Hospital Resource Utilization and Treatment Cost of Skeletal-Related Events in Patients with Metastatic Breast or Prostate Cancer: Estimation for the Portuguese National Health System

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A B S T R A C T

Background: Skeletal-related events (SREs) occur frequently in patients with bone metastases as a result of breast (BC) and prostate (PC) cancers. They increase both morbidity and mortality and lead to extensive health-care resource utilization. **Methods:** Health care resource utilization by BC/PC patients with at least one SRE during the preceding 12 months was assessed through retrospective chart review. SRE-treatment costs were estimated using the Portuguese Ministry of Health cost database and analyzed using generalized linear models. **Results:** This study included 152 patients from nine hospitals. The mean (SD) annual SRE-treatment cost per patient was €5963 (€3646) and €5711 (€4347), for BC (n=121) and PC (n=31) patients, respectively. Mean cost per single episode ranged between €1485 (radiotherapy) and €13,203 (spinal cord compression). Early onset of bone metastasis (P = 0.03) and diagnosis of bone metastases at or after the occurrence of the first SRE (P < 0.001) were associated with higher SRE-treatment costs. **Conclusion:** These results reveal the high hospital SRE-treatment costs, highlighting the need for early diagnosis and treatment, and identify key factors determining the economic value of therapies for patients with skeletal metastases.

Keywords: breast cancer, costs, hospital, prostate cancer, skeletal-related events.

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Introduction

Breast (BC) and prostate cancer (PC) are the first- and second-most diagnosed cancers in their respective genders worldwide [1]. Together they were estimated to account for more than 630,000 deaths in 2002 [1]. The socioeconomic implications of BC and PC in developed countries are staggering. Direct treatment costs for PC and BC patients account for approximately 20% of cancer care costs in the United States and Europe, and indirect costs may contribute to a similar burden, especially in advanced cancer and the end-of-life settings [2–4]. In 2005, BC and PC accounted for 16% and 12%, respectively, of cancer deaths in Portugal [5].

Pathologic fracture (PF), spinal cord compression (SCC), surgery to bone (SB), radiation therapy to bone (RT), and hypercalcemia of malignancy (HCM) are common skeletal-related events (SREs) as a consequence of bone metastases [6]. Approximately 65% to 75% of patients with metastatic BC or PC will develop skeletal metastases [6], and 68% of BC and 49% of PC patients with bone metastases will develop one or more SRE in a time frame of 2 years if not treated with bisphosphonates [7,8].

The onset of SREs is associated with significant morbidity (including intractable bone pain, impaired mobility, and decreased health-related quality of life [QOL]) and decreased survival [9,10]. Pathologic fractures have been associated with up to a 32% increase in the risk of death in patients with bone metastases from solid tumors [10], and SREs were associated with a 27% decrease in survival among men with metastatic PC [11]. Delaying the onset of the first SRE is an important goal, particularly because of its strong association with cumulative events and poor survival [12].

Costs related to SRE treatment add substantially to the overall costs of cancer care in patients with metastatic BC or PC, and may account for more than 50% of their total health care costs [13,14]. Retrospective analyses have shown that total treatment costs for patients with BC who develop SREs may be US$14,000 to US$22,000 higher than for patients without SREs [15].

Bisphosphonates (BPs) have demonstrated efficacy in reducing the incidence of SREs in patients with bone metastases. Intravenous BP therapy for the prevention of SREs may reduce the need for expensive health care, particularly when PF, SCC, and the need for RT are prevented [16,17].

The costs of SRE treatment versus prevention using BP therapy have not been evaluated previously in the context of the
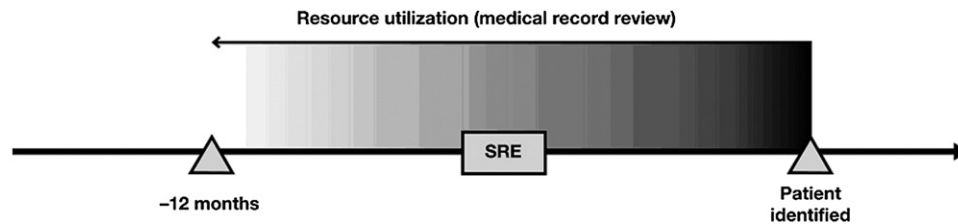
Fig. 1 – Data Collection Scheme. Patients eligible for inclusion had undergone treatment for ≥ 1 skeletal-related event (SRE) in the 12 months prior to study entry. Resource utilization during these 12 months was used to determine the cost of treating SREs.

Portuguese National Health Service (PNHS). In order to determine the economic burden of SREs and the economic value of BP utilization, accurate estimation of treatment costs is important. The objective of this study was to determine the SRE-related direct hospital costs and factors determining these costs in Portuguese patients with metastatic BC or PC.

Patients and methods

Study design

This was a multicenter, single-country, retrospective descriptive study. Publicly funded hospitals in Portugal were ranked using the number of oncology clinical visits in the latest hospital productivity statistics from the Portuguese Ministry of Health [18]. Of the 18 PNHS hospitals with oncology and urology clinical services invited, nine agreed to participate. These include two of the three oncology hospitals and two of the three University hospitals in Portugal. The study protocol was approved by hospital ethics committees, and informed consent was obtained from patients before inclusion. The study and data collection schemes were designed to avoid influencing future treatment decisions for the included patients.

Patients

Adult patients with bone metastases and at least one SRE in the preceding 12 months were eligible. SREs were defined as pathologic fracture, spinal cord compression, surgery to bone, radiation therapy to bone, or hypercalcemia of malignancy attributable by center clinicians to bone metastasis. Initially, patients were required to be alive when their records were reviewed. However, this criterion was later relaxed because it limited patient accrual. Hence, informed consent could not be obtained for patients who deceased before their records were reviewed. Exclusion criteria were diagnosis of other cancer/s as co-morbidity, pregnancy, and regular follow-up for BC/PC management in more than one hospital (to avoid the same patient being enrolled on the study through two different hospitals). This was important in the context of the Portuguese health system because patients may be initially diagnosed in general hospitals and later transferred to oncology hospitals.

Data collection

Cancer diagnosis electronic data sets were used (where available) to identify eligible patients. In hospitals without such data sets, RT records and hospital pharmacy records of BP therapy, or paper clinical records (three hospitals), were used. Data for SRE treatment were obtained from patients' hospital records. In order to accommodate inter-hospital variations in the timing of study approval, a period of 1 year (October 2004 to September 2005) was allowed for patient enrollment. Therefore, SREs would have oc-

curred between October 2003 and September 2005, and resource utilization refers to this observation period (Fig. 1).

Clinical data included the date of primary cancer diagnosis, occurrence of first bone metastasis diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status at study entry, date of first SRE, number of SREs since diagnosis of bone metastasis, and total number of SREs during the observation period. Health care utilization included frequency and duration of hospitalization, courses of RT and number of days of treatment, palliative radionuclide therapy (e.g., Sr^{89} and Sm^{153}), diagnostic tests, number and type of clinical visits, and all medications used including BPs.

It is important to note that the data collected pertain to hospital resource utilization only. Patient-reported costs (e.g., over-the-counter analgesics, medical services outside the hospital setting, transportation) and indirect costs related to the loss of productivity or premature death were not included. Because the participating hospitals all belong to the publicly funded PNHS, estimated treatment costs may be lower than costs in other (private) hospitals.

Cost estimation

Investigators were not granted direct access to hospital accounting systems. Therefore, costs for procedures such as hospitalization, RT, diagnostics, and clinical visits, were estimated using the PNHS price list, which is used by publicly funded hospitals to price services provided to third parties such as private insurers or the Portuguese Civil Servants Health System [19]. Prices for hospital drugs were obtained from the Institute for Financial Management and Informatics (IGIF) price catalog (2003–2005) used by hospitals as a maximum reference price list for acquisition of medications. Resource utilization and costs considered were limited to those related to the treatment of SREs.

Data analysis/modeling

Differences in age, time from cancer diagnosis to bone metastasis, and frequency of diagnosis of bone metastases after SRE onset were assessed using t test, log-rank test, and chi-square test, respectively. The 95% confidence interval for median 12-month SRE-related costs was estimated using the binomial exact method. Non-parametric Wilcox and Kruskal-Wallis tests were used to assess differences in total SRE-treatment cost according to patient characteristics. The costs of SRE hospital treatment were modeled assuming two different dependent variables. For the total sample, total SRE-treatment cost was used as the dependent variable. For the BC patients' sample, SRE-treatment cost excluding the cost of the BPs and its administration was also used as the dependent variable in order to include the type of BP used as a covariate in the model. Generalized linear models (GLMs) with gamma distribution and logarithm link function were fitted to estimate the effects of independent variables in the expected SRE treatment costs [20]. These models allow the measurement of the association be-

Table 1 – Patients' characteristics.			
	All (n = 152)	BC (n = 121)	PC (n = 31)
Status at chart review (alive/dead), n*	98/45	76/39	22/6
Bone metastases			
Age at dx, mean yrs ± SD	58.3 ± 13.0	56.8 ±13.2	65.3 ± 9.1
Time from cancer dx, median mo [95% CI]	34.5 [15.9; 49.7]	38.3 [23.9; 57.2]	4.8 [2.1; 49.7]
After onset of SREs (yes/no), n*	20/130	18/102	2/28
SRE, n (%)†			
Any	183 (100)	142 (100)	41 (100)
Surgery	4 (2.2)	3 (2.1)	1 (2.7)
Spinal cord compression	14 (7.7)	9 (6.2)	5 (13.5)
Pathologic fracture	27 (14.8)	20 (13.7)	7 (18.9)
Radiation therapy to bone	128 (69.9)	105 (71.9)	23 (62.2)
Hypercalcemia of malignancy	10 (5.5)	9 (6.2)	1 (2.7)
ECOG PS, n (%)‡			
0	17 (21.2)	15 (24.6)	2 (10.5)
1	34 (42.5)	28 (45.9)	6 (31.6)
2	14 (17.5)	11 (18.0)	3 (15.8)
3	8 (10.0)	5 (8.2)	3 (15.8)
4	7 (8.8)	2 (3.3)	5 (26.3)
Bisphosphonate treatment, n (%)§			
ZOL	91 (65.4)	77 (65.8)	14 (63.6)
PAM	30 (21.6)	30 (25.6)	0
PAM → ZOL	4 (2.9)	1 (0.9)	3 (13.7)
Oral BP	5 (3.6)	5 (4.3)	0
No BP	9 (6.5)	4 (3.4)	5 (22.7)
Unknown	13 (8.6)	4 (3.3)	9 (29.0)

BC, breast cancer; BP, bisphosphonate; dx, diagnosis; ECOG PS, Eastern Cooperative Oncology Group performance status; mo, months; PAM, pamidronate; PAM → ZOL, patients initially treated with PAM but switched to ZOL during the observation period; PC, prostate cancer; SD, standard deviation; SRE, skeletal-related event; yrs, years; ZOL, zoledronic acid.

* Numbers of patients do not equal total sample because of missing data for 9 patients.
† Percentage of total SREs (e.g., 183 = 100% for the total sample).
‡ ECOG PS data were collected only for patients alive at study initiation; data were not available for 18 patients.
§ Percentage of patients for whom BP utilization data were available.

tween independent variables and SRE cost through the exponential of regression coefficients (e^β), while controlling for patients' and clinical characteristics. Independent variables approaching the statistical significance level of 0.10 in the bivariate analysis were included in multivariate models. Standardized deviance residuals and likelihood ratio test were used for model diagnostics. All statistical analyses were performed using R software version 2.8 [21].

Results

Patient demographics and clinical characteristics

The study enrolled 152 patients with bone metastases from BC (n = 121) or PC (n = 31). All patients had experienced at least 1 SRE during the 12-month observation period. Mean (SD) age at diagnosis of bone metastasis was 58.3 (13) years (Table 1). Overall, compared with BC, patients with PC were older (P < 0.001) and had a longer median duration from cancer diagnosis to diagnosis of bone metastasis (38 vs. 5 months, P < 0.01), a higher frequency of bone metastasis diagnosis after the onset of SREs, (17% vs. 7%, P < 0.01), and worse ECOG performance status (Table 1).

Over the 12-month observation period, 183 SREs were registered, 146 (79.8%) in patients with BC. The mean number of SREs per patient was 1.2 (range: 1 to 3). Radiotherapy to bone was the most frequent SRE (69.9%). Among patients for whom BP utilization data were available (n = 139, 13 missing), 65.4% received zoledronic acid (ZOL), 21.6% received pamidronate (PAM); 2.9% initi-

ated therapy with PAM and later switched to ZOL during the study period, 3.6% received oral BPs, and the remainder (6.5%) were not treated with BPs. At the time of data collection, 98 patients were alive, of whom the majority had a good ECOG performance status (Table 1).

Table 2 – Resource utilization.			
	N	Mean	SD
Radioisotopes	5	1.0	—
Clinic visits	152	2.8	3.0
Hospitalization (duration in days)	38	19.7	13.7
Diagnostics*	42	22.0	52
Radiotherapy	118	1.1	0.36
Sessions per treatment		8.38	3.25
Medications†			
Analgesic‡	20	1.35	0.79
IV BP (duration in days)	121	263	63
Oral BP (duration in days)	5	333	34

BP, bisphosphonates; IV, intravenous; SD, standard deviation.

* Refers to the number of different diagnostics procedures, including blood tests, x-ray, computed tomography, magnetic resonance imaging, scintigraphy, bone densitometry, and bone biopsy.
† Excluding chemotherapy and hormonal therapy for primary cancer.
‡ Morphine or fentanyl.

Table 3 – SRE treatment costs by type of resource.					
	Treatment costs				
	Breast			Prostate		
	Mean, €	SD	Percent of total	Mean, €	SD	Percent of total
Radioisotopes	14	153	0.2	218	575	3.8
Clinic visits	36	101	0.6	27	53	0.5
Hospitalization	1312	3056	22.0	2213	3993	38.7
Diagnostics	103	370	1.7	83	196	1.5
Radiotherapy	1467	882	24.6	1402	1148	24.5
Medications*	3031	1290	50.8	1768	1668	31.0
Total, mean ± SD		€5963 ± 3646			€5711 ± 4346	

SD, standard deviation; SRE, skeletal-related event.

All monetary units are given in Euros (€).

* Including bisphosphonates, but excluding chemotherapy and hormonal therapy.

Resource utilization and SRE-treatment costs

In the total sample (BC+PC), 38 (25%) patients were hospitalized within the 12-month observation period of the study. The mean length of stay was 19.7 days (SD = 13.7 days; min-max [1–45]). On average (SD), each patient (n = 118) using RT was submitted to 1.1 (0.36) treatments, consisting of 8.4 (3.3) RT sessions. Radiotherapy with Sm^{153} (radioisotope) was used in five patients. Overall, 86% and 3.3% of patients received IV and oral BPs, with mean treatment duration of 263 and 333 days, respectively (Table 2).

The estimated mean 12-month SRE-related costs per patient were €5963 (median = €5105, 95%CI [€4846; €5,321]) and €5711 (median = €4723, 95%CI [€3467; €6052]) for patients with BC and PC, respectively. In BC patients the costs of medications (including BPs but excluding chemo/hormonal treatment) accounted for approximately 50.8% of the total, whereas hospitalization accounted for the largest proportion of costs (38.8%) in PC patients. Utilization of these two resources together accounted for approximately 70% of total SRE costs in both patient groups (Table 3). The average cost per type of SRE was also examined (Fig. 2). Spinal cord compression was the most expensive (€13,203), whereas RT to bone had the lowest cost (€1485) per episode. Bivariate analyses revealed no dif-

ferences in total SRE costs by cancer type (P = 0.43), patient status at the time of chart review (alive or dead; P = 0.11), or age at bone metastasis diagnosis (P = 0.71). Diagnosis of bone metastasis at or after the onset of SREs was associated with significantly higher costs compared to diagnosis prior to the onset of SREs (mean = €10,363 vs. €5280; P < 0.01). Other factors influencing total cost of SRE treatment were poor ECOG performance status (P = 0.01) and type of BP used (P < 0.01). On average, higher costs were associated with patients started on PAM and then switched to ZOL (€11,673) compared with those receiving PAM only (€6767), ZOL only (€681) or no BPs at all (€4757). The bivariate analysis of SRE total costs showed similar results in the "BC patients" subset, whereas the only significant variable in the PC subset was the type of BP.

Modeling of SRE-treatment costs

In the total sample, the expected total SRE cost was €5924 for the reference patient (BC) (Table 4). The independent multiplicative effect of the reported covariates can be found from the exponential coefficient relative to the constant. Thus, with all other vari-
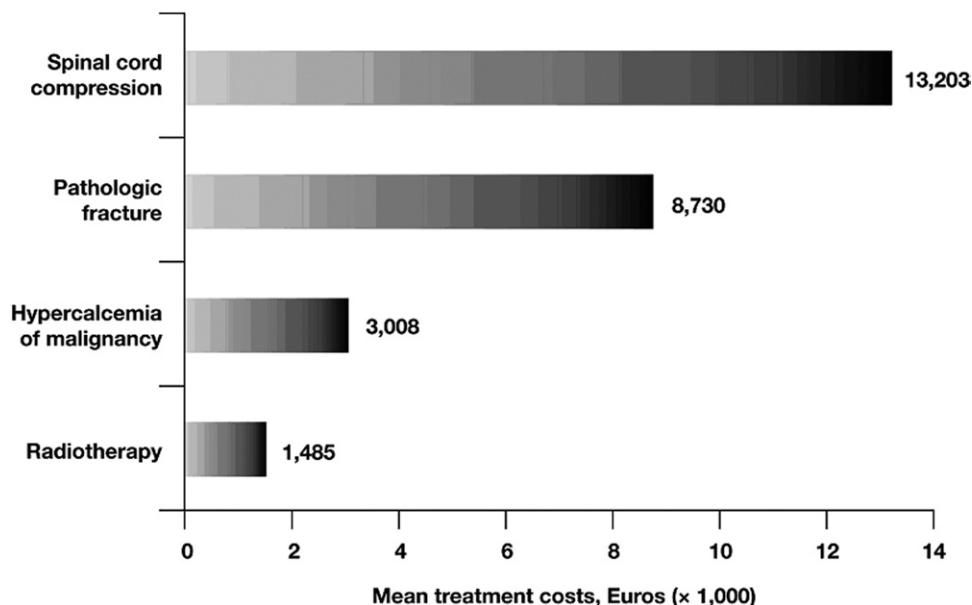

Fig. 2 – Mean Treatment Cost by SRE Type. Mean cost of treatment for each type of skeletal-related event (SRE) was determined using hospital records of direct treatment-costs (excluding chemo/hormonal therapy for cancer and patient-reported costs).

Table 4 – GLM modeling of total SRE treatment costs: total sample (n = 107).					
	β	SE	P value	e^β	(95% CI)
Prostate cancer*	0.239	0.170	0.163	1.27	(0.91; 1.77)
Alive at data collection	0.117	0.104	0.266	1.12	(0.92; 1.38)
Age at bone metastasis, years	−0.001	0.004	0.728	1.00	(0.99; 1.01)
Time between cancer diagnosis and bone metastasis, years	−0.024	0.012	0.041	0.98	(0.95; 1.00)
Bone metastasis diagnosis after SRE	0.446	0.140	0.002	1.56	(1.19; 2.06)
Constant	8.687	0.235	<0.001	5924	(3736; 9392)

β, regression coefficient; CI, confidence interval; e^β, exponential of the regression coefficient; GLM, generalized linear model; SE, standard error; SRE, skeletal-related event.
* Reference category: Breast cancer patients

ables kept constant, diagnosis of bone metastasis after the onset of SREs was associated with a 56% increase in total SRE-treatment costs ($P = 0.002$, total cost = €9241). Each 12-month increment in time from cancer diagnosis to diagnosis of bone metastasis was associated with a 2.4% decrease in SRE treatment costs ($P = 0.041$).

There were no PAM-treated patients in our PC sample. Therefore, modeling SRE treatment costs using the type of IV BP as covariate was limited to the breast cancer subset. Such modeling of SRE-related costs with and without cost of the BP (Table 5) helps test the hypothesis that drugs with higher acquisition costs may be cost-effective if their use results in subsequent treatment cost offsets and/or improvements in clinical outcomes.

In modeling of SRE-related costs in BC patients, bone metastasis diagnosis after the onset of SREs was associated with a 61% increase in total SRE treatment costs ($P < 0.001$), and shorter time between cancer diagnosis and bone metastasis was associated with a 2.1% increment in cost per year decrease. In contrast to the overall sample, SRE-related treatment costs for patients with BC who were alive at the time of data collection were 22% higher than for patients who died before data collection ($P = 0.031$). After controlling for all other variables, PAM treatment was associated with a nonsignificant numeric cost increment of 12% versus ZOL despite the lower procurement cost of PAM. Thus, there were no significant differences in overall treatment costs between the PAM-treated and ZOL-treated groups. However, patients who received PAM experienced significantly more SREs compared with patients receiving ZOL (1.3 vs. 1.1; $P = 0.04$).

A secondary hypothesis-generating analysis excluding the cost of BP therapy in the BC group of our retrospective, observational study estimated an 84% (95%CI [27%; 167%]) increment in the costs of resource use among patients receiving PAM versus ZOL (Table 5). Similar to outcomes from the model including

BP costs, diagnosis of bone metastasis at or after SRE onset was associated with a significant 180% increase in treatment costs ($P < 0.001$), whereas longer time between diagnosis of cancer and the development of bone metastasis was associated with a significant 5% reduction per year in SRE-treatment costs (excluding the cost of BPs).

Discussion

To our knowledge, this study is one of the few estimating SRE treatment costs in patients being treated in day-to-day clinical practice, and applying statistical techniques for SRE cost modeling while controlling for differences in the sample population potentially related to observational retrospective data collection. As with all retrospective studies, however, our study design has certain limitations that might influence the results.

Our study was dependent on hospitals' willingness to participate. Therefore, both the hospitals and patients are convenience samples. No formal assessment was made to determine the study sample representativeness because raw statistics were not available from public hospitals in Portugal. If we consider, however, medical oncology visits as proxy for hospital activity (i.e., reflecting the number of oncology patients treated in each hospital), then our sample can be considered reasonably representative. It included two thirds of all oncology and university hospitals, accounting for 52% and 68% of the medical oncology visits in such institutions, respectively. The remaining were a mixture of major urban-area hospitals (central) and smaller size hospitals, far from large metropolitan areas (responsible for 32% of the oncology visits nationwide) [18]. The latter may be underrepresented compared with the former. Nationwide, the nine hospitals partici-

Table 5 – GLM modeling of SRE treatment costs: breast cancer patient sample (n = 97).										
	Total costs					Excluding BP costs				
	β	SE	P value	e^β	(95% CI)	β	SE	P value	e^β	(95% CI)
Alive at data collection	0.199	0.092	0.031	1.22	(1.02; 1.46)	0.156	0.179	0.388	1.17	(0.82; 1.66)
Age at bone metastasis, years	−0.001	0.003	0.867	1.00	(0.99; 1.01)	0.000	0.006	0.942	1.00	(0.99; 1.01)
Time between cancer diagnosis and bone metastasis, years	−0.022	0.01	0.036	0.98	(0.96; 1.00)	−0.048	0.002	0.031	0.95	(0.91; 0.99)
Bone metastasis diagnosis after SRE	0.476	0.126	<0.001	1.61	(1.26; 2.06)	1.027	0.243	<0.001	2.8	(1.74; 4.49)
PAM*	0.116	0.099	0.241	1.12	(0.93; 1.36)	0.61	0.19	0.002	1.84	(1.27; 2.67)
Oral BP*	−1.493	0.214	<0.001	0.22	(0.15; 0.34)	−0.505	0.413	0.225	0.6	(0.27; 1.36)
Without BP*	−0.513	0.249	0.039	0.60	(0.37; 0.98)	0.653	0.478	0.175	1.92	(0.75; 4.90)
Constant	8.581	0.212	<0.001	5329	(3519; 8072)	7.583	0.422	<0.001	1964	(859; 4491)

β, regression coefficient; BP, bisphosphonate; CI, confidence interval; e^β, exponential of the regression coefficient (multiplicative effect relative to the reference category); GLM, generalized linear model; PAM, pamidronate; SE, standard error; SRE, skeletal-related event.
* Reference category: zoledronic acid treatment.

pating in our study accounted for approximately 43% of all oncology visits to PNHS hospitals in 2005.

The number and characteristics of patients recruited from each hospital were physicians' decisions based on study protocol inclusion and exclusion criteria. Therefore, there might have been some selection bias, which could not be controlled for by researchers. Few hospitals had fully electronic clinical records. Another possible source of bias relates to inter-institution differences in how clinical records were maintained, potentially resulting in imbalanced registration of resource use. The use of regression models including treatment center as a covariate may help minimize these potential biases; however, this was not possible without reducing the number of hospitals included in the statistical analysis and compromising overall sample size (five hospitals included contributed < 10 patients each). Also, there were some important clinical parameters that were not recorded, and therefore could not be included in the model, e.g., non-osseous metastatic disease and bone pain. Thus, these caveats must be kept in mind when interpreting our results.

The 1-year SRE treatment costs estimated in our study are remarkably similar to the costs of SRE treatment reported in other studies conducted in Europe using either hospital records data [14] or even cost analysis derived from clinical trials [22]. They are somewhat lower than those reported by researchers in the United States using insurance claims databases for cost analysis [15,16,23]. For example, in a retrospective analysis from a community and a university hospital in The Netherlands based on chart review of 31 patients with prostate cancer metastatic to bone, it was found that the average total cost of care was around €13,000, of which approximately 50% was attributable to the treatment of SREs [14]. In another single-institution study, the total cost incurred by patients with malignant osteolytic bone disease (60% breast cancer, 21% multiple myeloma, and 19% other tumors) amounted to an average of €12,060 with 48% of this cost being incurred during the BP-treatment phase [22]. Two studies from the USA, based on insurance claims data and aiming to estimate the cost of treating SREs in metastatic breast [15] and prostate cancer [16], reported a 1-year SRE mean treatment cost of US$13,940 and US$12,469, respectively. These costs are roughly equivalent to €9791 and €8758 (1 EURO = 1.4238 USD, European Central Bank, June 2, 2009). The differences in SRE costs compared with those from our study may be related to a different mix of SREs as well as to differences in unit costs of health care procedures on both sides of the Atlantic. Compared with the BC population studied by Delea et al. [15], the BC patients in our study received more RT (88% vs. 56%) and had fewer PF (15% vs. 34%). On the other hand, the PC patients experienced an identical proportion of episodes of HCM (0.3% vs. 0.3%), more SCC (13% vs. 8.5%) and similar PF rates (23% vs. 23.4%), versus the study by Lage et al. [16].

Our observations of increased SRE incidence in PAM-treated patients (vs. ZOL) are also consistent with reported outcomes in the BC stratum from the phase III head-to-head trial of PAM versus ZOL in patients with bone lesions from multiple myeloma or BC [24], as well as the Cochrane meta-analysis of placebo-controlled trials of BPs in metastatic BC [25]. In view of the higher SRE incidence in PAM- versus ZOL-treated patients in our study, the increased treatment costs (excluding BPs) in the PAM group are not surprising.

In contrast to our results, other studies have reported similar efficacy as well as cost-effectiveness for PAM versus ZOL in the metastatic BC and PC settings [26–29]. However, in analyses that rely on clinical trial data to estimate cost-effectiveness [26,28,29], the applicability to the real-world setting may be confounded by factors such as higher-than-normal rates of persistence with therapy (in the case of oral BPs).

Also in the context of our study, because we limited our patient sample to a small number of tertiary hospitals and a relatively short duration for accrual, variables such as concomitant chemotherapy and diagnostic practices may be better controlled for compared with analyses based on clinical trial data. In routine clinical practice, persistence rates with daily oral BPs are very low (~35% over 6 months in patients with bone metastases) [30]. Therefore, calculations of cost-effectiveness of oral therapies based on SRE-prevention outcomes in clinical trials may substantially overestimate true efficacy and cost-effectiveness in normal practice. On the other hand, interpretation of the results from our study is complicated by the unknown effects of retrospective data collection and lack of randomization. Therefore, our findings lack additional validation from prospective pragmatic trials.

Modeling SRE treatment costs using multivariate analysis (GLM) is particularly useful to account for patients and clinical differences arising from the study design. For example, in the modeling analysis of the total sample, each additional year between diagnosis of cancer and development of bone metastasis was independently associated with a 2.4% decrease in SRE costs, after controlling for the other covariates present in the model. On the other hand, diagnosis of bone metastasis at or after SRE onset was associated with a 19% to 106% increase in treatment costs, suggesting that the late diagnosis of bone metastasis may lead to more frequent or more severe SREs, hence increasing resource utilization and costs.

Modeling SRE treatment costs including and excluding the costs of BPs allows for an alternative perspective on the cost differences in utilization of other health care resources, such as hospitalizations, diagnostics, and non-drug treatments (e.g., RT), all of which may vary substantially depending on the BP used to prevent or treat SREs. This perspective is appealing in economic terms because it can reveal different patterns of resource utilization and costs in relation to differences in effectiveness of different agents. In the BC subset, if overall resource use is considered, no difference was observed between ZOL and PAM. However, the higher SRE incidence in PAM-treated patients, combined with the overall high cost of treating SREs, suggests that increased acquisition costs for more expensive agents might be offset by improved effectiveness. Prospective, randomized trials comparing these two BPs in a real-world setting are needed to directly evaluate the differences between costs and health outcomes with the use of these two BPs in metastatic BC. Such a pragmatic study may also include data collection on bottom-up direct and indirect costs.

The cost estimates for our sample of patients underestimate the true societal costs of SREs for three reasons: 1) no assessment of private and out-of-hospital resource utilization; 2) the retrospective nature of the study design; and 3) no inclusion of indirect cost.

Our study did not assess private and out-of-hospital resource utilization; therefore, costs incurred by patients and their families are not taken into account. These costs may be important because in contemporary health care management there is a trend to restrict expensive hospital care to strictly necessary aspects, and to discharge patients to ambulatory care as soon as possible [31,32]. Other studies found that these costs can represent a substantial burden [17] and can outweigh inpatient costs [16]. In the context of the Portuguese health care system, private expenditure on health care represents about 30% of the total health expenses [33].

The problems related to retrospective data collection from clinical records were more evident in missing data from clinical visits and diagnostics. In both groups of patients, costs for clinical visits represented less than 1% of the total, and diagnostics represented less than 2%. These are extremely low values compared with other studies wherein these resources contributed to approximately 15% of total costs and up to 43% of the additional costs associated with SREs [14,15].

The inclusion of patients who had already died at the time of data review (approximately one-third of the patients in our study)

may also have influenced SRE treatment costs. Close proximity to death has been associated with higher costs of care [34,35], especially for cancer patients [36]. However, in our study no significant differences in SRE treatment costs were observed based on survival at the time data collection was initiated.

Unlike other studies that attempt to account for indirect costs and generate an estimate of total costs (an estimate that inherently has substantial variability), the costs in the present study were calculated by actual resource utilization and cost assigned by the Portuguese Ministry of Health. The exclusion of indirect costs in this analysis is not attempt to minimize their importance. Indirect costs can impose a large burden on society. Nonetheless, their accurate measurement is difficult and prone to considerable subjective variation [37]. Inclusion of only direct costs minimizes variability, allowing better comparison of the costs for each SRE and for modeling to determine factors that influence SRE-treatment costs.

Conclusion

This observational, retrospective study analyzed resource use related to SRE from a Portuguese hospital perspective, and identified several factors that may influence the cost of treating and/or preventing SREs. Moreover, these results underscore the importance of timely diagnosis and treatment of bone metastases, and highlight the need for a pragmatic prospective evaluation of the most cost-effective BP treatment for patients with skeletal metastases from BC.

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