. doi: 10.1371/journal.pone.0149722 PMID: 26894507

38. Hu P, Shen H, Wang G, Zhang P, Liu Q, Du J. Prognostic significance of systemic inflammation-based lymphocyte- monocyte ratio in patients with lung cancer: based on a large cohort study. PloS one. 2014; 9(9):e108062. doi: 10.1371/journal.pone.0108062 PMID: 25275631

39. Li J, Jiang R, Liu WS, Liu Q, Xu M, Feng QS, et al. A large cohort study reveals the association of elevated peripheral blood lymphocyte-to-monocyte ratio with favorable prognosis in nasopharyngeal carcinoma. PloS one. 2013; 8(12):e83069. doi: 10.1371/journal.pone.0083069 PMID: 24386144

40. Porrata LF, Ristow K, Habermann TM, Ozsan N, Dogan A, Macon W, et al. Absolute monocyte/lymphocyte count prognostic score is independent of immunohistochemically determined cell of origin in predicting survival in diffuse large B-cell lymphoma. Leukemia & lymphoma. 2012; 53(11):2159–65.

41. Lin B, Chen C, Qian Y, Feng J. Prognostic role of peripheral blood lymphocyte/monocyte ratio at diagnosis in diffuse large B-cell lymphoma: a meta-analysis. Leukemia & lymphoma. 2015:1–6.

42. Lin GN, Peng JW, Xiao JJ, Liu DY, Xia ZJ. Prognostic impact of circulating monocytes and lymphocyte-to-monocyte ratio on previously untreated metastatic non-small cell lung cancer patients receiving platinum-based doublet. Medical oncology. 2014; 31(7):70. doi: 10.1007/s12032-014-0070-0 PMID: 24927957

43. Ni XJ, Zhang XL, Ou-Yang QW, Qian GW, Wang L, Chen S, et al. An elevated peripheral blood lymphocyte-to-monocyte ratio predicts favorable response and prognosis in locally advanced breast cancer following neoadjuvant chemotherapy. PloS one. 2014; 9(11):e111886. doi: 10.1371/journal.pone.0111886 PMID: 25372468