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Original Article

The protective effects of surgery according to the spinal instability neoplastic score for patients with the EGFR mutation, lung adenocarcinoma, and spinal metastatic instability

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Abstract: Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) allow remarkable improvement of the overall survival (OS) of lung adenocarcinoma patients with sensitizing EGFR mutations. This retrospective study was aimed at determining whether spinal surgery improves the quality of life and OS of patients with spinal metastatic instability. Methods: We reviewed the data of 362 lung adenocarcinoma patients with EGFR sensitizing mutations which were administered EGFR-TKIs as first-line therapy. Eighty-six of these patients had spinal instability neoplastic scores (SINS) of ≥7 points; 45 of these patients subsequently required surgery (the surgery group), but the rest did not (the non-surgery group). The patients were evaluated for quality of life, pain severity, and spinal cord function at the time of diagnosis and after the failure of the EGFR-TKI treatment. Results: The OS of all the patients was 24.0 months, with 59.1% of the patients having bone metastases (spinal in 81.8%) at the time of the initial diagnosis. The OS was significantly lower in patients with bone metastasis than it was in those without it (19.0 months vs. 31.0 months, $P<0.001$) and in patients with SINS of ≥7 points than it was in patients with SINS of <7 (15.0 months vs. 21.0 months, $P=0.038$). Among patients with SINS of ≥7, those who underwent spinal surgery did not show any significant improvement in the OS as compared to those who did not undergo surgical treatment (17.0 vs. 10.0 months, $P=0.119$). At the time of EGFR-TKIs failure, pain and neurological function were significantly better among the patients who received surgical treatment than those who did not undergo surgery. The proportion of patients requiring secondary treatment in the surgery group was greater than the proportion requiring secondary treatment in the non-surgery group (88.8% vs. 68.2%, $P=0.032$). Conclusions: Bone metastasis, particularly if the SINS score is ≥7 points, is associated with poor survival in patients with EGFR-positive lung adenocarcinoma. We found that surgical treatment can be effectively used to prevent spinal cord dysfunction, provide pain relief for patients, and improve treatment acceptance and compliance.

Keywords: EGFR mutation, lung adenocarcinoma, spinal instability, bone metastases, spinal instability neoplastic score (SINS), survival

Introduction

Non-small-cell lung cancer (NSCLC) is a common cause of bone metastases. The spine is the most common site for bone metastases from NSCLC, followed by the pelvis, sacrum, and extremities, in that order [1]. Studies have shown that the median overall survival (OS) of patients with bone metastases at the time of NSCLC diagnosis is as low as 7.0 months, while the 2-year survival rate is 23.5% [1]. However, the development of further generations of tyrosine kinase inhibitors (TKIs) for epidermal growth factor receptors (EGFR) has significantly increased the survival rate of NSCLC patients exhibiting sensitizing EGFR mutations. The use of EGFR-TKIs has been reported to improve the OS of bone metastasis patients with sensitizing EGFR mutations to 21.1 months, which is greater than the OS of 6.0 months reported for patients without these mutations [1, 2]. Nevertheless, even with treatment with first-

generation EGFR-TKIs, the presence of bone metastases is associated with significantly poor progression-free survival (PFS) (8.8 vs. 15.4 months) and OS (24.0 vs. 32.1 months) in comparison with patients without bone metastases [3].

Metastatic bone lesions compromise the structural integrity of the bone, increasing the risk for skeletal-related events (SREs) such as pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and severe bone pain that may require palliative radiotherapy or surgery [4]. The incidence rate of SREs associated with bone metastases in patients with squamous cell carcinoma and adenocarcinoma lung cancer is 87.5% and 47.3%, respectively [1]. Surgical treatment has been associated with better prognosis for patients with bone metastasis or SREs [1]. Spinal metastasis compromises bone strength and stability, even leading to spinal cord compression, which in turn affects the patient's quality of life. Surgical treatment enables tumor removal and spinal stabilization, thereby providing pain relief by cord decompression. The Spinal Oncology Study Group put forth the Spinal Instability Neoplastic Score (SINS) in 2010 for the categorization of patients with spinal instability and the identification of patients who may benefit from surgical treatment [5]. The score covers the following six domains: position, pain, bone lesion, spinal alignment, bone compression, and posterolateral invasion. The total score was then graded according to three degrees of stability: stable (0-6 points), potentially unstable (7-12 points), and unstable (13-18 points). Additionally, the total score was also used as an indicator of the need for surgery; scores of 0-6 points indicated a stable status, while scores of 7-18 points indicated an unstable status and therefore the need for surgical consultation [5, 6]. In patients with NSCLC, SRE incidence is significantly lower in the stable group than in the unstable group (15% vs. 44%) when classified by SINS, and good spinal stability is a favorable prognostic factor [7].

Another tool, the Eastern Cooperative Oncology Group (ECOG) scale, is widely used to assess the physical state and has been reported to be a reliable indicator of life expectancy [8]. ECOG grades of 3 and 4 indicate poor prognosis in lung cancer patients with bone metastasis [9]. Further, the Numerical Rating Scale (NRS) allows for the assessment of pain in cancer patients [10]. Its ease of use and standardized format makes this tool popular in China for the assessment of tumor-related pain. Similarly, the Frankel Grade, which encompasses five variables (A-E), is often used to evaluate the pre- and post-operative neurological status of the spine and is related to survival in patients with spinal metastasis [11-13].

EGFR-TKI improves the OS of patients with sensitizing EGFR mutations to more than two years [14]. Once they develop SREs, the physical state of patients worsens [15, 16], with increased depression and anxiety [15, 16] and a short life expectancy [17]. These beneficial effects of EGFR-TKIs on survival are countered by SREs. In this study, we sought to determine whether a spinal surgery operation performed on the basis of SINS can reduce pain and prevent the deterioration of the physical state and spinal neurological status, as well as improve the OS in patients with sensitizing EGFR mutations.

Materials and methods

Data collection

We conducted a retrospective investigation of the data obtained for 362 lung adenocarcinoma patients with EGFR-sensitizing mutations who were administered EGFR-TKIs as first-line therapy between January 2012 and March 2016 at the Oncology Department of The Fourth Hospital of Hebei Medical University and the Orthopedics Department of Hebei General Hospital. The Ethics Committee approved the data collection of this study.

Among the 362 patients reviewed, 214 had bone metastases at their initial diagnosis. One hundred and seventy five of these patients had spinal metastasis and the data of these patients were analyzed independently by two orthopedic surgeons to determine the SINS, and 86 of these patients were found to have had SINS of ≥7 points. The patients with SINS of ≥7 points were divided into two groups according to whether they did (surgery group; n=45) or did not (non-surgery group; n=41) undergo spinal surgery while receiving EGFR-TKI treatment. A cohort diagram indicating the

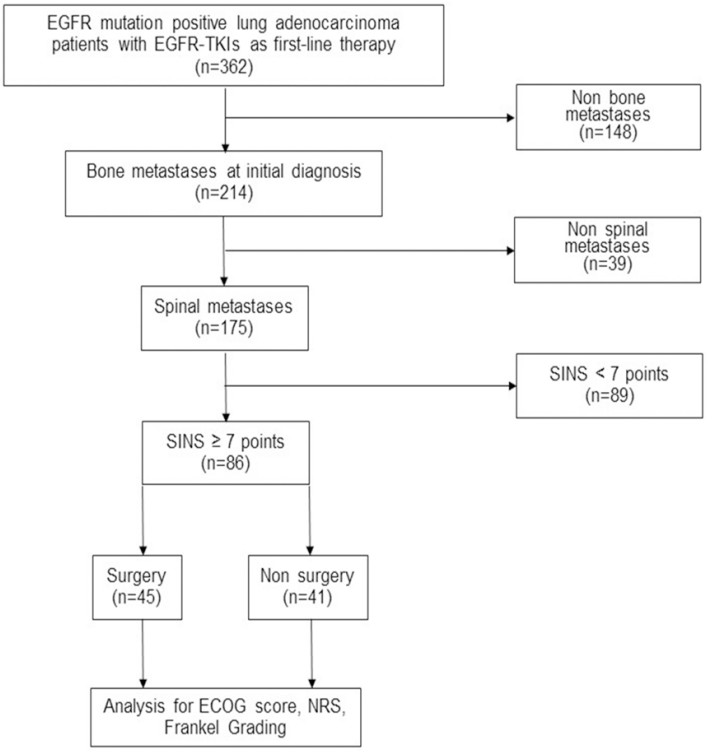

Figure 1. Schematic representation of the study group distribution. From 362 EGFR mutation-positive patients with lung adenocarcinoma who received EGFR-TKIs as first-line therapy, 214 patients were confirmed to have bone metastases at the time of the initial diagnosis. A total of 175 of these patients had spinal metastases, with 86 of them having SINS scores of ≥7 points; 45 of these patients underwent surgery, but 41 refused surgery. EGFR-TKIs, epithelial growth factor receptor-tyrosine kinase inhibitors; SINS, The Spinal Instability Neoplastic Score; ECOG Eastern Cooperative Oncology Group; NRS Numerical Rating Scale.

distribution of the various groups is shown in **Figure 1**.

The surgical treatments performed were percutaneous vertebroplasty, percutaneous biopsy vertebroplasty, laminectomy, spinal canal decompression, and pedicle screw internal fixation. Moreover, surgically removed bones and soft tissues were confirmed to be metastases by pathological analyses.

The data of the 86 patients with spinal metastasis having SINS ≥7 points were analyzed to determine the scores according to the ECOG, NRS, and Frankel Grading at the time of diagnosis, after surgery, and on treatment failure. Both the participating departments use the abovementioned assessment tools regularly for the assessment of bone metastasis patients. The treatment efficacy was evaluated by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

Statistical analysis

All the statistical analyses were performed using SPSS 21.0 software. The numerical data were evaluated using a chi-squared test, and a Kaplan-Meier analysis was used to determine survival. The statistical significance of the differences was defined in terms of $P<0.05$.

Results

Survival of the lung adenocarcinoma patients

Among the 362 patients (median age: 59.2 years; range: 31.0-85.0 years) with lung adenocarcinoma with EGFR-sensitizing mutations, 194 (53.6%) were male. The median follow-up period for all the patients was 23.6 months (range: 1.0-128.0 months). The median time to treatment failure (TTF) for first-line EGFR-TKIs was 8.6 months (range: 1.2-71.6 months). The median OS (mOS) was 24.0 months (95% CI: 19.5-38.4) (**Figure 2**).

Survival of bone metastases patients

In all, 59.1% (214/362) of the patients were diagnosed with bone metastases at the time of cancer detection. The median TTF of the first-line EGFR-TKIs for patients with and without bone metastasis was 6.9 and 8.7 months, respectively ($P=0.409$). The Kaplan-Meier analysis showed that the mOS was 19.0 months (95% CI: 13.6-24.4) and 31.0 months (5% CI: 26.6-35.4), respectively, for patients with and without bone metastasis ($P<0.001$) (**Figure 3**).

Survival of the spinal metastases patients

We found that 81.8% (175/214) of the patients with bone metastasis at the initial diagnosis had spinal metastases. According to the SINS system, a score of ≥7 points was associated with spinal instability or potential instability, while a score of <7 points indicated spinal stability. Among the 175 patients with spinal metastases, 86 and 89 patients, respectively, had SINS scores of ≥7 and <7. The OS of

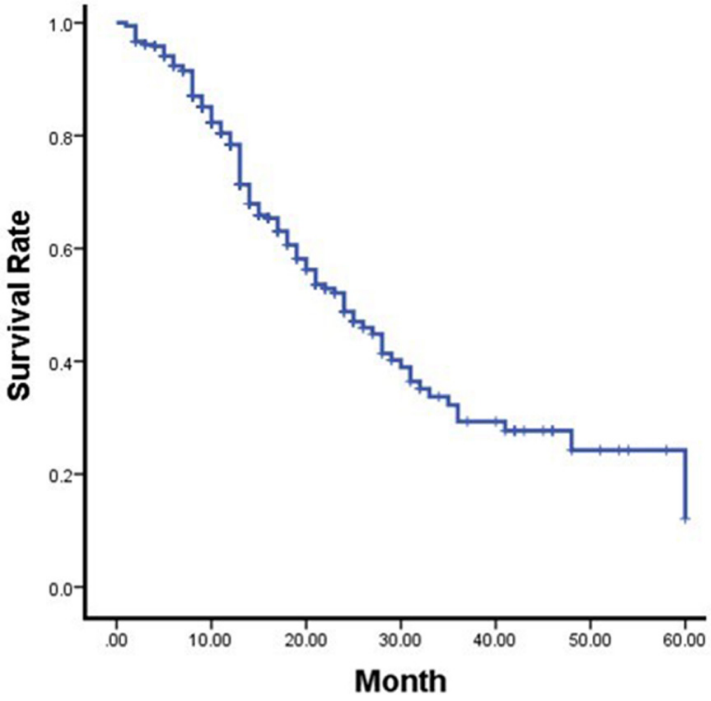

Figure 2. A Kaplan-Meier survival analysis of the overall survival (OS) for lung adenocarcinoma (n=362). The median OS was 24.0 months (95% CI: 19.5-38.4).

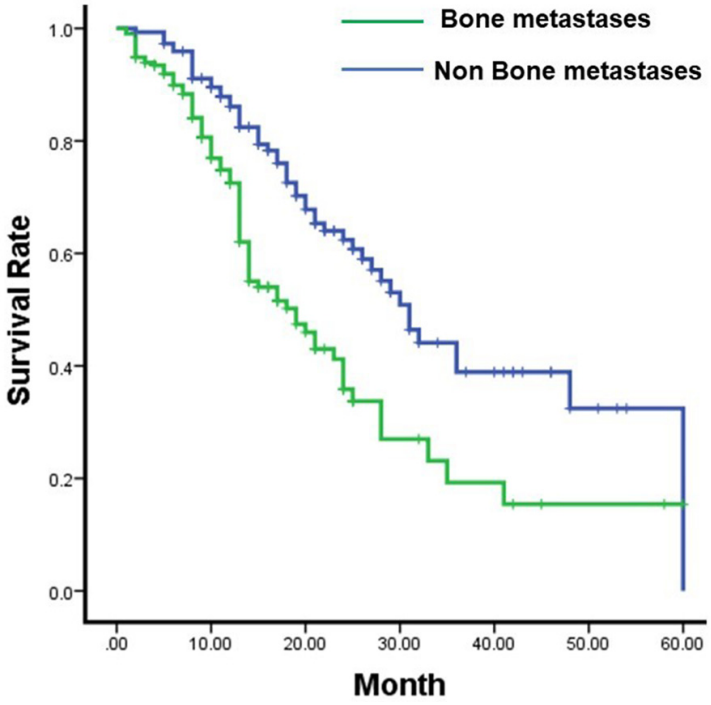

Figure 3. The median OS for lung adenocarcinoma patients with (n=214) or without (n=148) bone metastases. The mOS was 19.0 months (95% CI: 13.6-24.4) for patients with bone metastasis and 31.0 months (5% CI: 26.6-35.4) for patients without bone metastasis (P<0.001).

patients with SINS ≥7 was 15.0 months (95% CI: 9.5-20.4), which was significantly lower than the OS (21.0 months; 95% CI: 18.3-23.7) for patients with SINS <7 (P=0.038) (**Figure 4**).

SINS ≥7 with surgery versus without

Among patients with SINS ≥7, 45 underwent spinal surgery, while 41 did not undergo surgical treatment, and their OS was 17.0 months (95% CI: 8.4-25.5 months) and 10.0 months (95% CI: 5.9-14.1 months), respectively (P= 0.119) (**Figure 5**).

At the time of the initial diagnosis, patients with SINS ≥7 who did and did not undergo surgical treatment showed similar levels of neurological function, spinal pain, and quality of life, as determined by the Frankel Grading, NRS, and ECOG scales, respectively (**Table 1**). However, when assessed after the failure of the EGFR-TKI treatment, the patients who had received surgical treatment showed significantly lower levels of spinal pain as compared to those who did not, although no such intergroup difference was noted in terms of the other two parameters, i.e., neurological function and quality of life (**Table 2**). When compared with the measurements obtained at the time of diagnosis, those obtained at the time of failure of the EGFR-TKI treatment showed no significant change in the quality of life in both the groups (surgery group: χ^2=0.769, P=0.761; non-surgery group: χ^2= 4.100, P=0.152), but pain (surgery group: χ^2=2.632, P=0.292; non-surgery group: χ^2=6.967, P=0.029) and neurological dysfunction (surgery group: χ^2=0.450, P=0.739; non-surgery group: χ^2=6.248, P= 0.026) were significantly more severe in the non-surgery group,

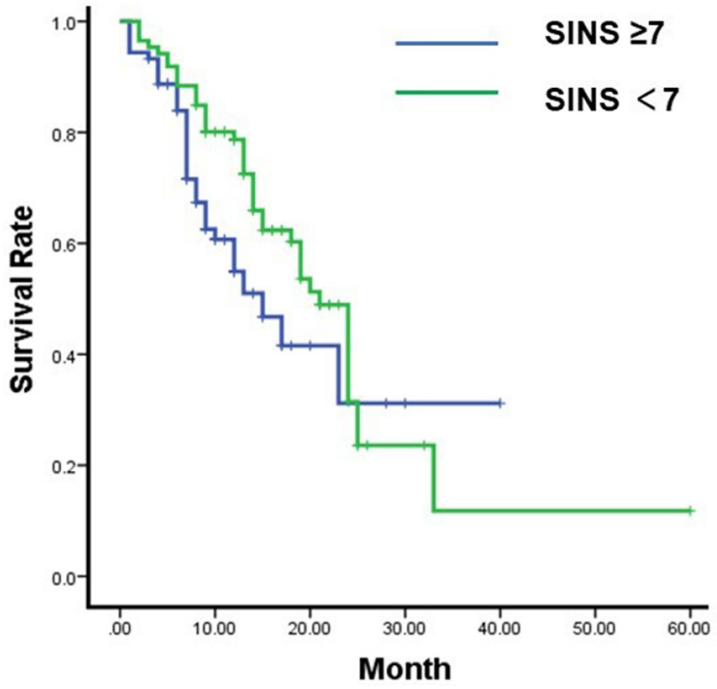

Figure 4. The median OS for lung adenocarcinoma patients with SINS scores of ≥7 (n=86) or SINS score of <7 (n=89). The OS was 15.0 months (95% CI: 9.5-20.4) for patients with SINS scores of ≥7 and 21.0 months (95% CI: 18.3-23.7) for patients with SINS scores of <7 (*P*=0.038). SINS ≥7 was associated with poor OS.

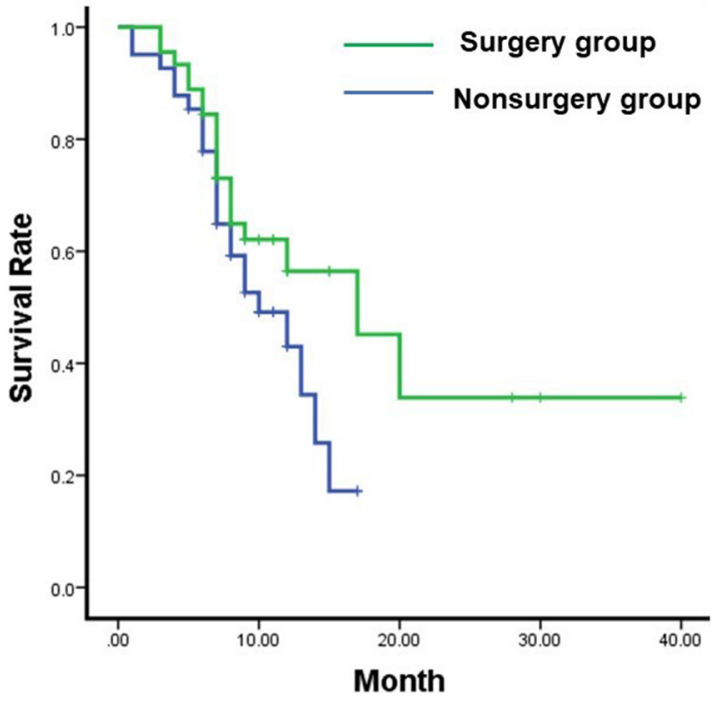

Figure 5. The median OS for patients with SINS score of ≥7 in the surgery group (n=45) and the non-surgery group (n=41). The OS was 17.0 months (95% CI: 8.4-25.5 months) for patients who underwent surgery and 10.0 months (95% CI: 5.9-14.1 months) for patients who did not undergo surgery (*P*=0.119).

but the parameters did not show any significant change in the surgery group. Further, the disease control rate (DCR) with EGFR-TKI treatment did not show any significant difference between the surgery group (39/45) and the non-surgery group (35/41) (86.7% vs. 85.5%, χ^2=0.030, *P*=0.862). The proportion of patients requiring secondary treatment was higher in the surgery group (40/45) than in the non-surgery group (28/41) (88.8% vs. 68.2%, χ^2=5.499, *P*= 0.032).

Discussion

Bones are one of the most common sites for metastases of lung cancer [18]. Among the various types of lung cancer, adenocarcinoma is associated with the highest incidence of bone metastases, with approximately 35-39% of patients with lung adenocarcinoma eventually developing bone metastases [18, 19]. Synchronous bone metastases (70.4%) have been reported to be more frequent than metachronous bone metastases (29.6%) in lung cancer, and 68.7% of patients with lung adenocarcinoma exhibit synchronous metastases [18]. Bone metastasis is associated with a high risk of death [20]. In the present study, we found that the mOS of patients with advanced lung adenocarcinoma occurring with EGFR-sensitizing mutations was 24.0 months and that 59.1% (214/362) of our patients presented with synchronous bone metastases at the time of their initial diagnosis. We also confirmed that the OS of patients with bone metastases was significantly less than that of patients without bone metastases (19.0 months vs. 31.0 months, P<0.001).

The most common site for bone metastasis in lung cancer is the spine, accounting for 32.1-59.5% of all cases of skeletal metastases

Table 1. Comparison of spinal cord function, pain, and ECOG scores in the surgery group and the non-surgery group at the time of initial diagnosis by the Frankel Grading, NRS, and ECOG scales, respectively

	Surgery group	Non-surgery group	χ^2	*P*
Frankel Grading				
A-D	6	2	1.818	0.270
E	39	39		
NRS score				
0-3	11	20	6.345	0.042
4-6	15	12		
7-10	19	9		
ECOG score				
0-1	21	20	0.139	1.000
2-3	21	19		
4-5	3	2		

ECOG: Eastern Cooperative Oncology Group; NRS: Numerical Rating Scale.

Table 2. Comparison of the spinal cord function, pain, and ECOG in the surgery group and the non-surgery group at the time of EGFR-TKI failure by the Frankel Grading, NRS, and ECOG scales, respectively

	Surgery group	Non-surgery group	χ^2	*P*
Frankel Grading				
A-D	4	10	3.782	0.078
E	41	31		
NRS score				
0-3	16	9	2.767	0.262
4-6	17	15		
7-10	12	17		
ECOG score				
0-1	25	17	3.649	0.174
2-3	17	16		
4-5	3	8		

ECOG: Eastern Cooperative Oncology Group; NRS: Numerical Rating Scale.

[18, 21, 22]. Spinal metastases can severely impair the stability of the spine, manifesting most commonly as pain in patients with symptomatic spinal metastases [23]. Mechanical (activity-related) pain is consistently observed in patients with spinal instability of oncologic origin [5]. The stability of the spine is also affected by the size and location of the tumor [5]. Up to 50% of the patients with spinal metastasis require treatment, with 5-10% of the patients requiring surgical management [9, 23-26]. Spinal surgery has been shown to considerably improve the pain and neurologic dysfunction [27]. In this study, 81.8% (175/214) of the patients with bone metastasis showed spinal involvement, with 49.1% (86/175) of these patients requiring surgery, as determined by the SINS scores. We observed that for patients who underwent surgical treatment, the spinal cord dysfunction and pain did not worsen significantly when EGFR-TKI failed; we believe that this finding would be useful in treatment compliance.

While spinal stability may not be directly associated with OS, it impedes the patient's mobility and quality of life; in fact, the survival of patients without pathological fractures of the vertebrae was greater than that of patients with such fractures [6]. Compression of the spinal cord severely impacts the patients' quality of life and increases the burden of family care, thereby affecting the patient's desire for treatment. Spinal surgery has been shown to significantly enhance the performance status, ability to perform activities of daily living, and overall neurological condition of patients with spinal metastasis, all of which are deteriorated for the non-surgery patients [28]. Research has also shown that survival is better for patients who had intact motor function before surgery [29]. The recent discovery of molecular-targeted drugs has greatly improved life expectancy in lung cancer patients with sensitizing genes. The third-generation EGFR-TKI, osimertinib, has been shown to improve PFS up to 18.9 months in patients with EGFR mutation-positive advanced NSCLC without any prior treatment [30]. Thus, an important aspect of treatment would be to ensure spinal stability, minimizing spinal cord compression, and promoting the patient's quality of life. Moreover, it is necessary to identify patients who need surgery before they develop a neurological deficit, which is associated with poor survival. Apart from the risk of nerve compression, other factors to be considered before surgical treatment include patient age, symptoms, physical status, and expected survival. Several scales have been developed to identify patients who will ultimately benefit from surgeries; SINS is one

such tool. The SINS classification system was formulated as a tool to identify patients with impending or existing spinal instability, with a score of 7 or greater suggesting a possible benefit from surgical intervention [6]. Our study revealed that a SINS score of ≥7 was associated with poor OS for lung adenocarcinoma patients with a sensitizing EGFR mutation, and if such patients received surgical treatment, survival could be improved. However, we were unable to identify a statistically significant increase in survival due to the limited sample size. At the time of EGFR-TKI failure, pain due to bone metastasis was significantly less for patients in the surgery group than for those in the non-surgery group, although it was similar in both the groups at the time of diagnosis. Compared to the levels at the time of diagnosis, the pain and spinal neurological dysfunction at the time of EGFR-TKI failure were significantly greater in the non-surgery group, but not in the surgery group. The beneficial effects on the patient's neurological function and quality of life made the patients in the surgery group more willing to accept follow-up treatment. Therefore, for lung adenocarcinoma patients who are deemed to have an unstable or potentially unstable vertebral column according to the SINS score, surgical treatment is effective in maintaining spinal stability, preventing or alleviating symptoms due to spinal cord compression, preventing the deterioration of spinal cord function, and providing pain relief. Since EGFR-TKI treatment is beneficial in extending their survival, surgical intervention should be considered for patients with spinal metastases.

This study has some limitations. To specifically evaluate the benefits of spinal surgery, we evaluated cases from the orthopedics department, without limiting our investigations to cases primarily pertaining to oncology, which resulted in a higher proportion of patients with bone metastases and surgery as compared to the other studies. Other limitations of the study include the small sample size and the retrospective nature.

Conclusions

Bone metastasis is one of the indicators of poor survival in patients with lung adenocarcinoma associated with sensitizing EGFR mutation. Extensive spinal metastases result in spine instability. We found that SINS is useful in identifying patients who have spinal instability and are likely to benefit from surgical treatment. Timely surgical management would prevent nerve damage, provide pain relief, and improve the patient's quality of life. The administration of EGFR-TKI has been associated with prolonged survival in lung cancer patients with a sensitizing EGFR mutation, and a timely surgical correction can further prevent the deterioration of nerve function and, therefore, the quality of life. This, in turn, is expected to enhance patient compliance to continue treatment and help improve survival.

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Disclosure of conflict of interest

None.

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