RESEARCH ARTICLE

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

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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 ≤ 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
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
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
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 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                    |                     |                         |                       |                          |                       |                      |
| >60                           | 127                 | 8.8                      | 0.135                 | 1.29                     | 0.102                 | 0.951–1.753          |
| ≤60                           | 107                 | 12.1                     |                       | 1.00                     |                       |                      |
| BMI                           |                     |                          |                       |                          |                       |                      |
| >22                           | 122                 | 12.4                     | 0.173                 | 1.00                     | 0.795                 |                      |
| ≤22                           | 112                 | 9.0                      |                       | 1.04                     |                       |                      |
| Sex                           |                     |                          |                       |                          |                       |                      |
| Male                          | 102                 | 8.4                      | 0.001                 | 1.24                     | 0.337                 |                      |
| Female                        | 132                 | 12.0                     |                       | 1.00                     |                       |                      |
| DM                            |                     |                          |                       |                          |                       |                      |
| YES                           | 22                  | 5.5                      | 0.007                 | 1.49                     | 0.120                 |                      |
| NO                            | 212                 | 10.9                     |                       | 1.00                     |                       |                      |
| Smoking history               |                     |                          |                       |                          |                       |                      |
| Never                         | 155                 | 12.0                     | 0.007                 | 1.00                     | 0.449                 |                      |
| Former / current              | 79                  | 8.2                      |                       | 1.04                     |                       |                      |
| Performance status            | ≤0.001              |                          |                       | ≤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              |                          |                       | ≤0.001                   | 0.004                 |                      |
| Yes                           | 121                 | 15.2                     | 1.00                   |                          | 1.161–2.212           |                      |
| No                            | 113                 | 6.5                      |                       | 1.60                     |                       |                      |
| Tumor type                    |                     |                          |                       |                          |                       |                      |
| Adenocarcinoma                | 194                 | 10.8                     | 0.248                 | 1.00                     | 0.923                 |                      |
| Non-adenocarcinoma            | 40                  | 9.3                      |                       | 1.02                     |                       |                      |
| Extraosseous metastasis       |                     |                          |                       |                          |                       |                      |
| Yes                           | 147                 | 8.8                      | 0.003                 | 1.59                     | 0.008                 |                      |
| No                            | 87                  | 14.0                     |                       | 1.00                     |                       |                      |
| LMR                           | ≤0.001              |                          |                       | ≤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
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

| 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

![Fig 3](image)

**Table 2. Scoring system for NSCLC with bone metastasis.**

**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
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**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.

| 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 |         |

Number at risk/events

| Group   | 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 |

*doi:10.1371/journal.pone.0167923.g004*
prolongation than those with BMI ≤ 22, the result did not meet statistical significance. Female, non-smoker and adenocarcinoma histology were predictor of having positive EGFR mutation. 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.

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