The Cost of Treating Skeletal-Related Events in Patients With Prostate Cancer

Maureen J. Lage, PhD; Beth L. Barber, PhD; David J. Harrison, PhD; and Sun Jun, MD, PhD

Objectives: To examine the economic burden of skeletal-related events (SREs) and to assess the frequency of different types of SREs in this population.

Study Design: Retrospective claims analysis.

Methods: Data were obtained from i3's Lab Rx Database from May 1, 2000, through March 31, 2005. Patients included had at least 2 claims with a diagnosis of prostate cancer, at least 2 subsequent claims with a diagnosis of bone metastasis, and at least 1 SRE on or after the date of the initial diagnosis of bone metastasis. Descriptive statistics for 342 patients who fit all inclusion and exclusion criteria are provided, along with Kaplan-Meier curves, which were used to estimate annual costs, adjusting for the censoring of the data.

Results: Patients most frequently had radiation therapy (89%), followed by pathologic fracture (23%) and bone surgery (12%). Among patients diagnosed as having at least 1 SRE, 78% experienced 1 type of SRE, 17% had 2 types of SREs, and 5% had 3 or more distinct types of SREs. The mean costs associated with SREs in the year after the initial diagnosis of an SRE, adjusted for the censoring of the data, was $12,469, with the highest costs associated with radiation therapy ($5930), followed by pathologic fracture ($3179) and bone surgery ($2218).

Conclusion: This study of patients with prostate cancer and bone metastases revealed that the annual economic effect of medically treating SREs for these patients was $12,469.

(Am J Manag Care. 2008;14(5):317-322)

Prostate cancer has the highest incidence of any nonskin cancer in the United States and is the second leading cause of cancer-related deaths among US men.[1-3] It was projected that 218,890 new cases of prostate cancer would be identified in the United States in 2007 and that an estimated 27,050 men would die of the disease.[4]

Bone metastasis is a common form of metastatic disease among patients with prostate cancer. Yuen et al[5] report that 80% of men with metastatic disease have bone metastasis, and others report percentages between 65% and 70%.[6,7] In addition, as many as 20% of men who are newly diagnosed as having prostate cancer already have bone metastases.[8] Bone metastases are complicated by significant morbidity, including skeletal-related events (SREs), which are local irreversible changes and include pathologic fracture, bone surgery, radiation therapy to the bone, and spinal cord compression.[9-12] These events negatively affect quality of life[10,13,14] and present a challenge for the goals of palliative therapy, which include managing these patients' pain, preventing further deterioration, and preserving quality of life.[15-18]

Although the humanistic burden of SREs is well documented, little research has focused on the economic effects of medically treating SREs. To our knowledge, only one study[19] has looked specifically at the costs of SREs in patients with prostate cancer and bone metastases; the sample of patients in the analysis was small (n = 28), and the costs were based on care in The Netherlands. However, studies of SREs among patients with lung cancer[20] and breast cancer[9,21] have consistently shown SREs to be common and costly.

In the present study, the objectives were to elucidate further the US costs associated with SREs among patients with prostate cancer and bone metastases and to determine the relative frequency at which the different types of SREs occur. To this end, we conducted a retrospective analysis using a large US health insurance claims database to examine the incidence and costs associated with SREs among patients with bone metastases secondary to prostate cancer.

METHODS

We analyzed longitudinal deidentified patient data from a large US health insurance plan containing medical, prescription, and laboratory test result claims. The database contains information from more than 5.3 million patients older than 40 years, is updated monthly, and is representative of the commercially insured as opposed

In this issue
Take-away Points / p321
www.ajmc.com
Full text and PDF

For author information and disclosures, see end of text.

to the general population. This study used claims from May 1, 2000, through March 31, 2005.

Patients were included in the analysis if they had at least 2 claims with a diagnosis code of prostate cancer (based on an *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code of 185.xx; 35,382 patients had ≥1 claim, and 27,393 patients had ≥2 claims) and had at least 2 claims with a diagnosis code of bone metastasis (code 198.5x) on or after the first claim for prostate cancer (1269 patients had ≥1 claim, and 878 patients had ≥2 claims). In addition, patients were required to have an SRE on or after the initial claim for bone metastasis (435 patients had an SRE).

An SRE was defined as a pathologic fracture, radiation therapy, bone surgery, or spinal cord compression. We identified these conditions in our database using a previously published algorithm[9]; radiation therapy was also identified by receipt of treatment from a radiation oncologist or a therapeutic radiologist. To identify cases of bone surgery, the published algorithm uses *ICD-9-CM* and *Current Procedural Terminology 4* codes, which include, for example, "repair of plastic operations on bone" and "internal fixation of bone without fracture." To identify cases of pathologic fracture, the algorithm excludes fractures with concurrent severe trauma such as a car crash. Finally, patients were required to have at least 1 month of data after their first SRE (identified as the index date), 6 months of data before the index date, and continuous insurance through both periods (342 patients met these criteria).

Although previous research has included hypercalcemia as an SRE, this analysis was unable to examine this condition. Specifically, previous research estimated that 10% to 20% of individuals with advanced cancer have hypercalcemia[22]; in this database, only 0.3% of individuals identified as having bone metastases also had claims with a diagnostic code of hypercalcemia. Although this low incidence precludes an examination of hypercalcemia in this cohort, this finding is consistent with the literature demonstrating that hypercalcemia is generally underdiagnosed.[22,23]

Table 1. Patient Characteristics

Variable	Value (n = 342)
Age, mean (SD), y	68.1 (9.7)
Preperiod value, mean (SD)	
Charlson severity score	1.4 (1.6)
Office visits	14.2 (10.7)
Visits to oncologist	5.9 (9.3)
Days hospitalized	6.6 (19.2)
Region, No. (%)	
Northeast	45 (13.2)
Midwest	109 (31.9)
South	166 (48.5)
West	22 (6.4)
Insurance, No. (%)	
Business	
Commercial	226 (66.1)
Medicaid	2 (0.6)
Medicare	114 (33.3)
Product type	
Exclusive provider organization	30 (8.8)
Health maintenance organization	179 (52.3)
Independent	5 (1.5)
Point of service	73 (21.3)
Preferred provider organization	55 (16.1)
Preperiod comorbidity, No. (%)	
Cardiovascular disease	126 (36.8)
Chronic obstructive pulmonary disease	45 (13.2)
Diabetes mellitus	55 (16.1)
Cerebrovascular disease	30 (8.8)

We gathered information on patient demographic and clinical characteristics and on resources and costs associated with SREs. Consistent with prior research,[24,25] costs were proxied by total charges, were defined as total allowed payment, and were converted to 2006 US dollars using the medical component of the consumer price index. In addition, we examined patient survival after diagnosis of an SRE. We estimated a Kaplan-Meier curve to calculate the probability of remaining insured during a 24-month interval, which we use as a proxy for survival. Such a method is appropriate when there is censoring of data. Specifically, the data for some patients were censored as of March 31, 2005, when the data collection period ended. We then combined these probabilities with annual cost data to estimate expected cumulative costs over time, adjusting for the censoring of the data. We calculated the mean monthly costs for patients who were not censored and multiplied these costs by the probability of "survival" for that month. Finally, we summed the results of this calculation during 12 months to examine annual SRE-related costs.[26] All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Half of all patients with at least 2 claims for prostate cancer (n = 342) and at least 2 claims for bone metastasis (n = 878) experienced 1 or more SREs (n = 435). For men who had at least 1 SRE, 87% were identified as having had an SRE within 1 year of their initial diagnosis of bone metastasis. Their mean age was 68.1 years, with most men residing in the South (49%) or in the Midwest (32%) (Table 1), which is consistent with the population in the database. Most patients were commercially insured (66%), and the most common type of insurance was a health maintenance organization (52%). An examination of prior resource utilization, the severity score by Charlson et al,[27] and comorbidities revealed that, as expected, patients in this study were severely ill. For example, the mean (SD) Charlson severity score was 1.43 (1.55), and the patients had been hospitalized in the 6 months before the index date for a mean of 6.6 days and had a mean number of office visits of 14.2. In addition, 37% of patients included in the study had also been diagnosed as having cardiovascular disease, and 16.1% had been diagnosed as having comorbid diabetes mellitus.

Most patients received radiation therapy (89%), as shown in Figure 1. Approximately 23% experienced a pathologic fracture, and 12% had bone surgery. Some SREs occurred in clusters, meaning that it was possible that someone had a fracture that required bone surgery, and in this case both events are captured as separate types of SREs.

Among patients diagnosed as having at least 1 SRE, 78% experienced 1 type of SRE, although some of these patients may have had more than 1 SREs of that same type (Figure 2). Seventeen percent had 2 types of SREs, and 5% had 3 or more distinct types of SREs. For patients with more than 1 type of SREs, the mean time between identification of the first type and the second type of SREs was 2.9 months.

Figure 3 shows the Kaplan-Meier estimated probability of continuation in the database (survival proxy) for the population from the time of initial diagnosis of an SRE. After 2 years, the proxy survival rate was 16%, and the median proxy survival was approximately 8.5 months.

Table 2 gives the Kaplan-Meier cost estimates associated with SREs. The mean per-patient costs associated with SREs in the first year after initial identification of an SRE, adjusted for the censoring of the data, was $12,469. More than 47% of this amount is attributable to radiation therapy ($5930), with this cost being driven by the large proportion of patients who received this treatment. Pathologic fractures accounted for $3179 of the total SRE-related costs, while bone surgery accounted for $2218. Costs were distributed approximately equally between inpatients ($5641) and outpatients ($5951). The SRE-related costs for the 22% of the population who had more than 1 type of SREs ($26,384) were significantly higher than the SRE-related costs for the patients who had only 1 type of SRE ($8484) ($P < .001$).

As a test of the robustness of the results, we reexamined the analysis, omitting service from a radiation oncologist as a criteria in defining therapeutic radiology. Although the percentage of individuals with an SRE identified as having therapeutic radiology declined from 89% to 78%, the general results were consistent with those reported herein. For example, this analysis found 1-year costs associated with an SRE to be $12,649, while omitting service from a radiation oncologist reduces this amount to $12,007. In addition, this analysis estimated the 2-year survival rate to be 15%, while the reexamined subset of data resulted in an estimated 2-year survival rate of 16%.

Figure 1. Percentage of Patients Experiencing Each Type of Skeletal-related Event (Patients Can Experience >1 Type)

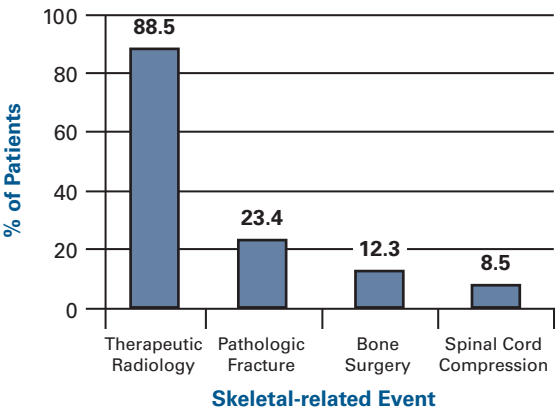


Figure 2. Percentage of Patients Experiencing 1 or More Types of Skeletal-related Events

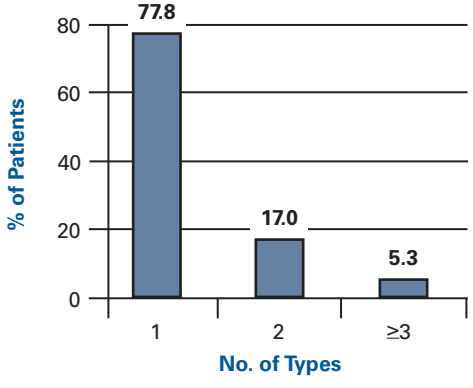
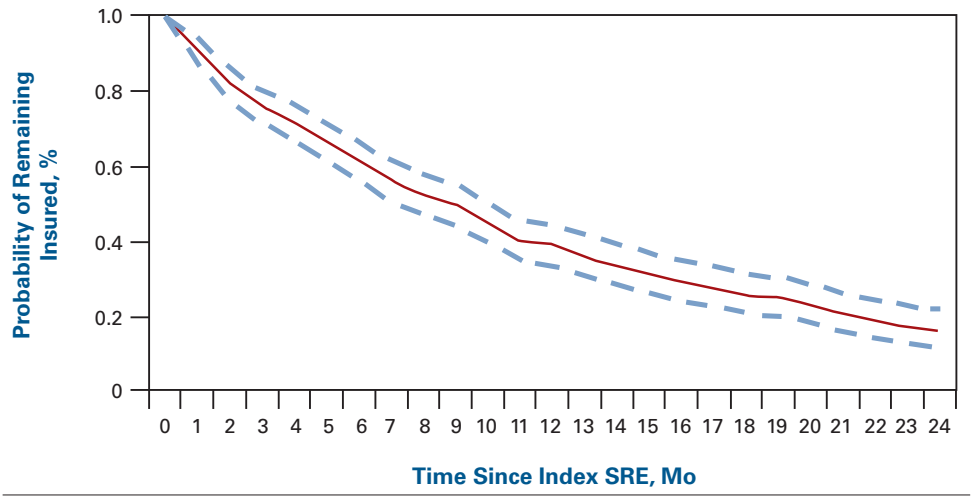


Figure 3. Estimated Continuation of Insurance Coverage From the Time of the Index Skeletal-related Event (SRE)



Continuation of insurance coverage is used as a proxy for survival.
The mean (SD) length of the postperiod (from the time of the first diagnosis of an SRE to the end of data collection or last eligibility, whichever came first) adjusted for censoring of data was 13.08 (0.75) months.
Dashed lines represent 95% confidence intervals.

DISCUSSION

This retrospective analysis produced several significant findings. Skeletal-related events are costly and common among patients with prostate cancer and bone metastases, and they are significantly more costly for patients who experience multiple SREs.

Approximately half of all patients with prostate cancer and bone metastases experienced 1 or more SREs. This finding is consistent with earlier studies[9,20] among patients with bone metastases secondary to other types of cancer. We also found that the mean 1-year cumulative costs associated with SREs totaled $12,469 per patient. These cost data are consistent with an earlier study[20] of patients with bone metastases secondary to lung cancer, in which the per-patient cost of SREs was determined to be $11,979.

On the other hand, the costs associated with SREs in the present study were higher than those reported in an analysis of Dutch patients with metastatic prostate cancer.[19] Specifically, the study by Groot et al[19] found the per-patient cost to treat SREs to be 6973 (US $11,014). Differences in the sample populations may in part account for this discrepancy in cost findings. The analysis by Groot et al looked at the records of 28 patients from 2 different hospitals in The Netherlands, whereas our study evaluated the records of 342 patients from various hospitals throughout the United States.

The costs associated with SREs in this study are higher than the costs reported in a study[28] of patients with breast cancer metastasized to the bone, in which the net cost per SRE ranged from $3940 to $9390, and these costs are lower than the costs published in another study[21] of patients with breast cancer, in which the cost of SREs ranged from £11,314 to £18,662 (US $22,689-US $37,414). These disparities may be attributable, at least in part, to differences in study design. Hillner et al[28] and Botteman et al[21] derived costs largely from expert opinion and assumption. In contrast, costs were collected in the present study from actual billed charges stated on insurance claims within a large, geographically diverse database.

To our knowledge, no previous study has examined the economic effect of multiple types of SREs vs

Table 2. 1-Year Costs of Skeletal-related Events (SREs)

Variable	No.	Mean (95% Confidence Interval), $
Total SRE costs		
All patients	342	12,469 (10,007-14,861)
Patients with 1 SRE	266	8484 (6810-10,177)
Patients with >1 SREs	76	26,384 (17,959-34,809)
Costs of SREs		
By component		
Therapeutic radiology	342	5930 (4829-7032)
Pathologic fracture	342	3179 (1745-4614)
Bone surgery	342	2218 (1059-3378)
Spinal cord compression	342	460 (116-803)
Other	342	681 (316-1047)
Inpatient vs outpatient		
Inpatient	342	5641 (3738-7543)
Outpatient	342	5951 (4849-7052)

only 1 type of SRE. We found that patients diagnosed as having 2 or more types of SREs incurred significantly higher costs than patients having only 1 type of SRE (ie, $26,384 vs $8484). This finding is consistent with earlier research indicating that patients' health-related quality of life decreases as the number of SREs increases,[29] as a more intensely ill individual would likely incur higher medical costs.

In terms of the severity of illness, the men in this study had a mean (SD) rating of 1.43 (1.55) on the Charlson severity score index. Developed for use in longitudinal studies, the Charlson severity score predicts the risk of mortality from comorbid illness during 1 year.[27] To put the Charlson severity score into perspective, proposed guidelines for using the "watchful waiting" strategy to treat nonmetastatic prostate cancer define "general good health" in a man younger than 75 years as having, among other characteristics, a Charlson severity score of 1 or lower.[30] Therefore, the men in our study with prostate cancer metastasized to the bone and SREs have a risk of death approximately 1.5 times higher than that of an older man in general good health. In addition, the comorbidity found among men in our study is consistent with previous research demonstrating that comorbidity in patients with prostate cancer (ie, as evidenced by Charlson severity scores >0) is associated with more advanced forms of prostate cancer and with higher overall mortality.[31]

The findings of this study should be interpreted within the context of the limitations of the study design. First, this study was conducted using an administrative claims database and included only patients with medical and prescription benefit coverage; therefore, the results may not be generalizable to other populations and may underrepresent patients older than 65 years. Second, the use of diagnostic codes to identify patients is not as rigorous as formal diagnostic assessments for identifying patients with bone metastases or other conditions, and diagnostic codes can lack specificity in some instances. This was the case when identifying radiation therapy to the bone. With the codes we used, it is possible that some cases of radiation therapy were, in fact, for the purpose of treating the primary tumor and not for the treatment of a bone lesion. Hence, our estimate of radiation therapy to the bone may be an overestimate. Third, because of low reporting of hypercalcemia, the analysis was unable to examine this condition. Fourth, to ensure the accuracy of diagnoses, we mandated that patients must have at least 2 claims for prostate cancer and at least 2 claims for bone metastasis. This requirement may have resulted in the exclusion of some patients with prostate cancer who, for instance, may not have lived long enough for 2 encounters with the healthcare system to occur and so did not generate 2 diagnoses in the claims database. We decided to err on the side of including only patients whom we were more certain had the diseases. Fifth, the use of medical claims data precludes the use of patient assessments; as a result, the analysis cannot examine quality of life, functioning, any clinical outcomes, or dates or causes of death. Sixth, patient mortality data were not available; hence, we used a proxy for survival by assessing insurance coverage. Although it is possible that some patients who lose insurance have not died but simply have run out of insurance, we believe that most have died. Seventh, this study focused on those costs directly attributable to SREs. However, it has been shown that events such as fractures are associated with functional limitation,[32] which in turn is associated with increased costs.[33] A richer dataset would be necessary to explore the effect of the increased use of other medical care services and other indirect costs associated with SREs.

Take-away Points

Prostate cancer has the highest incidence of any nonskin cancer in the United States, and bone metastasis is a common form of metastatic disease among patients with prostate cancer. Bone metastasis is complicated by the occurrence of skeletal-related events (SREs).

- This research quantifies the costs of SREs among patients with prostate cancer and bone metastases. Results reveal that the mean annualized costs of SREs for this population was $12,469.
- The research illustrates the relative frequency at which different types of SREs occur, with patients most likely to undergo therapeutic radiology or to have a pathologic fracture.

CONCLUSIONS

Many patients with prostate cancer metastasized to the bone experience SREs. In addition to physical adversity associated with these events, these patients will also incur high costs for medical treatment of the SREs. The findings of this analysis suggest that safe measures to mitigate or prevent SREs have the potential to yield cost offsets. Although earlier studies looking at costs of SREs in cancer paients[9,20] have come to similar conclusions, this analysis uses the largest sample of patients with prostate cancer, bone metastases, and SREs examined to date, to our knowledge.

Acknowledgment

We thank Patricia Platt for her help with the manuscript.

Author Affiliations: HealthMetrics Outcomes Research, LLC (MJL), Groton CT; Department of Global Health Economics (BLB, DJH) and Department of Clinical Development (SJ), Amgen Inc, Thousand Oaks, CA.

Funding Source: This study was funded by Amgen, Inc.

Author Disclosure: Drs Lage and Jun consult for Amgen and received payment for their involvement in the preparation of this manuscript. Drs Barber and Harrison are employees of Amgen and report owning stock in that company.

Authorship Information: Concept and design (BLB, DJH); acquisition of data (BLB); analysis and interpretation of data (MJL,BLB, DJH, SJ); drafting of the manuscript (MJL, BLB, SJ); critical revision of the manuscript for important intellectual content (MJL, BLB, DJH, SJ); statistical analysis (MJL); obtaining funding (BLB); administrative, technical, or logistic support (BLB); and supervision (BLB).

Address correspondence to: Maureen J. Lage, PhD, HealthMetrics Outcomes Research, LLC, 120 Anchorage Cir, Groton CT 06340. E-mail: lagemj@hlthmetrics.com.

REFERENCES

1. Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. *Front Biosci.* 2006;11:1388-1413.

2. Sharifi N, Gulley J, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA.* 2005;294(2):238-244.

3. Stewart AB, Lwaleed BA, Douglas DA, Birch BR. Current drug therapy for prostate cancer: an overview. *Curr Med Anticancer Agents.* 2005;5(6):603-612.

4. American Cancer Society. Cancer facts & figures 2007: estimated new cancer cases and deaths by sex for all sites, US, 2007. http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf. Accessed February 6, 2007.

5. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev.* 2006;4:CD006250.

6. Tubaro A, De Nunzio C. Bone health in prostate cancer patients. *Business Briefing: European Kidney and Urological Disease 2006.* http://www.touchbriefings.com/pdf/1599/Tubaro.pdf. Accessed December 14, 2007.

7. Higher costs may justify prophylaxis in prostate and lung cancer patients with bone metastases. *J Support Oncol.* 2004;2(5):456.

8. Drudge-Coates L. Skeletal complications and the use of bisphosphonates in metastatic prostate cancer. *Int J Palliat Nurs.* 2006;12(10): 462-469.

9. Delea T, McKiernan J, Brandman J, et al. Retrospective study of the effect of skeletal complications on total medical care costs in patients with bone metastases of breast cancer seen in typical clinical practice. *J Support Oncol.* 2006;4(7):341-347.

10. Lipton A. Management of bone metastases in breast cancer. *Curr Treat Options Oncol.* 2005;6(2):161-171.

11. LoRusso P. Analysis of skeletal-related events in breast cancer and response to therapy. *Semin Oncol.* 2001;28(4 suppl 11):22-27.

12. Coleman RE. Skeletal complications of malignancy. *Cancer.* 1997;80(8 Suppl):1588-1594.

13. Clemons MJ, Dranitsaris G, Ooi WS, et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. *J Clin Oncol.* 2006;24(30):4895-4900.

14. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. *Br J Cancer.* 2005;92(10):1869-1876.

15. Karamouzis MV, Ioannidis G, Rigatos G. Quality of life in metastatic breast cancer patients under chemotherapy or supportive care: a single-institution comparative study. *Eur J Cancer Care (Engl).* 2007;16(5):433-438.

16. Manders K, van de Poll-Franse LV, Creemers GJ, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer.* 2006;6:e179.

17. Ito Y, Tokudome N. Chemotherapy for metastatic breast cancer [in Japanese]. *Gan To Kagaku Ryoho.* 2006;33(6):742-746.

18. McMillan SC. Quality-of-life assessment in palliative care. *Cancer Control J.* 1996;e3. http://moffitt.org/moffittapps/ccj/v3n3/article4.html. Accessed December 14, 2007.

19. Groot MT, Boeken Kruger CG, Pelger RC, Uyl-de Groot CA. Costs of prostate cancer, metastatic to the bone, in the Netherlands. *Eur Urol.* 2003;43(3):226-232.

20. Delea T, Langer C, McKiernan J, et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. *Oncology.* 2004;67(5-6):390-396.

21. Botteman M, Barghout V, Stephens J, Hay J, Brandman J, Aapro M. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol.* 2006;17(7): 1072-1082.

22. Lamy O, Burckhardt P. Hypercalcemia of malignancy: diagnosis and treatment options. *Am J Cancer.* 2002;1(4):277-292.

23. Lamy O, Jenzer-Closuit A, Burckhardt P. Hypercalcemia of malignancy: an undiagnosed and undertreated disease. *J Intern Med.* 2001;250(1):73-79.

24. Fisher JA, Fikry C, Troxel AB. Cutting cost and increasing access to colorectal cancer screening: another approach to following the guidelines. *Cancer Epidemiol Biomarkers Prev.* 2006;15(1):108-113.

25. Rex DK, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and costs of colonoscopy. *Am J Gastroenterol.* 2002;97(7):1696-1700.

26. Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating costs from incomplete follow-up data. *Biometrics.* 1997;53(2):419-434.

27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

28. Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol.* 2000;18(1):72-79.

29. DePuy V, Anstrom KJ, Castel LD, Schulman KA, Weinfurt KP, Saad F. Effects of skeletal morbidities on longitudinal patient-reported outcomes and survival in patients with metastatic prostate cancer. *Support Care Cancer.* 2007;15(7):869-876.

30. Schröder FH, de Vries SH, Bangma CH. Watchful waiting in prostate cancer: review and policy proposals. *BJU Int.* 2003;92(8):851-859.

31. Gonzalez EC, Ferrante JM, Van Durme DJ, Pal N, Roetzheim RG. Comorbid illness and the early detection of cancer. *South Med J.* 2001;94(9):913-920.

32. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med.* 1997;103(2A):12S-19S.

33. Guralnik JM, Alecxih L, Branch LG, Wiener JM. Medical and long-term care costs when older persons become more dependent. *Am J Public Health.* 2002;92(8):1244-1245. ■