Support Care Cancer (2016) 24:731–736
DOI 10.1007/s00520-015-2835-1

ORIGINAL ARTICLE

Skeletal related events in patients with bone metastasis arising from non-small cell lung cancer

Gustavo Telles da Silva[1] · **Anke Bergmann**[2] · **Luiz Claudio Santos Thuler**[1,3]

Received: 25 February 2015 / Accepted: 22 June 2015 / Published online: 5 July 2015

Abstract
Purpose The skeleton is one of the most common sites of metastasis in patients with non-small cell lung cancer (NSCLC). Metastasis increases the risk of skeletal-related events (SREs). The purpose of this study is to evaluate the incidence of SREs and the factors associated with the development of SREs in patients with bone metastases (BM) arising from NSCLC.
Methods A cohort study was carried out involving 95 patients with BM associated with NSCLC who were enrolled between 2007 and 2011. Clinical and sociodemographic data were extracted from the physical and electronic records. The association between exposure variables and outcome (SREs) was assessed using crude odds ratio (OR). Survival analysis of patients with BM was conducted using the Kaplan-Meier method. A log-rank test was used to assess differences between the curves of those who did and did not experience SREs.
Results Sixty-two out of 95 patients with BM (65.3 %) showed evidence of at least one SRE. Multiple analysis revealed that patients with a history of smoking (OR=6.76; 95% CI=1.3–33.0; $p<0.01$), performance status ≥2 (OR=3.38; 95% CI=1.2–9.3; $p<0.01$), and multiple BM (OR=3.31; 95% CI=1.1–9.9; $p<0.03$) were at greater risk of SREs. Median survival time was 4.6 months (95% CI=2.9–6.2) in patients who experienced SREs and 6.8 months (95% CI=2.2–11.4) in patients who did not, a statistically significant difference ($p=0.03$).
Conclusion Patients with NSCLC are more likely to experience SREs if they have poor performance status, a history of smoking or multiple BM. Global survival was shorter in patients who suffer SREs.

Keywords Bone metastasis · Skeletal-related events · Non-small cell lung cancer · Associated factors

Introduction

Lung cancer (LC) is one of the most common cancers, and it remains the leading cause of death from cancer in men and women in Brazil and across the world [1–3].

Detection of LC normally occurs when the disease has already progressed locally or is associated with detection of metastases as there are few symptoms during the early stages [4, 5]. The skeleton is one of the most common sites of metastasis in patients with non-small cell LC (NSCLC) [6]. Bone metastases (BM) are observed in about 30–40 % of patients with advanced LC, and this number is higher if more sensitive diagnostic technologies are used [7, 8]. The median survival time after BM is 7 months [9].

In patients with BM, a complex cascade of biochemical signaling events involving tumor cells and bone cells results in a vicious cycle of tumor growth and a destruction of bone tissue that compromises skeletal integrity [10]. These alterations in the skeletal system increase the risk of skeletal-related events (SREs) such as pathological fracture, spinal cord compression, malignant hypercalcemia, and requirement for

✉ Luiz Claudio Santos Thuler
lthuler@inca.gov.br

[1] National Cancer Institute and Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

[2] National Cancer Institute and Augusto Motta University Center, Rio de Janeiro, Brazil

[3] Instituto Nacional de Câncer-Coordenação de Pesquisa Clínica, Rua André Cavalcanti, 37 / 2o andar, Centro-Rio de Janeiro, RJ 20231-050, Brazil

radiotherapy or surgery of the bone [10]. A retrospective study of patients with NSCLC and BM reported that 50 % of patients had SREs [11], and that occurrence of SREs was linked to loss of mobility and deterioration in quality of life [12].

Knowledge of predictors of SREs is required to develop effective preventive treatment and optimise the use of current therapeutic resources. Smoking, performance status, the histological type of NSCLC, and a history of use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) are independent risk factors for SREs; however, evidence on SREs is scarce [13].

The aim of this study was to evaluate the incidence of SREs and the factors associated with their occurrence in patients with BM associated with NSCLC. A secondary objective was to relate global survival to the occurrence of SREs.

Methodology

A cohort study of patients diagnosed with NSCLC between 2007 and 2011 and treated at the Brazilian National Cancer Institute (*Instituto Nacional de Câncer–INCA*) was conducted. The histological types represented in the sample were squamous cell carcinoma (International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) codes 8050–8076), adenocarcinoma (8140–8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8560, and 8570–8572), and large-cell carcinoma (8012–8031 and 8310). Diagnoses of BM were confirmed using one of the following methods: standard radiography, bone scintigraphy, computerised tomography (CT), or magnetic resonance imaging (MRI).

Clinical and sociodemographic data for the period between cancer diagnosis and December 31, 2013 were extracted from physical and electronic patient records. The independent variables evaluated were gender, age, race, marital status, schooling, history of smoking, alcohol consumption, histology, staging, body mass index (BMI), performance status, number of vertebrae involved per metastasis, presence of other BM sites, and the method of LC treatment.

The main time-dependent outcome was defined as the SREs. In this study, an SRE was defined as the occurrence of a pathological fracture, spinal cord compression, malignant hypercalcemia, or the requirement for radiotherapy or surgery of the bone.

A descriptive study of the population was carried out, using measures of central tendency and dispersion for the continuous variables and frequency distribution for the categorical variables. The association between the independent variables and the outcome variable (SREs) was assessed by using crude odds ratio (OR). Variables that showed a p value <0.20 or variables of clinical significance were selected for the multiple regression modeling. Only variables with p value <0.05 were retained in the final model.

Analysis of the survival of patients with BM was carried out using the Kaplan-Meier method. Patients were followed for up to 24 months. Differences between the survival curves of those who did and did not experience SREs were assessed with a log-rank test. The significance level was set at p value <0.05 for all analyses. The data were analysed using SPSS (*Statistical Package for Social Science for Windows*, *São Paulo*, Brazil) software version 21.0.

This work was approved by the Research Ethics Committee of the National Cancer Institute (*Instituto Nacional de Câncer*, protocol CAAE: 11556513.2.0000.5274, number 233 245/2013) and was conducted in accordance with the ethical principles established by the National Health Council (CNS), Resolution 466/12.

Results

Ninety-five patients who had been diagnosed with BM arising from NSCLC between 2007 and 2011 were identified and followed for a median period of 4.4 months from the diagnosis of BM.

Table 1 summarises the clinical and sociodemographic data for the sample of NSCLC patients with BM. Sixty-one percent of eligible patients were men. The average age at the time of BM diagnosis was 60.9 years (±SD 9.0). Patients were predominantly Caucasian (72.6 %) with a history of smoking (86.3 %). Most of the tumors were histologically classified

Table 1 Clinical and sociodemographic characteristics of the population studied (n=95)

Features	*N* (%)
Age (years, mean±SD)	60.9±9.0
Male	58 (61.1 %)
Caucasians	69 (72.6 %)
Married	62 (65.3 %)
Schooling ≤8 years of study	61 (64.2 %)
History of smoking	82 (86.3 %)
History of alcoholism	51 (53.5 %)
Normal BMI	43 (45.3 %)
Performance status 0–1	73 (76.9 %)
Solitary bone metastasis	57 (60.0 %)
Histological type: adenocarcinoma	56 (58.9 %)
Stage IIIb and IV at diagnostic NSCLC	71 (74.7 %)
Treatment with chemotherapy, radiotherapy, or chemotherapy+radiotherapy	74 (77.9 %)
History of bisphosphonates therapy	14 (14.7 %)
History of EGFR-TKI therapy	7 (7.4 %)

NSCLC non-small cell lung cancer, *BMI* body mass index, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor

as adenocarcinomas (58.9 %). Approximately three quarters (74.7 %) of the patients were in the advanced stage at the time of NSCLC diagnosis; of these, 48 were stage IV. The sites of metastasis at the time of cancer diagnosis were bone (n=31), brain (n=10), adrenal gland (n=9), and liver (n=4). After diagnosis of BM, 14.7 % of patients received one or more doses of bisphosphonates and 7.4 % used EGFR-TKI therapy. Many cases of BM involved multiple locations. The most common sites were spine (38.6 %), ribs (20.2 %), pelvis (12.4 %), humerus (5.9 %), and skull (4.6 %). Other less frequent sites were scapula, sacrum, clavicle, radius, sternum, and hand.

Sixty-two (65.3 %) of the 95 patients with BM showed evidence of at least one SRE during the study period. Thirty-three (53.2 %) patients suffered only one SRE, whilst 29 (46.8 %) suffered multiple events. SREs occurred at the same time as BM diagnosis in 42 (67.7 %) patients and during the follow-up period in 20 (32.3 %) patients. In total, 53 patients underwent radiotherapy to bone (55.8 %), 25 suffered a pathological fracture (26.3 %), 24 developed spinal cord compression (25.3 %), three developed malignant hypercalcemia (3.2 %), and one underwent bone surgery (1.0 %) (Table 2).

The incidence of SREs was not influenced by gender, age, BMI, histological type, or stage of NSCLC. Univariate analysis showed, however, that patients with a history of smoking and performance status ≥2 were at increased risk of SREs (Table 3).

Patients with a history of smoking were 6.7 times more likely to suffer SREs than those with no history of smoking (OR=6.76; 95 % CI=1.3–33.0; p<0.01). Patients with a performance status ≥2 were 3.3 times more likely to experience SREs than those with a performance status <2 (OR=3.38; 95 % CI=1.2–9.3; p<0.01), and the patients with multiple BM were 3.3 times more likely to experience SREs than those with a single BM (OR=3.31; 95 % CI=1.1–9.9; p<0.03) (Table 4).

The median survival time for patients diagnosed with BM was 4.7 months (95 % CI=2.9–6.4). The average survival time was 4.6 months (95 % CI=2.9–6.2) for those who experienced at least one SRE and 6.8 months (95 % CI=2.2–11.4) for those who did not experience an SRE. This difference was statistically significant (p=0.03) (Fig. 1).

Table 2 Incidence of skeletal-related events in the sample (n=95)

Skeletal-related events	*N* (%)
Radiotherapy to bone	53 (55.8 %)
Pathological fracture	25 (26.3 %)
Spinal cord compression	24 (25.3 %)
Hypercalcemia	3 (3.2 %)
Surgery to bone	1 (1.0 %)

Discussion

There has been increasing interest in BM and in the complications that may occur in the skeletal system as a consequence. However, this was the first study to investigate SREs in patients with NSCLC in Brazil.

In this study, the mean age of the patients at the time of BM diagnosis was 60.9 years and 61.1 % were men, similar to other authors' findings [14–16]. Previous studies have reported that 57.8–65.0 % of patients with NSCLC have an adenocarcinoma [14–16]; the proportion of patients in this study was within this range (58.9 %).

LC has a high potential for metastasis and is normally diagnosed when the disease has already progressed locally or systemically because there are few symptoms in the early stages of the disease [5, 17]. In this study, 74.7 % of the diagnosis had stage IIIb or IV disease patients at the time of the NSCLC. A recent study [17] reported that 41 % of patients had distant disease at the time of the diagnosis and of these 38 % suffered BM during the first year following their cancer diagnosis.

The skeletal system is one of the most common sites of metastasis in patients with LC [6, 17]. Progression of BM may result in SREs which, as well as being associated with pain and reduced quality of life, place a substantial demand on healthcare resources [12, 18]. In this study, 65.3 % of patients experienced at least one SRE. Another study including patients from four European countries reported that the frequency of SREs in patients with BM arising from LC, breast cancer, prostate cancer, or multiple myeloma ranged from 39 % in England to 70 % in Spain [12]. SRE history ranged between 38.2 and 67.8 % in studies limited to patients with LC [11, 15–17, 19–22]. Tsuya et al. [11] reported that 45 % of patients diagnosed with stage IV NSCLC and 71 % of patients diagnosed with stage III disease experienced at least one type of SRE. The incidence of SREs in our population was at the upper end of the range; studies reporting lower incidences of SREs tend to have been conducted in developed countries where drugs such as bisphosphonates and inhibitors of receptor activator of nuclear factor kappa-b ligand (RANKL) like denosumab are available. Bisphosphonates and denosumab are effective in reducing the incidence of SRE and delayed the time to SRE [23–29]. By the time this study was conducted (2007–2011), bisphosphonates were not routinely used in the institution. A systematic review and meta-analysis of patients with LC demonstrated that treatment with bisphosphonates produced a 19 % reduction in the risk of experiencing new SREs during the first 2 years of treatment [28]. A phase III clinical trial [29] reported that denosumab extended the time to first SRE by a median of 6 months compared to zoledronic acid, resulting in a risk reduction for a first SRE of 19 % and in an improvement of pain outcomes in patients with bone metastasis due to solid tumours including NSCLC.

Table 3 Univariate analysis of the effects of various demographic and clinical variables on incidence of skeletal system-related events in patients with bone metastasis arising from non-small cell lung cancer

Features	SRE		OR (95 % CI)	*p value*
	Yes	No		
Gender				
Male	36 (58.1)	22 (66.7)	Reference	
Female	26 (41.9)	11 (33.3)	1.4 (0.5–3.4)	0.41
Age to diagnosis				
>60 years old	28 (45.2)	20 (60.6)	Reference	
≤60 years old	34 (54.8)	13 (39.4)	1.8 (0.7–4.4)	0.15
Race/skin color				
Caucasian	43 (71.7)	26 (81.2)	Reference	
Non-caucasian	17 (28.3)	6 (18.8)	1.7 (0.5–4.8)	0.31
Marital status				
With partner	39 (63.9)	23 (71.9)	Reference	
Without partner	22 (36.1)	9 (28.1)	1.4 (0.5–3.6)	0.44
Schooling				
>8 years of study	25 (41.0)	15 (48.4)	Reference	
≤8 years of study	36 (59.0)	16 (51.6)	1.3 (0.5–3.2)	0.49
Smoking				
No	4 (6.5)	7 (22.6)	Reference	*0.03*
Yes	58 (93.5)	24 (77.4)	4.2 (1.1–15.5)	
Alcoholism				
Yes	32 (58.2)	19 (70.4)	Reference	
No	23 (41.8)	8 (29.6)	1.7 (0.6–4.5)	0.28
BMI				
Underweight or normal weight	32 (66.7)	19 (73.1)	Reference	
Pre-obese or overweight	16 (33.3)	7 (26.9)	1.3 (0.4–3.8)	0.57
Performance status				
<2	26 (43.3)	20 (66.7)	Reference	
≥2	34 (56.7)	10 (33.3)	2.6 (1.0–6.5)	*0.03*
Bone metastasis				
Single	33 (53.2)	24 (72.7)	Reference	
Multiple	29 (46.8)	9 (27.3)	2.34 (0.9–5.8)	0.06
Histology				
Adenocarcinoma	36 (58.1)	20 (60.6)	Reference	
Non-adenocarcinoma	26 (41.9)	13 (39.4)	1.1 (0.4–2.6)	0.81
Staging				
≤IIIa	11 (18.6)	9 (28.1)	Reference	
IIIb-V	48 (81.4)	23 (71.9)	1.7 (0.6–4.6)	0.30
LC Treatment				
Surgery, Surgery+Chemo	7 (11.3)	5 (15.2)	Reference	
Chemo, radiotherapy, chemo + radiotherapy	47 (75.8)	27 (81.8)	1.2 (0.3–4.3)	0.73
None	8 (12.9)	1 (3.0)	5.7 (0.5–61.4)	0.15

SRE skeletal-related events, *LC* lung cancer, *NSCLC* non-small cell lung cancer, *BMI* body mass index, *Chemo* chemotherapy, *NA* not applicable, *OR* odds ratio, *CI* confidence interval

In italics, the statistically significant *p* values

This study evaluated factors associated with the occurrence of SREs in patients with NSCLC with BM. Patients with a history of smoking, poor performance status (≥2), or multiple sites of BM were at greater risk of experiencing SREs. These associations are consistent with previous research on patients with NSCLC [13, 30]. Sekine et al. [30] reported that having

Table 4 Multiple analysis of factors associated with occurrence of skeletal-related events following diagnosis of bone metastasis

	OR	95 % CI	*p* value
Smoking			
Yes vs. No	6.8	1.3–33.0	0.01
Performance status			
≥2 vs. <2	3.4	1.2–9.3	0.01
Number of bone metastasis			
Multiple vs. Single	3.3	1.1–9.9	0.03

OR odds ratio, *CI* confidence interval

multiple sites of BM was a risk factor for SREs in patients treated with systemic chemotherapy. Sun et al. [13] reported that lack of treatment with EGFR-TKI, poor performance status (≥2), non-adenocarcinoma disease, and being a current or ex-smoker were independent risk factors for SREs. Smoking has an independent effect on bone loss and increases the risk of osteoporotic fractures [31, 32]. Decroisette et al. [14] defined a SRE as a pathological fracture, spinal cord compression, or malignant hypercalcemia and, in contrast with this study, found that the incidence of SREs was highest in patients with good performance status; however, when radiotherapy or surgery was included in the definition of an SRE, performance status was no longer a predictor of SREs. Other studies of patients with LC have demonstrated a positive association between occurrences of SREs and having stage IV disease, age<64 years, and male sex [19, 20]. In this study, we found no associations between age, gender, or disease stage and occurrence of SREs in patients with BM arising from NSCLC, perhaps due to the small sample size.

SREs are the main complication associated with BM, but their harmful association with survival has been controversial. Two previous studies failed to find a statistically significant difference between the survival time of patients with BM and a history of SREs [11, 13]. However, in this study, overall survival times were lower (p=0.03) for patients who experienced SREs (4.6 months) than for patients with no history of SREs (6.8 months). This finding is in line with other studies [14, 16, 33].

This research has some limitations. The study included only a small number of patients, which may have resulted in type II errors. As it was a "real-life study," the criteria for BM and SREs were those used by assistant doctors in the clinical practice, with no standardization. In addition, patients might not have been systematically investigated for hypercalcemia during follow-up, which would have reduced the chances of it being detected. The fact that this was a retrospective study, based on the review of medical records, is an additional limitation. Prospective studies of patients with NSCLC and BM are necessary to improve our understanding of the incidence of SREs and the relationship between different risk factors.

In conclusion, our findings suggest that patients with NSCLC who have a poor performance status, a history of smoking, or multiple BM sites are more likely to experience SREs. Survival was worse overall in patients who suffered SREs. The identification of factors associated with the development of an SRE can be helpful for implementing early bone targeting treatments to prevent SREs.

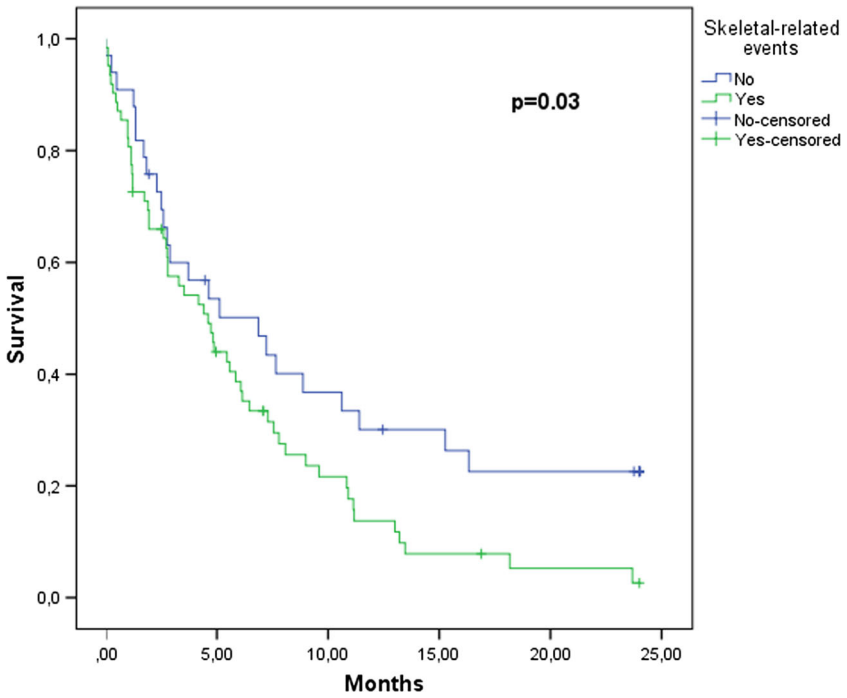

Fig. 1 Survival time for patients with bone metastasis who did and did not experience skeletal-related events

Conflict of Interest The authors declare that they have no competing interests.

Consent to Participate For this type of study informed consent is not required.

References

1. Brasil. Instituto Nacional de Câncer (2014) Estimativa 2014: Incidência de Câncer no Brasil. http://www.inca.gov.br/. Accessed 10 Dec 2013
2. Parkin DM, Bray F, Ferlay J et al (2001) Estimating the world cancer burden: GLOBOCAN 2000. Int J Cancer 94:153
3. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63(1):11–30
4. Kohler BA, Wand E, McCarthy BJ et al (2011) Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 103:714–736
5. Hirsh V (2009) Skeletal disease contributes substantially to morbidity and mortality in patients with lung cancer. Clin Lung Cancer 10(4):223–229
6. Roodman GD (2004) Mechanisms of bone metastasis. N Engl J Med 350:1655–1664
7. Al Husaini H, Wheatley-Price P, Clemons M et al (2009) Prevention and management of bone metastases in lung cancer: a review. J Thorac Oncol 4:251–259
8. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 27:165–176
9. Coleman RE (1997) Skeletal complications of malignancy. Cancer 80:1588–1594
10. Coleman RE (2004) Bisphosphonates: clinical experience. Oncologist 9(suppl 4):14–27
11. Tsuya A, Kurata T, Tamura K et al (2007) Skeletal metastases in non-small cell lung cancer: a retrospective study. Lung Cancer 57(2):229–232
12. Hoefeler H, Duran I, Hechmati G et al (2014) Health resource utilization associated with skeletal-related events in patients with bone metastases: Results from a multinational retrospective–prospective observational study—a cohort from 4 European countries. J Bone Oncol 3(2):40–48
13. Mu Sun J, Ahn JS, Lee S et al (2011) Predictors of skeletal-related events in non-small cell lung cancer patients with bone metastases. Lung Cancer 71(1):89–93
14. Decroisette C, Monnet I, Berard H et al (2011) Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study. J Thorac Oncol 6(3):573–582
15. Oster G, Lamerato L, Glass AG et al (2013) Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer 21(12):3279–3286
16. Bae HM, Lee SH, Kim TM et al (2012) Prognostic factors for non-small cell lung cancer with bone metastasis at the time diagnosis. Lung Cancer 77(3):572–577
17. Sathiakumar N, Delzell E, Morrisey MA et al (2013) Mortality following bone metastasis and skeletal-related events among patients 65 years and above with lung cancer: a population-based analysis of U.S Medicare beneficiaries, 1999–2006. Lung Ind 30(1):20–26
18. De Marini F, Eberhardt W, Harper PG et al (2009) Bisphosphonate use in patients with lung cancer and bone metastases: recommendations of a European expert panel. J Thorac Oncol 4(10):1280–1288
19. Wei J, Jun T, Pinghai Z et al (2011) Factors associated with the development of skeletal-related events in non-small cell lung cancer patients with bone metastases. Int J Radiat Oncol Biol Phys 81(2):S596
20. Katakami N, Kunikane H, Takeda K et al (2014) Prospective study on the incidence of bone metastasis (BM) and skeletal-related events (SREs) in patients (pts) with stage IIIB and IV lung cancer-CSP-HOR 13. J Thorac Oncol 9(2):231–238
21. Nagata M, Kudoh S, Mitsuoka S et al (2013) Skeletal-related events in advanced lung adenocarcinoma patients evaluated EGFR mutations. Osaka City Med J 59(1):45–52
22. Cetin K, Christiansen CF, Jacobsen JB, NØrgarrd M, SØrensen HT (2014) Bone metastasis, skeletal-related events, and mortality in lung cancer patients: a Danish population-based cohort study. Lung Cancer 86(2):247–254
23. Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krazakowski M, Pawlicki M, De Souza P, Zheng M, Urbanowitz G, Reitsma D, Seaman J (2004) Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 100:2613–2621
24. Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME (2013) Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat Rev 39(1):97–104
25. Lipton A, Fizazi K, Stopeck AT, Henry DA, Brown JE, Yardley DA, Richardson GA, Siena S, Maroto P, Clemens M, Bilynskyy B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun SJ (2012) Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 48(16):3082–3092
26. Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, Royle P, Jones R, Mulatero C, Todd R, Mowatt G (2013) Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess 17(29): 1–386
27. Wang Z, Qiao D, Lu Y, Curtis D, Wen X, Yao Y, Zhao H (2015) Systematic literature review and network meta-analysis comparing bone-targeted agents for the prevention of sketetal-related events in cancer patients with bone metastasis. Oncologist 20(4):440–449
28. Lopez-Olivo MA, Shah NA, Pratt G et al (2012) Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. Support Care Cancer 20(11):2985–2998
29. Henry D, Vadhan-Raj S, Hirsh V, Von Moos R, Hungria V, Costa L, Woll PJ, Scagliotti G, Smith G, Feng A, Jun S, Dansey R, Yeh H (2014) Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 22(3):679–687
30. Sekine I, Nokihara H, Yamamoto N et al (2009) Risk factors for skeletal-related events in patients with non-small cell lung cancer treated by chemotherapy. Lung Cancer 65(2):219–222
31. Ward KD, Klesges RC (2001) A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int 68: 259–270
32. Williams AR, Weiss NS, Ure CL et al (1982) Effect of weight, smoking, and estrogen use on the risk of hip and forearm fractures in postmenopausal women. Obstet Gyncecol 60:695–699
33. Oster G, Lamerato L, Glass AG, Richert-Boe KE, Lopez A, Chung K, Richhariya A, Dodge T, Wolff GG, Balakumaran A, Edelsberg J (2014) Use of intravenous bisphosphonates in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer 22(4):1363–1373