Impact of Skeletal Complications on Total Medical Care Costs among Patients with Bone Metastases of Lung Cancer

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Introduction: Previous studies have estimated the costs of skeletal-related events (SREs) for patients with bone metastases of solid tumors by tallying costs for services specifically attributable to these events. This approach may underestimate costs if SREs indirectly increase use of other services.

Methods: This is a retrospective observational study using a large health insurance claims database. Patients with bone metastases of lung cancer who experienced ≥1 SRE were matched to similar patients without SREs based on propensity scores. Kaplan-Meier estimated total medical care costs were compared for propensity-matched samples of patients with SREs and without SREs.

Results: We identified 534 patients with lung cancer and bone metastases, including 295 (55%) with ≥1 SRE. After matching, there were 162 patients each in the SRE and no-SRE groups with mean follow-up of 5.3 and 3.9 months, respectively. In the SRE group, costs of treatment of SREs were $9,480 (95% CI $7,625 to $11,374) per patient. Total medical care costs were $27,982 (95% CI $15,921 to $40,625) greater for SRE versus no-SRE patients ($p < 0.001$).

Conclusions: The costs of SREs in patients with lung cancer and bone metastases are substantial and potentially greater than previously estimated.

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Bone metastases are estimated to occur in 30% to 40% of patients with lung cancer.[1] Metastatic tumor cells that colonize the bone matrix induce activity of osteoclasts or osteoblasts, resulting in osteolysis and potential excessive bone formation, respectively, at the sites of tumor cell deposits. The abnormal bone metabolism leads to significant skeletal morbidity, including the following skeletal-related events (SREs): bone pain, pathologic fracture, spinal cord compression, and hypercalcemia of malignancy. Radiotherapy to bone or opioid analgesic therapy to palliate severe bone pain and surgery to correct fractures or spinal deformities may be required. These SREs result in impaired mobility and reduced quality of life[2,3] and have a significant negative impact on survival.[4]

Bisphosphonates are potent inhibitors of resorption and have proven safe and effective in the prevention of SREs in patients with bone metastases of a variety of solid tumors.[5–7] A recently completed phase III, double-blind, randomized trial reported that treatment with intravenous zoledronic acid reduces the incidence of skeletal complications among patients with lung cancer.[8] Although the clinical benefits of intravenous bisphosphonates in preventing SREs are now well established, concerns have been expressed about the costs of these agents.[9] A study of pamidronate in the prevention of SREs among patients with metastatic breast cancer reported that its cost-effectiveness was relatively unfavorable compared with other generally accepted medical therapies.[10] However, the results of this analysis were particularly sensitive to the assumed costs of SREs ($3,200-$3,500), which were estimated based on expert opinion and assumption. In more recent studies, the costs of SREs have been found to be two to three times greater than these estimates. In a study that used retrospective chart review to estimate the costs of treatment of SREs in Dutch patients with prostate cancer, the costs of treatment of SRE were approximately €7,000 ($7,300).[11] In a study using a large health insurance claims database, the costs of treatment of SREs among patients with bone metastases of lung cancer ($n = 295$) in the United States was estimated to be almost $12,000.[12]

Although these two studies suggest that the costs of treatment of SREs may be greater than previously estimated, all previous studies considered only the costs of services of that were specifically for the treatment of SREs. This approach may underestimate the total economic burden of SREs if indirect effects of such events—such as impaired functional status as a consequence of fracture—increase the use of other medical care services (e.g., office visits, need for long-term care). To accurately assess the benefits of therapies to prevent SREs, it is necessary to consider the both the direct and indirect effects of SREs on total medical care costs. The purpose of this study was to estimate the impact of SREs on total medical care costs for patients with bone metastases of lung cancer.

METHODS

Overview

This was a retrospective observational study using data from a large health insurance claims database. From a cohort of patients with diagnoses of lung cancer and bone metastases, we identified patients who experienced one or more SRE (SRE patients). These patients were then matched to similar patients who did not experience a SRE (no-SRE patients) based on propensity scores.[13,14] Total medical care costs were then compared for SRE and no-SRE patients.

Data Source

The Constella Health Strategies Private Benefit Plan Database I is comprised of all health insurance claims (medical and pharmacy bills submitted by providers) for persons enrolled in various managed care plans of one of the largest health benefits companies in the United States. Plans represented in the database provide coverage to approximately 3 million members annually. The database contains information on member demographics, dates of eligibility for health benefits, and use and billed charges for covered services, including hospitalizations, outpatient procedures, physicians' office visits, outpatient prescriptions, and home and long-term care. Data available for each facility (e.g., hospital) and professional service (e.g., physician) claim include dates of service and International Classification of Diseases (ICD-9-CM) diagnosis codes. Facility claims also include ICD-9-CM procedure codes and discharge disposition. Professional service claims also include Current Procedural Terminology (CPT-4) procedure codes. Data available for each prescription include the drug dispensed (in National Drug Code [NDC] format), the dispensing date, and the quantity and number of therapy-days dispensed. Most claims also include information on billed charges and paid amounts. Information on date of death is available from enrollment files, discharge disposition on facility claims, and, for persons who died on or before August 31, 2000, linked data from the United States Social Security Administration. The dataset is updated and archived on a periodic basis. Data for this study spanned the period from July 1, 1994 to June 30, 2002, the most recent 8-year period for which complete claims and enrollment information were available (the study period).

Study Subjects

We selected all persons in the database with two or more encounters (an encounter being defined as one or more medical claims on a given day) between July 1, 1995 and June 30, 2002 with a diagnosis of primary lung cancer (ICD-9-CM 162) and two or more encounters with a diagnosis of secondary malignant neoplasms of bone and bone marrow (ICD-9-CM 198.5; bone metastases) anytime on or after the date of the first claim with a diagnosis of lung cancer. Persons with a diagnosis for other primary malignancy (e.g., breast or prostate cancer) before the date of first claim for lung cancer were excluded, as were those with Medicare supplemental insurance (for whom complete claims data may not be available), those with less than 6 months of continuous enrollment before the date of first diagnosis of bone metastases (for whom data with which to identify comorbid conditions would be limited), and those younger than 35 years of age at the first diagnosis of bone metastases.

SRE patients were then identified based on the presence of either: (1) one or more encounters with a diagnosis code for pathological fracture, spinal cord compression, or hypercalcemia; or (2) a procedure code for bone surgery or therapeutic radiology (although body site modifiers are unavailable for procedure codes for radiotherapy, most such procedures in this population are likely directed to bone); or (3) initiation of opioid analgesic therapy. Patients were considered to have experienced pathological fracture if they had either: (1) two or more encounters with a diagnosis of pathological fracture of bones commonly involved in metastatic disease (i.e., the skull, ribs, sternum, vertebrae, or long bones of the arms and legs); or (2) two or more encounters with a diagnosis of non-pathological fracture of such bones in the absence of concurrent severe trauma. Concurrent severe trauma was identified based on one or more encounter, on the date of the encounter for the non-pathological fracture, of any of the following: (1) two or more fractures on the same day; (2) multiple trauma or trauma to other systems; or (3) accident or injury other than fall on the same level.

Patients with bone metastases of lung cancer who experienced SREs were matched to similar patients who did not experience SREs using propensity-score matching.[13,14] This technique is useful for matching subjects on multiple characteristics simultaneously to control for differences between groups in these characteristics. A propensity score was calculated for all patients by estimating a logistic regression model with occurrence of a SRE as the dependent variable and other patient characteristics (i.e., age, sex, additional sites of metastases, etc.) as independent variables. The propensity score for each patient was defined as the predicted probability (range, 0-1) of experiencing a SRE conditional on the observed values of other characteristics. To match patients, we arrayed all possible pairs of SRE and no-SRE patients, calculated for each pair the difference in the propensity score, and discarded all pairs for which this difference was >0.01. To avoid potential immortal time bias,[15] we excluded all pairs for which survival time of the no-SRE patient was less than the time from diagnosis of bone metastases to date of first SRE of the corresponding SRE patient. Matched pairs were ranked by difference in propensity score. The pair with the smallest difference in propensity score was selected for the analysis. This process was repeated until there were no pairs remaining. Patients for whom a match could not be obtained were excluded from the analysis.

For each patient in the SRE group, we defined the index date as the date of the first SRE, and the time to SRE as the difference between the date of the first diagnosis of bone metastases and the index date. For each patient in the no-SRE group, we defined the index date as the date of first diagnosis for bone metastases plus the time to SRE for the matched SRE patient. The follow-up period was defined for each patient as the period beginning with the index date and ending with the date of disenrollment from the health plan, end of the study period, death, or 24 months post-index, whichever occurred first.

Patient Characteristics

Information on age, gender, region (South or other), and plan type (health maintenance organization or other) was obtained from enrollment files. Diagnosis codes on facility and professional service claims before the index date were scanned to identify evidence of additional metastases to brain, liver, or other sites, and comorbid conditions including anemia, congestive heart failure, chronic obstructive pulmonary disease, cardiovascular disease (ischemic heart disease, stroke/transient ischemic attack, peripheral arterial disease), diabetes, gastrointestinal and fluid disturbances, osteoarthritis, and osteoporosis. Deyo's version of the Charlson Comorbidity Index was calculated for each patient based on comorbidities present on or before the index date.[16] Receipt of hormonal therapy, chemotherapy, or radiotherapy during the 6 months before the index date was identified. The numbers of outpatient and emergency room visits, inpatient days, and hospitalizations during this period also were calculated, as were total costs. Hospital costs were estimated by stepping down billed charges using the national average Medicare cost-to-charge ratio.[17] Costs of all other services were approximated by billed charges. Because the dataset has missing or invalid charge data for a proportion of claims (because of capitation arrangements with providers), charges for these claims were imputed using data from claims for which charge data were available. All costs were adjusted to 2002 price levels using the United States Consumer Price Index for Medical Care.[18]

Outcome Measures

Measures of interest included the cost of medical care for the treatment of SREs, other medical care costs, and total medical care costs. All costs were examined during a maximal follow-up of 24 months post-index. The cost of SRE treatment included the costs of all claims with a diagnosis of pathological fracture; spinal cord compression; or hypercalcemia, bone surgery, or radiotherapy procedures; new prescription for opioid analgesics; or diagnostic radiology, physical therapy, or acupuncture procedure or prescription for a non-steroidal anti-inflammatory drug (NSAID) within 7 days of another SRE-related claim. Costs of care for specific types of SRE and costs for specific categories of medical care service (inpatient care, outpatient care, outpatient pharmacy, etc.) also were examined. Because any given claim might qualify for more than one type of SRE, claims were assigned to specific types using a hierarchy based on contribution to total costs among all patients in the sample. As we were interested in estimating costs that might be avoided by preventive therapies, costs of bisphosphonate therapy were conservatively excluded from all calculations. Fewer than 10% of lung cancer patients with bone metastases received such therapy.

Statistical Analysis

Baseline demographic and clinical characteristics were compared between SRE patients and matched no-SRE controls using the signed rank test for continuous variables and the McNemar test for categorical variables. Expected costs for each group were calculated using the Kaplan-Meier sample average method.[19] This approach combines survival curves (probabilities) with cost histories to estimate expected cumulative costs over time, and it is useful when there is censoring (loss to follow-up) and costs are not incurred uniformly over time. To implement this approach, follow-up was partitioned into 24 monthly intervals, and the probabilities of survival to the beginning of each interval were calculated for each group using Kaplan-Meier methods. Average costs during each month among subjects alive and not censored as of the beginning of the month were then calculated for each group (mean monthly costs). Survival probabilities were multiplied by corresponding mean monthly costs and summed across months to calculate expected cumulative costs at the end of each month for each group. Non-parametric bootstrapping (repeated resampling with replacement) was used to calculate 95% confidence intervals (CIs) for these estimates and standard deviations and p values for differences between groups. In calculating p values, differences in expected costs between groups were assumed to be normally distributed. Because estimated survival curves differed between SRE and no-SRE patients, we conducted a secondary analysis in which we adjusted for differences in survival between groups by using the pooled survival curve for the two groups combined to calculate expected total costs. All analyses were conducted using SAS statistical software, version 8.2 (SAS Institute, Cary, NC).

RESULTS

We identified 534 patients with bone metastases of lung cancer, of whom 295 (55%) experienced one or more SREs. Among patients with SREs, 68% underwent radiotherapy, 35% experienced fracture, 19% received an opioid or NSAID, 14% underwent bone surgery, 7% experienced hypercalcemia, and 6% experienced spinal cord compression. Of the patients with SREs, 64% experienced only one type of SRE, 25% experienced two types of SREs, and 11% experienced three or more types of SREs.

After matching, there were 162 pairs of SRE and no-SRE patients. The two groups were well matched with respect to all baseline demographic and clinical characteristics (Table 1). Mean (±SD) follow-up was 5.3 ± 5.6 months for SRE patients and 3.9 ± 4.8 months for no-SRE patients (p = 0.004). Kaplan-Meier estimated median survival was 3.8 versus 2.5 months for SRE patients versus no-SRE patients (p = 0.048) (Figure 1). The difference in follow-up between groups was therefore almost certainly a consequence of the difference in survival between groups.

Mean monthly total costs were nominally greater for SRE versus no-SRE patients in all months except month 24 post-index (Figure 2). The difference in mean monthly cost was greatest in the first month of follow-up ($7,570). Of the difference in costs between SRE and no-SRE patients, 66% was accrued during the first 6 months of follow-up.

Kaplan-Meier estimated cumulative total medical care costs at 24 months (obtained by multiplying survival probabilities at the beginning of each month by corresponding mean monthly costs among those remaining alive and not censored and summing across months) were $27,982 (95% CI, $15,921 to $40,625) greater for SRE patients ($59,391, 95% CI $48,642 to $70,314) than in no-SRE patients ($31,409, 95% CI $25,745 to $37,884) (P<.001) (Figure 3). Of the difference (SRE vs no-SRE) in total costs, 39% was for inpatient hospital care, 34% for physicians' office visits, 23% for hospital outpatient care, and 4% for other services.

For patients with SREs, Kaplan-Meier estimated cost of SRE treatment at 24 months was $9,480 (95% CI, $7,625 to $11,374) (Figure 4). Of this cost, 55% was associated with radiotherapy, 25% with bone surgery, 15% with treatment of fractures, and 5% with other SREs. Inpatient hospital care accounted for 54% of the cost of SRE treatment, physicians' office visits accounted for 28%, hospital outpatient care accounted for 14%, and other services accounted for 3%. Other costs (at 24 months) were $18,502 (95% CI, $6,521 to $30,838) greater for SRE patients ($49,911; 95% CI, $39,762 to $60,538) than no-SRE patients ($31,409; 95% CI, $25,745 to $37,884) ($p$ = 0.004).

When we adjusted for the difference in survival between SRE and no-SRE patients by using the pooled survival curve for both groups, the difference in total costs between SRE and no-SRE patients was $22,162 ($55,655 vs.

TABLE 1. Patient Characteristics

	SRE (n = 162)	No SRE (n = 162)	p
Age (yr)	66.7 (9.6)	66.4 (9.7)	0.857
Male	105 (64.8)	104 (64.2)	0.907
Additional sites of metastases	46 (28.4)	49 (30.2)	0.696
Comorbid conditions			
Diabetes	33 (20.4)	33 (20.4)	1.000
CVD	42 (25.9)	41 (25.3)	0.896
COPD	98 (60.5)	94 (58.0)	0.655
Anemia	24 (14.8)	30 (18.5)	0.387
GI/Fluid disturbance	50 (30.9)	48 (29.6)	0.811
Osteoarthritis	38 (23.5)	38 (23.5)	1.000
Osteoporosis	7 (4.3)	7 (4.3)	1.000
Charlson index	3.8 (3.2)	3.8 (3.2)	0.976
Outpatient visits in past 6 mo	16.4 (15.5)	18.7 (20.8)	0.569
Inpatient days in past 6 mo	2.4 (6.2)	2.6 (5.8)	0.422
Duration of follow-up (mo)	5.3 (5.6)	3.9 (4.8)	0.004

Values are mean (SD) or n (%) and were calculated at index date. CVD, cardiovascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

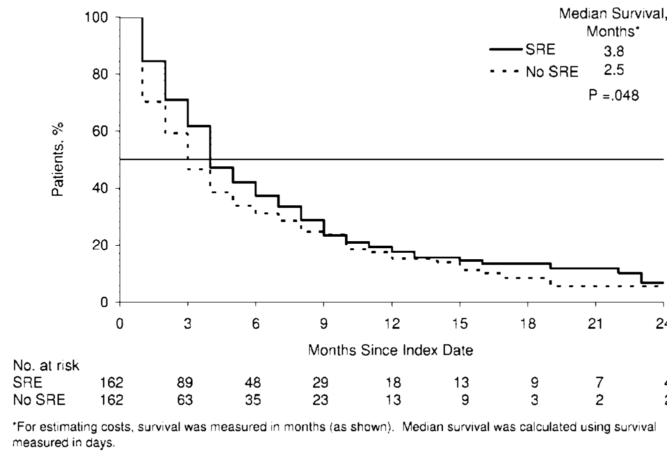

FIGURE 1. Kaplan-Meier estimated survival by month

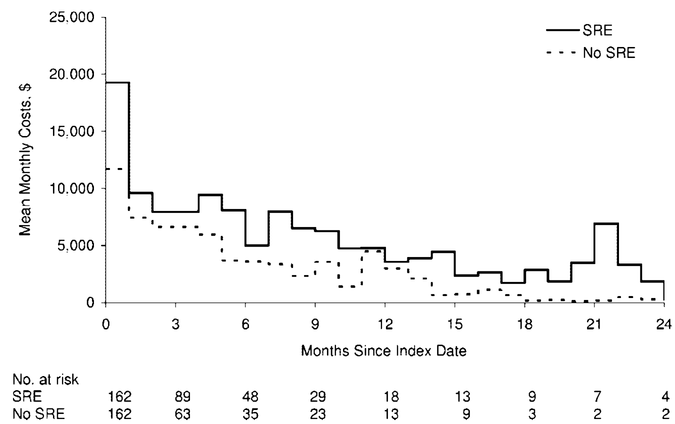

FIGURE 2. Mean monthly total medical care costs by month.

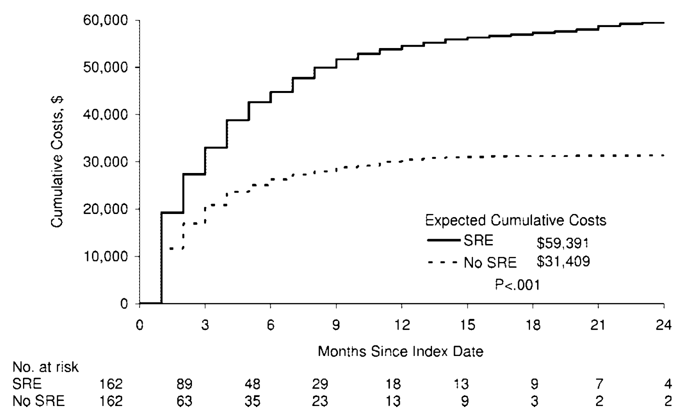

FIGURE 3. Kaplan-Meier estimated cumulative total medical care costs by month.

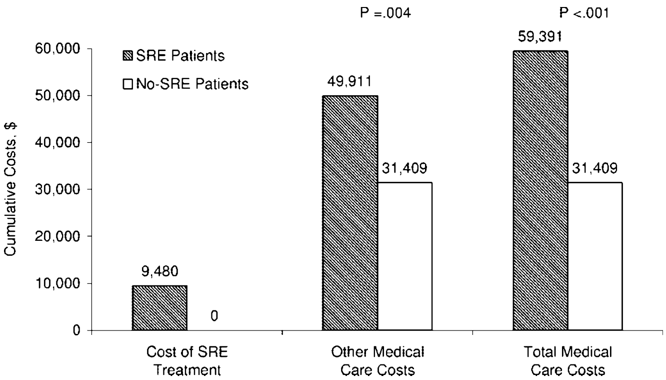

FIGURE 4. Kaplan-Meier estimated cumulative costs of SRE and non-SRE related care.

$33,493). Differences in survival between groups accounted for $5,820 (21%) of the unadjusted difference in costs between SRE and no-SRE patients.

DISCUSSION

In this retrospective observational study of lung cancer patients with bone metastases, we estimated the expected costs of treatment of SREs to be approximately $9,500. When patients with SREs were compared with a propensity-matched sample of patients without such events, we found that total costs of medical care during 24 months, including costs of care not specifically for the treatment of SREs, were almost $28,000 greater for SRE patients. These findings suggest that earlier estimates of the costs of SREs, which considered only the cost specifically for the treatment of SREs, may have underestimated the full economic impact of these events. It has been shown that events such as fracture are associated with functional limitation,[20] which in turn is associated with increased costs.[21] This may in part explain our findings.

Our estimate of the costs of SRE treatment is similar to that reported by Groot et al.[11] for patients with bone metastases of prostate cancer (€7,000 or $7,300) but substantially greater than that reported by Hillner et al.[10] in their study of the cost-effectiveness of pamidronate among patients with bone metastases of breast cancer ($3,200-$3,500). Estimates by Hillner et al. were obtained by multiplying Medicare payments by estimates of resources use for various SREs that were based largely on expert opinion and assumption. Our estimate, however, is based on actual health insurance claims for a geographically diverse group of patients with bone metastases of lung cancer seen in typical clinical practice and therefore may be more representative of the actual costs of these events.

Limitations of this study should be noted. First, patients were selected for inclusion in our study based on the presence of two or more claims with diagnosis of bone metastases. Because not all patients who experience bone metastases have claims with such a diagnosis, our sample may be weighted toward those with the most severe disease.

Second, our sample was drawn from patients enrolled in managed care plans located principally in the Midwestern and Southern United States. Our results may not be generalizable to patients in other countries, regions, or types of health plans.

Third, as a consequence of the matching procedure we used, approximately 45% of the 295 patients who experienced SREs were dropped from our sample. In a previous study of all 295 patients who experienced one or more SREs, the expected costs of SRE-specific care was approximately $12,000 per patient.[12] Thus, our estimate of the cost of treatment of SREs may be conservative.

Fourth, ICD-9-CM and CPT codes for radiotherapy do not permit identification of the body site to which such therapy was directed. We therefore assumed that all claims for therapeutic radiotherapy were to bone. Although we believe that most radiotherapy procedures in patients with bone metastases of lung cancer are to bone, it is possible that these procedures were directed at other metastatic sites. Our estimate of SRE-related costs therefore may have been upwardly biased by the inclusion of the costs of radiotherapy to non-bone sites. Patients who received radiotherapy only for the treatment of non-osseous metastases could have been misclassified as SRE patients. This might have biased our comparison of SRE and no-SRE patients. We believe that any such misclassification and bias were minimal, however, as the proportion of patients with diagnoses of metastases to sites other than bone was similar in the SRE and no-SRE groups (28.4% vs. 30.2%; $p = 0.696$). If radiotherapy to other sites was common, one would have expected the SRE patients to have a higher incidence of metastases to other sites.

Finally, because our study relied on health insurance claims data and lacked information on a variety of clinical characteristics that might be associated with risk of SRE on the one hand and survival and costs on the other, it is possible that the difference that we observed between SRE and no-SRE patients in the costs of care not specifically for treatment of SREs was the result of confounding from factors not accounted for in our analysis. Our estimates of the additional costs of such care should be interpreted cautiously.

CONCLUSION

The total costs of SREs in patients with lung cancer and bone metastases are substantial and potentially greater than previously estimated.

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