Epidemiology and Treatment Costs of Bone Metastases from Lung Cancer

A French Prospective, Observational, Multicenter Study (GFPC 0601)

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Introduction: The aim of this prospective, observational, multicenter study was to examine the epidemiology and management costs of bone metastatic disease (BMD) in patients with lung cancer.
Methods: The analysis included all patients with BMD from lung cancer diagnosed between May 2006 and May 2007 in 40 centers. We analyzed their management and the direct costs of BMD from the health care provider's perspective, using a Markov model. Skeletal-related event (SRE) was defined as pathological fractures, spinal cord compression, or hypercalcemia (clinical SRE [cSRE]) for an initial analysis; a second analysis included palliative radiotherapy and surgery (therapeutic SRE [tSRE]).
Results: Among the 554 patients enrolled (62 ± 11 years, 76.5% males, 69.3% performance status 0/1, 91% non-small cell lung cancer), 24.7% had a cSRE and 26.7% a tSRE at baseline and 9% and 39% during follow-up, respectively; 81.8% received at least one chemotherapy cycle. The median survival time was 5.8 months, and the 1- and 2-year survival rates were 22% and 7%, respectively; there was no significant difference in overall survival between the patients with and without SRE at enrollment. The main BMD treatments were opiate therapy (77.7%), biphosphonates (52.3%), radiotherapy (42.1%), and surgery (9.2%). The mean monthly BMD treatment costs in euros were €190, €374, and €4672 for asymptomatic patients, symptomatic patients, and patients with SRE, respectively. The average first-year BMD management cost in euros was €3999 ± 4135 (95% confidence interval: 374–15,886), and 49.5% of this cost was attributable to patients with SRE.
Conclusions: This analysis confirms the poor prognosis of BMD from lung cancer and underlines the burden of SRE in overall treatment costs.

Key Words: Bone metastases, Non-small cell lung cancer, Costs, Biphosphonates, Zoledronic acid.

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The number of patients diagnosed with advanced-stage lung cancer is expected to increase in coming years, and, even though the prognosis remains dismal, median survival is also increasing as new treatments are developed. Given the limitations of current therapeutic options, palliation of symptoms due to metastatic disease remains a primary concern. In particular, bone metastases occur in 30 to 65% of patients with lung cancer,[1] and most patients with bone metastatic disease (BMD) experience skeletal-related events (SREs; clinical SRE [cSRE]), defined as pathological fractures, spinal cord compression, or hypercalcemia. Such complications frequently require bone irradiation, opiate analgesics for severe pain, and surgery to correct fractures or spinal deformities.[2] SRE can occur regardless of the radiographic appearance of bone lesions. In a recent clinical trial, most patients with BMD from non-small cell lung cancer (NSCLC) experienced SRE during the first 5 months of the study.[3] These events result in impaired mobility and quality of life, have a significant negative impact on survival, and are associated with increased health care costs.[4–9] Nevertheless, despite the importance of this problem, there are no prospective epidemiological studies of the characteristics and natural history of patients with lung cancer with BMD. Biphosphonates and especially intravenous zoledronic acid, have been shown in a double-blinded randomized trial to reduce the incidence of SRE in patients with solid tumors.[3,7,10–12] Other new treatments are being developed. For example, denosumab, which specifically targets the receptor activator of nuclear factor

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The chief investigators (C. Decroisette and C. Chouaid) had full control of the study design, data analysis, interpretation, and preparation of the manuscript. All the authors were involved in planning the analysis and drafting the manuscript. The final draft of the manuscript has been approved by all the authors.

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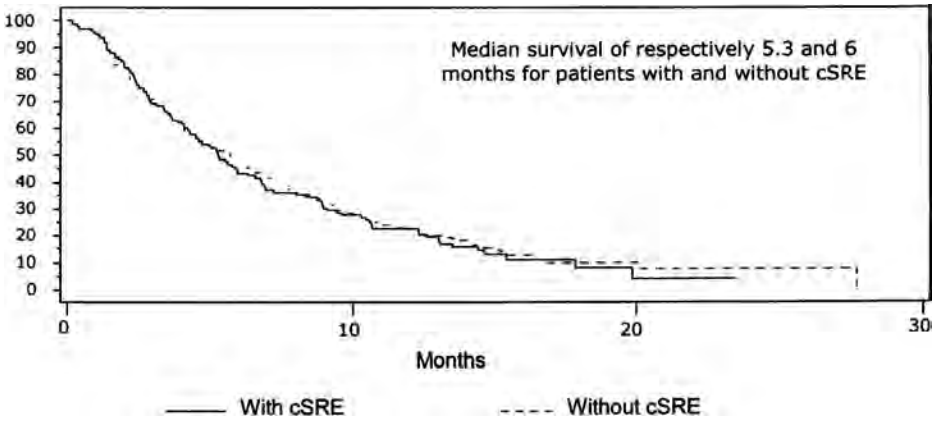

FIGURE 1. Median survival of patients with and without skeletal-related events defined as pathological fractures, spinal cord compression, or hypercalcemia (cSRE).

kappa B ligand, a key osteoclast regulatory factor, is being studied for its potential to delay the onset of BMD and to inhibit and treat bone destruction in patients with advanced-stage lung cancer.[2,13] The cost-effectiveness of these treatments is poorly established.[14–16] The objective of this prospective, observational, multicenter study was to document the epidemiology, management, and BMD treatment costs of patients with lung cancer with BMD.

MATERIALS AND METHODS

The study involved all patients aged at least 18 years who were managed in 1 of the 40 participating centers for histologically or cytologically proven lung cancer and a diagnosis of bone metastasis between May 1, 2006, and May 1, 2007. The patients were enrolled prospectively to this purely observational study, and the investigators were asked to provide 1 month of follow-up information retrospectively to avoid the risk of modifying usual practices. Regardless of symptoms, bone metastasis had to be confirmed either by standard radiography and technetium 99 bone scintigraphy, or by computed tomography or magnetic resonance imaging. Concurrent bone disease (i.e., Paget's disease or myeloma) was an exclusion criterion. The analysis focused on sociodemographic characteristics, lung cancer characteristics, BMD characteristics (diagnosis, location, and management), and laboratory findings. Monthly follow-up visits focused on the course of bone metastases and especially SRE, SRE management, and related health care consumption. SRE was defined as pathological fractures, spinal cord compression, or hypercalcemia (cSRE) for the initial analysis, then a second analysis included palliative radiotherapy or surgery for BMD in the definition (therapeutic SRE [tSRE]). Follow-up lasted for 12 months after BMD diagnosis or until death.

We used a Markov approach (implemented with decision analysis software from TreeAge, Williamstown, MA) to model first-year management costs in this cohort of patients with lung cancer with BMD. We distinguished the different management phases, both for each patient and for each 1-month period (patients were classified by two of the authors—C.D. and C.C.). The simulation was run as shown in Figure 1. After initial diagnosis of BMD, each patient is in one of the following four exhaustive and mutually exclusive health states: asymptomatic bone metastasis (ABM); symptomatic bone disease (SBM; escalation of specific treatment for more than 3 days); SRE, acute bone-related event (at least one SRE, defined as a fracture, vertebral compression, spinal compression, or acute hypercalcemia); and death (absorbent state).

Between each monthly clinical assessment, each patient is in one of the four following health states: ABM, SBM, SRE, or death. In the next cycle, the cohort was partitioned among the four states, resulting in a new distribution. Baseline probabilities and probabilities of transition from one health state to another over time were established by analyzing the management modalities of the study cohort. We used a Markov model to analyze the expected monetary cost of BMD management. Confidence intervals (95%) were obtained by Monte-Carlo simulation.

Economic Valorization

The economic analysis adopted the health care payer's perspective and took into account only direct costs (i.e., consumption of health care resources). Indirect costs (e.g., lost income) and intangible costs (e.g., pain and suffering) were not assessed. Hospitalization costs (administration, security, maintenance, general equipment, central supply, dietetics, and social services) were assessed on a per diem basis (national unit cost scale for each event) for fixed costs and from drug purchase prices in the establishments concerned.[17] Medical costs (nursing, care, ward supplies, pharmacy, diagnostic tests, laboratory tests, and professional services) were determined by chart review. Transport costs were estimated from the national scale. A mean monthly cost was calculated for each of the four health states.

Statistical Analysis

Quantitative variables are expressed as means and SD and were compared with one way analysis of variance, Student's *t* test, or the Mann-Whitney *U* test depending on the variable. Qualitative variables are expressed as numbers and percentages and were compared with the χ^2 test or Fisher's exact test.

Significance was assumed at p less than 0.05. Overall survival rates were estimated with the Kaplan-Meier method, and groups were compared using the log-rank test. The Cox model was used to identify factors predictive of survival.

TABLE 1. Patient Characteristics

Characteristics	$n = 554$
Gender (male/female)	76.5%/23.5%
Age (yr, mean ± SD)	62 ± 11
Performance status	
0/1	384 (69.3%)
2/3/4	170 (30.7%)
Histology	
NSCLC	498 (91%)
Adenocarcinoma/squamous/others	57.8%/15.3%/17.9%
SCLC	49 (9%)
Metastases others than bone	350 (64.6%)
Liver/lung/brain/adrenals/others	23.9%/33.9%/18.2%/19.9%/8.2%
Prior lung cancer treatments	
None	361 (65.2%)
Chemotherapy/radiotherapy/surgery	193 (34.8%)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Multivariate logistic regression analysis was used to identify baseline variables with independent predictive value for SRE.

The study was approved by the Limoges University Hospital ethics committee on March 4, 2006. The sponsors had no role in the study design, study realization, data analysis, or manuscript preparation. Groupe Français de Pneumo-Cancérologie (GFPC) is the proprietor of the results. The data were analyzed and interpreted by the authors.

RESULTS

Five hundred fifty-four patients were enrolled in the 40 centers between May 2006 and May 2007. Mean age was 62 ± 11 years, and 76.5% of the patients were men. The patients were in good general condition (performance status [PS], 0/1) in 69.3% of cases. The lung cancer was NSCLC in 91% of cases (Table 1). BMD was diagnosed before, at the same time, or after lung cancer in 151 (27.3%), 72 (13%), and 331 (59.7%) cases, respectively. In this last case, BMD was diagnosed a mean of 192 ± 336 days after lung cancer. The diagnosis was based on technetium scintigraphy in 62.2% of cases (Table 2) and on positron emission tomography scan, computed tomography scan, or magnetic resonance imaging in the others cases. The mean metastatic bone sites at BMD diagnosis was 3.6 ± 3.5; the most frequent locations being the spine (56.3%), ribs (38.1%), and pelvis (30.1%). At baseline, BMD was revealed by 93 cSRE in 87 patients. During follow-up, 73 new cSRE occurred in 73 patients, of whom 23 had already had a cSRE (Table 2). The analysis of tSREs showed that 148 patients (26.7%) had a tSRE at baseline and that 234 tSREs occurred during follow-up (62.2% and 35% of patients with and without tSREs at inclusion, respectively). There is no significant difference of incidence of cSRE when we compare patients with PS 0/1 and patients with PS more than 1 (13.8% and 20% at inclusion, $p = 0.064$, and 25% and 24.1% during follow-up, respectively).

After BMD diagnosis, 453 (81.8%) patients received at least one cycle of chemotherapy (88.8% for PS 0/1 patients, 65.9% for patients with PS >1, $p < 0.001$). Table 3 lists the specific treatments received for BMD. Most patients received analgesics (mainly opiates). Slightly more than half of the patients (52.3%) received biphosphonates, usually by the intravenous route, every 3 or 4 weeks (zoledronic acid, 4 mg),

TABLE 2. Characteristics of Bone Metastasis Disease (BMD)

Characteristics of Bone Metastasis Disease (BMD)	$n = 554$
Time between lung cancer diagnosis and BMD (n, mean ± SD days)	
BMD before lung cancer diagnosis	151 (27.3%), 14.4 ± 17
Simultaneous diagnosis of BM and lung cancer	72 (13%)
BM after lung cancer diagnosis	331 (59.7%), 192 ± 336
Diagnostic modalities	
Standard radiography	15 (2.7%)
Technetium scintigraphy	347 (62.2%)
TEP-CT and/or CT and/or MRI	192 (35.1%)
Number of bone metastasis sites at diagnosis (mean ± SD)	3.6 ± 3.5
Types of SRE at diagnosis	
Hypercalcemia	37
Pathological fracture	27
Vertebral collapse	13
Spinal compression	16
Radiotherapy or surgery	148
Types of SRE during follow-up	
Hypercalcemia	14
Pathological fracture	31
Vertebral collapse	7
Spinal compression	21
Radiotherapy or surgery	234
Biological values (mean ± SD)	
Calcemia (mmol/liter), $n = 429$	2.31 ± 0.2
Corrected calcemia (mmol/liter), $n = 173$	2.40 ± 0.2
Alkaline phosphatase (IU/liter), $n = 419$	166 ± 167
Proteinemia (g/liter), $n = 412$	67 ± 8
Albuminemia (g/liter), $n = 412$	34 ± 7
Creatinemia (μmol/liter), $n = 500$	81.1 ± 56.86
Creatinine clearance (ml/min), $n = 450$	88.4 ± 58
<50 ml/min	57 (12.5%)

SRE, skeletal-related event; MRI, magnetic resonance imaging; CT, computed tomography; TEP, positron emission tomography.

TABLE 3. Treatments for Bone Metastatic Disease

Management	$N = 554$
Analgesics[a]	498 (89.9%)
Nonopioid therapy	111 (22.3%)
Opioid therapy	387 (77.7%)
Biphosphonates	290 (52.3%)
IV	279 (96.2%)
Oral	11 (3.8%)
Radiotherapy	233 (42.1%)
Surgery	51 (9.2%)

[a] Patients are classified according to the highest level of analgesics received during the study.

IV, intravenous.

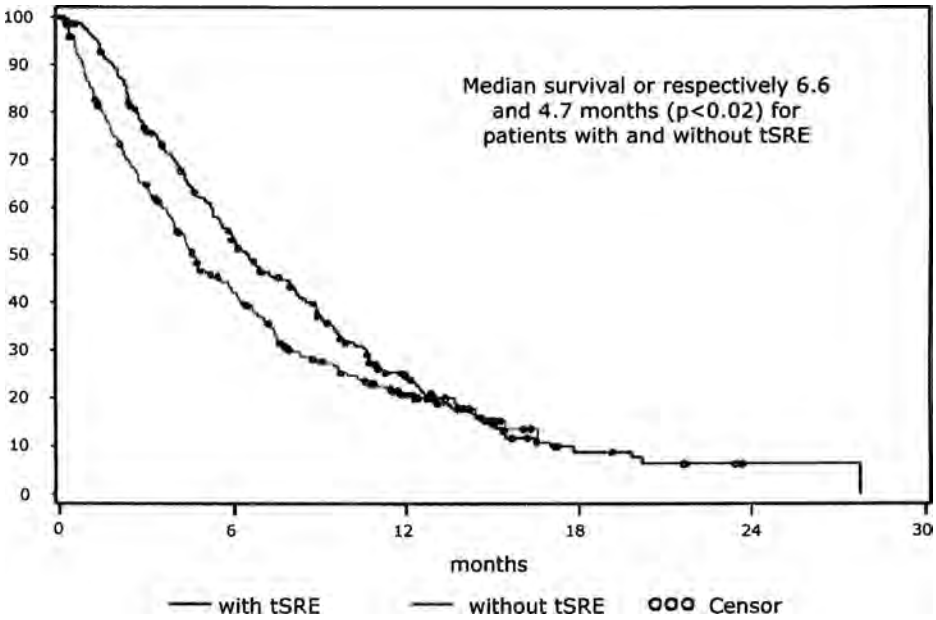

FIGURE 2. Median survival of patients with and without skeletal-related events defined as pathological fractures, spinal cord compression, hypercalcemia, radiotherapy, or surgery (tSRE).

TABLE 4. Factors Predictive of Skeletal-Related Events Defined as Pathological Fractures, Spinal Cord Compression, or Hypercalcemia (cSRE) during Follow-Up: Univariate and Multivariate Analysis

	SRE, $n = 73$	No SRE, $n = 477$	Univariate Analysis, OR, 95% CI, p	Multivariate Analysis, OR, 95% CI, p
Age, mean (SD)	60.3 (11.34)	62.3 (10.95)	0.983 (0.961–1.006), $p = 0.1455$	NA
Gender				
Male (ref.)	54 (12.9%)	366 (87.1%)		
Female	19 (14.6%)	111 (85.4%)	1.160 (0.660–2.040), $p = 0.6058$	NA
Performance status				
0/1 (ref.)	59 (15.5%)	322 (84.5%)		
2/3/4	14 (8.3%)	155 (91.7%)	0.493 (0.267–0.910), $p = 0.0238$	0.448 (0.239–0.842), $p = 0.0126$
SRE at enrollment				
Yes (ref.)	23 (26.7%)	63 (73.3%)		
No	50 (10.8%)	414 (89.2%)	0.331 (0.189–0.579), $p = 0.0001$	0.317 (0.177–0.565), $p = 0.0001$
Chemotherapy				
No (ref.)	11 (11.3%)	86 (88.7%)		
Yes	62 (13.7%)	391 (86.3%)	1.240 (0.627–2.453), $p = 0.5372$	NA
Histological type				
Squamous (ref.)	7 (8.4%)	76 (91.6%)		
No squamous	65 (14.1%)	396 (85.9%)	1.782 (0.787–4.036), $p = 0.1659$	NA

CI, confidence interval; NA, not applicable.

and usually combined with chemotherapy. The presence of cSREs at inclusion did not influence biphosphonate prescription. In contrast, patients who experienced cSRE during follow-up were more likely to receive biphosphonates (65.8% versus 43.5%, $p < 0.001$). There was no correlation between biphosphonate prescription and the onset of cSREs.

The median survival time was 5.8 months, and the 1- and 2-year survival rates were 22% and 7%, respectively. There was a significant difference in overall survival between patients with PS 0/1 and patients with PS more than 1 (6.9 versus 3.1 months, $p < 0.001$). No difference was noted according to whether BDM was diagnosed before or after the diagnosis of cancer. Factors predictive of survival were adenocarcinoma ($p = 0.005$ versus other histological types, hazard ratio [HR]: 0.75 [0.62–0.92]), PS 0/1 ($p < 0.001$ versus PS >1, HR: 0.52 [0.42–0.64]), and female sex ($p < 0.001$ versus men, HR: 0.62 [0.49–0.80]). There was no significant difference in survival between patients with and without cSRE (median survival time, 5.3 and 6 months, respectively, Figure 1); in contrast, there was a significant difference between patients with and without tSREs (6.6 versus 4.7 months, $p < 0.02$, Figure 2). Factors predictive of cSRE during follow-up, in both univariate and multivariate analysis, were a history of SRE at enrollment and PS 0/1

TABLE 5. Consumption of Bone Metastasis Disease-Specific Health Care

Care	Quantity	Cost (€2009)
Hospitalizations (number)		
Outpatient care	111	115,731
Conventional hospitalization	238	472,430
Home hospitalization	8	7431
Total		595,592
Analgesics (months of treatment)		
Step 1	210	3150
Step 2	480	26,353
Step 3	1905	223,136
Total		252,639
Biphosphonates (months of treatment)		
IV	775	304,923
Oral	89	20,599
Total		325,522
Radiotherapy (patients treatments)	233	305,136
Medical transport	1405	236,324
Total costs		1,715,213

IV, intravenous.

(Table 4). BMD-specific health care consumption is summarized in Table 5. Fifty-one patients made 111 hospitalizations in outpatient clinics (for pain control and biphosphonate administration), 159 were hospitalized on 239 occasions for an average of 21 ± 18 days, mainly for surgery, hypercalcemia, pain control, or complications of BMD, and eight patients were hospitalized at home, on one occasion each, for a mean of 20 ± 11 days, for complications of BMD. The total cost of BMD in the entire cohort was €1,715,213 (Table 5). The monthly cost of the ABM, SBM, and SRE health states was €190, €374, and €4672, respectively. The Markov model showed that the mean BMD management cost during the first year after BMD onset was €3999 ± 4135 (95% confidence interval: 374–15,886), of which 49.5% was linked to management of patients with SRE and 38.9% and 11.6% to management of symptomatic patients without SRE and asymptomatic patients, respectively.

DISCUSSION

This prospective multicenter cohort study confirms the gravity of BMD in patients with lung cancer, with a median overall survival time of 5.8 months and 1- and 2-year survival rates of 22% and 7%, respectively. A recent prospective study[8] of 118 patients gave slightly better results, with a median survival time of 7.2 months and 1- and 2-year overall survival rates of 31.6% and 11.3%, respectively. Better outcome was associated with female sex, adenocarcinoma, PS ≤1, solitary bone metastases, no metastases of appendicular bone, no pathologic fractures, and systemic chemotherapy. Only the first three factors (female gender, adenocarcinoma, and PS 0/1) were also predictive of survival in our study. SRE is a major complication of MBD, but the correlation with poorer survival observed in several studies was confirmed in this study only when we included radiotherapy and surgery in the definition of SRE. Indeed, to better take into account disparities in practices across the participating centers, we first analyzed SREs without radiotherapy (cSRE) then with radiotherapy (tSRE). The use of radiotherapy in this setting depends on national practices, the existence of pain management teams, and the availability of radiotherapy facilities and staff. A higher incidence of SREs was found in patients with good PS, probably because of their greater longevity. Nevertheless, when we added radiotherapy to the definition of SREs, PS was no longer predictive of tSRE.

In a recent 2-year biphosphonate trial, among patients with BMD from NSCLC, most patients in the placebo group experienced a SRE during the first 5 months.[3] In our study, the median survival time after SRE was 5.3 months, in keeping with the results of Delea et al.,[4,5] who found that patients with NSCLC survived for a median of approximately 4 months after experiencing their first SRE.

Only 50% of our patients received biphosphonates, with no significant difference between patients with and without SRE. Nevertheless, the benefits of these drugs in patients with lung cancer with BMD have been shown in recent studies.[3]

Zoledronic acid is approved for use in patients with any solid tumor, based on the results of a randomized, placebo-controlled phase III trial, in which patients with BMD from solid tumors other than breast or prostate cancer received zoledronic acid or a placebo.[3] Among the 507 patients randomized in this trial, 249 had NSCLC and 36 had small cell lung cancer. In the overall trial population, zoledronic acid significantly reduced the proportion of patients who experienced at least one SRE relative to the placebo (39% versus 48%; $p = 0.039$), reduced the proportion of patients who experienced each type of SRE, significantly reduced the annual incidence of SRE, and significantly delayed the median time to a first SRE. Preexisting skeletal morbidity does not preclude the benefits of subsequent therapy. Indeed, patients who have already experienced an SRE are at an especially high risk of subsequent events. This was also the case in our study, a first SRE being associated with an increased risk of a second SRE. The efficacy of biphosphonates for primary and/or secondary SRE prevention is also confirmed by observational studies. A retrospective claim-based analysis[15] compared the outcomes of breast, lung, and prostate cancer in 4546 patients receiving ($n = 1508$) or not receiving ($n = 3038$) zoledronic acid. Patients on zoledronic acid were younger, had fewer comorbidities, and had longer follow-up. Zoledronic acid was associated with a 33% reduction in the monthly risk of SRE and delayed the onset of a second SRE.

The costs of BMD in patients with lung cancer had been analyzed in several recent reports.[4,5] MBD is a significant driver of oncology costs. In a retrospective registry-based study,[22] the mean direct medical cost of patients with MBD (all cancers) was $75,329, when compared with $31,382 in controls (patients with cancer but without BMD). SREs are also associated with increased health care costs. In a retrospective analysis of a large U.S. health insurance claims database of 534 patients with lung cancer and BMD,

including 295 (55%) with at least one SRE, the acute management cost for an SRE was $11,979 (2004 value). Radiotherapy accounted for 61% of this cost. In our study, 49.5% of BMD first-year management costs were linked to management of patients with cSREs. It should be stressed that, despite the short survival in this setting, BDM has an important economic impact.

Most cost-effectiveness analyses in this setting have focused on breast cancer.[14,18–20] An exhaustive economic/scientific impact analysis of reports and the literature (1966–2001) concluded that biphosphonates were likely to be cost-effective in patients with breast cancer with skeletal morbidity and in those with secondary BMD and that they might be cost-effective when fracture care and/or other variables are considered.[4] A cost-utility analysis[14] of pamidronate prevention of SRE in the same population of patients with advanced-stage breast cancer, adopting the Canadian health care system perspective, showed an incremental cost-effectiveness of $18,700 per quality-adjusted life-year. The results of the sensitivity analysis suggested that this estimate was dependent on the cost of treating SRE events.

Our study has certain limitations. First, we studied only patients with preexisting BMD, and cannot, therefore, speculate on primary prevention of BMD. The cost analysis did not take into account indirect costs that are probably an important part of total costs, especially in case of SRE. In addition, a cost-efficacy analysis focused on quality-adjusted life-year would greatly strengthen our results, but we found no published data on utilities for the different health states of BMD disease in lung cancer.

In conclusion, this study confirms the poor prognosis of patients with lung cancer with bone metastases and shows the importance of SRE in the specific costs of BMD management. Further prospective studies are needed to determine the cost-effectiveness of different drug-based strategies for preventing BMD and SRE in patients with lung cancer.

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