



Cost of illness of metastatic prostate cancer: a perspective of costs for new treatment options in The Netherlands

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Rob ter Heine^{*1}, Geert WJ Frederix², Joost W Geenen³, Anke M Hövels³, Marco van Vulpen⁴, Anko Kooistra⁵, John MH De Klerk⁶ & Haiko J Bloemendaal⁷

¹Radboudumc, Department of Pharmacy, Geert Grooteplein-Zuid 22, 6525 GA, Nijmegen, The Netherlands

²Julius Center for Health Sciences & Primary Care, University Medical Center, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

³University Utrecht, Faculty of Science, Department of Pharmaceutical Sciences, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands

⁴University Medical Centre Utrecht, Department of Radiotherapy, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

⁵Meander Medical Centre, Department of Urology, Maatweg 3, 3813 TZ, Amersfoort, The Netherlands

⁶Meander Medical Centre, Department of Nuclear Medicine, Maatweg 3, 3813 TZ, Amersfoort, The Netherlands

⁷Meander Medical Centre, Department of Internal Medicine, Maatweg 3, 3813 TZ, Amersfoort, The Netherlands

* Author for correspondence: Tel.: +31 24 3 616 405; r.terheine@radboudumc.nl

Aim: To assess the resource use and associated costs of treating patients with metastatic prostate cancer with a focus on skeletal-related events (SREs). **Methods:** We performed a bottom-up cost of illness study in The Netherlands. **Results:** A total of 136 patients were studied. The mean total costs were €17,931 per patient. SREs that required hospitalization ($n = 53$) were, at median costs of €2039–9346, depending on care. These SREs had median costs of €200–1912. **Conclusion:** Our data provide a basis to investigate the cost-effectiveness of novel treatment options for metastatic prostate cancer. The impact of SREs on total costs could justify policy aimed at actively preventing SREs, possibly resulting in better quality of life and cost-reduction.

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Prostate cancer is the most common noncutaneous cancer and the third most common cause of cancer related death among European men, with 85–100% of patients dying from prostate cancer feature bone involvement [1,2]. In Europe, more than 400,000 men are annually diagnosed with prostate cancer and that ~90,000 die from the disease per year, indicating that more men die with prostate cancer than as a result thereof [3]. While first-line treatment of advanced prostate cancer with androgen deprivation therapy is initially effective, often development of castration resistance is inevitable. Second-line treatment of metastatic castration resistant prostate cancer with docetaxel has proven to be effective but still does not halt disease progression [4]. Bone metastases are a major complication at the end-stage of the disease and the resulting skeletal-related events (SREs; complications like fractures, spinal cord compression and severe pain) are associated with considerable morbidity and mortality [5]. Also, these SREs are the major cost drivers in total healthcare costs of prostate cancer patients [6–9]. Localized bone metastases can be successfully treated by external beam radiotherapy (EBRT) [10]. Poorly localized multi-site osseous metastases require wide field radiotherapy where bone marrow- and gastrointestinal toxicity can compromise clinical benefit [4]. Therapeutic bone targeting radiopharmaceuticals specifically target osteoblastic metastases with minimal systemic side effects and proven efficacy [11,12]. They are therapeutically valuable for treatment of local as well as multisite painful bone metastases [10].

Although, advancing treatments have increased life expectancy, European healthcare budgets are on an increasing strain [13]. In 2011, prostate cancer care accounted for 11% (at €5.43 billion) of total cancer-related healthcare costs in the EU [14]. A report from 2007 states that, in the Nordic countries, when evaluating healthcare costs per cancer site, prostate cancer has the third highest healthcare costs and the highest share of extramural prescription drug

costs when compared with total treatment costs. In 2013, Dutch hospital care accounted for the biggest (25.8%) portion of the Dutch healthcare budget and showed the biggest annual increase (5.7%) [15]. The relation between prostate cancer and age, combined with current and predicted aging of the population, solid evidence on the costs of prostate cancer care is of paramount importance to keep European healthcare affordable and efficient [1,13,14,16,17].

However, with the lack of recent cost of illness studies for metastatic prostate cancer, the value of recently approved drugs for this indication like abiraterone acetate, radium-223-chloride and enzalutamide, cannot be put into perspective. Hence, the goal of our study was to assess the intramural resource use and associated costs of treating patients with prostate cancer, metastatic to the bone. Because SREs are one of the important determinants of quality of life as well as the primary cost drivers for treatment of metastatic prostate cancer, we focused on the impact of SREs in our study.

Materials & methods

Study design

This retrospective bottom-up cost of illness study was performed at the Meander Medical Centre, a large regional teaching hospital in Amersfoort (The Netherlands) and was performed according to published guidelines [18,19]. Ethical approval for this study was not deemed necessary as this study was a retrospective study of anonymous data and this was confirmed by the institutional review board.

Patient selection

Patients were selected for inclusion on the basis of having received either a bone scintigraphy or radionuclide therapy (RNT) in the period from 1 January 2006 until 31 December 2012. This period was chosen, because the treatment options for the studied indication were constant during this time frame. This allowed a proper assessment of costs for comparison with novel treatment options. RNT is defined as having received at least one course of Samarium-153-EDTMP (Quadramet[®], CIS Bio International, Gif-sur-Yvette, France), Strontium-89-chloride (Metastron[®], GE Healthcare, Eindhoven, The Netherlands), Rhenium-188-HEDP (produced in-house) or Rhenium-186-HEDP (ReBone[®], Mallinckrodt medical, Mallinckrodt LLC, MI, USA). Patients were included when they were diagnosed with prostate cancer, metastatic to the bone, and were deceased at time of data collection (November 2013). Patients were excluded on basis of clinical trial participation during follow-up, incomplete medical history or having received treatment in another hospital during follow-up.

Data collection

All data were retrospectively collected from the hospital information systems and patient records. The acquired data consisted of all the inpatient days, daycare treatments, intramural medication, outpatient care, surgeries, EBRT, visits to the emergency department, blood products used, diagnostics (imaging, laboratory analysis and clinical pathology) and intramural paramedical care like physical, psychological, speech and revalidation therapy. All individual units were linked to their unit costs.

Unit costs

Unit costs of resource use were derived from different sources. Reimbursement prices issued by the Dutch Healthcare Authority were used as individual unit costs for medical interventions, imaging and diagnostics, laboratory analysis, surgeries, paramedical care and clinical pathology [20–22]. Unit cost of radionuclide treatment of bone metastases (with Rhenium-188-HEDP) was established by a microcosting study. Resource use regarding diagnostics was divided into the categories nuclear diagnostics, radiology, pathology, endoscopy and others. For inpatient days, daycare treatment, blood products, emergency department visits and outpatient care, reference prices established by previous research were used [23]. The costs of intramural medication was assessed with the use of the prescription database and unit prices as listed in the Dutch Z-Index [24]. In absence of a prescribed dosage, the Defined Daily Dosage (DDD) as stated by the WHO Anatomical Therapeutic Chemical (ATC) classification system with DDD index was used [25]. If medication was prescribed as *pro re nata*, half the DDD was used. All prices were indexed to 2013 price levels using rates issued by the Dutch Healthcare Authority [20].

Table 1. Patient characteristics.

Characteristic	Value
Numbers included	136
Age at diagnosis of bone metastasis:	
– Mean, in years (median)	75 (76)
– Range (years)	53–92
– ≥ 75 years (%)	57
– ≥ 80 years (%)	35
Follow-up:	
– Mean, in years (median)	753 (500)
– Range (days)	18–3878
Prior treatment	
Hormonal [†] (%)	25.7
Chemotherapy (%)	1.5
Brachytherapy and/or external radiotherapy (%)	17.6
Radical prostatectomy (%)	1.5
Received none of the treatments above (%)	65.4
Serum PSA	
Mean (median) nadir serum PSA (ng/ml) during follow-up [‡] (n = 124)	75.6 (6.4)
Mean (median) zenith serum PSA (ng/ml) during follow-up [‡] (n = 124)	1010.6 (524.5)
Mean (median) zenith:nadir factor during follow-up [‡] (n = 124)	443.9 (59.0)
Skeletal-related events during follow-up (n = 218)	
SREs per patient:	
– 1	49 (number of patients)
– 2	25 (number of patients)
– 3	18 (number of patients)
– ≥ 4	13 (number of patients)

[†]Bilateral orchiectomy or hormone therapy.

[‡]Serum PSA measurements 30 days prior to follow-up until death were collected for each patient and used for the assessment of nadir and zenith serum PSA during this period. For 12 patients, there were insufficient measurements available ($n \leq 1$) during this period for a nadir and zenith serum PSA to be assessed. The factor of zenith:nadir was calculated for the 124 eligible patients.

SRE: Skeletal-related event.

Skeletal-related events

SREs were identified on basis of resource use and were considered an event if resource use featured RNT, EBRT or surgery to bone or if resource use was directly related to treating pathological fractures or spinal cord compression. If an SRE directly lead to hospitalization, all resource use during this hospitalization was incorporated in the SRE.

Results & discussion

Study population

A total of 136 patients were included in this study. Table 1 displays the characteristics of the study population. Unit costs are presented in Table 2. At start of follow-up, mean and median age of the population was 75 and 76 years, respectively. Difference between zenith and nadir serum PSA levels during follow-up were assessed per patient. The mean and median per patient zenith:nadir factor was 443.9 and 59.0, respectively. Hormonal therapy was the most common prior treatment. The majority of patients (65.4%) had not been actively treated for prostate cancer before diagnosis of bone metastases. At least, 74.3% were not castration resistant, as only 25.7% had already received any hormonal therapy at time of inclusion. In our study, the bottom-up approach allowed costing to be performed with great detail and on a per patient basis. Also, the real-world setting gave an adequate depiction of the daily clinical practice. Furthermore, the size of the cohort was relatively large and a requirement for proper cost assessment, as previously illustrated by the 156-fold difference in total cost in this population [27]. Last, the deliberately chosen study period (2006 until 2013) allowed proper assessment of treatment costs, as in this period no new treatment options were introduced for the studied indication.

Table 2. Costs and cost categories.

Cost category	Unit cost (€)	Mean number of units per patient (median)	Mean costs (€) per patient (median)	Total costs (%)	Ref.
Laboratory analysis	–	196.19 (136)	1.027 (789)	5.73	[18–20]
Inpatient days	399.52	14.90 (10)	5.955 (3.995)	33.21	[20]
Daycare treatment	273.24	1.84 (1)	502 (273)	2.80	[20]
Medication:					
– All medication	–	29.89 [†] (22 [†])	1.964 (266)	10.95	–
– Docetaxel	–	0.65 (0)	718 (0)	4.00	–
– Other medication	–	29.24 (22)	1.246 (162)	6.95	–
Treatment [‡]	–	8.57 (4,5)	2.047 (768)	11.41	[19,20]
Outpatient care	First visit: 95.25; Normal visit: 69.67	19.53 (14)	1.416 (1.039)	7.90	[19]
External beam radiotherapy [§]	1911.79	0.77 (0)	1476 (0)	8.23	[19,20,26]
Radionuclide therapy	–	0.74 (1)	995 (1.159)	5.55	[19,20]
Imaging and diagnostics	–	15.65 (13)	2.032 (1.692)	11.34	[19,20]
Emergency department visits	164,38	2.18 (1)	358 (164)	2.00	[20]
Blood products	–	0.35 (0)	158 (0)	0.88	[20]
Total costs (€)	587–92.004 (Range)	17.931 (Mean)	14.039 (Median)	100	–

[†]A unit represents the number of units consumed of a single drug used in a single consecutive period.
[‡]A medical intervention with a mainly therapeutic goal, excluding medication. For example, surgery, physical therapy and urinary catheterization.
[§]A unit defines a typical course of external beam radiotherapy.

Table 3. Distribution of diagnostic costs.

Cost category	Mean units per patient (median)	Mean cost (€) per patient (median)	Diagnostics cost (%)
Nuclear diagnostics	2.57 (2)	624 (445)	30.7
Radiology	7.46 (6)	881 (660)	43.4
Pathology	1.21 (0)	115 (0)	5.7
Endoscopy	0.45 (0)	115 (0)	5.7
Others [†]	3.95 (3)	298 (169)	14.7

[†]Diagnostic procedures not included in the given categories, as for example; ultrasonography, electrocardiography and spirometry.

Resource use & costs

As shown in Table 2, the mean total intramural healthcare resource use per patient during follow-up was €17,931. Table 3 presents the different categories that make up the total diagnostics costs. Radiology (computer tomography, MRI, x-ray) accounted for the largest share, followed by nuclear diagnostics. The patient with the highest cost (€92,004) was treated on the intensive care for 14 days, the total costs incurred during this period were €65,436. The patient with the least total costs (€587) had 18 days of follow-up. 18 patients received one or more courses of docetaxel. A total of 101 courses of RNT were received by 75 patients, EBRT was used 105-times on a total of 60 patients. Inpatient days were the largest cost driver. The share of total costs of imaging & diagnostics, treatment and medication were roughly equal at €6043. Medical treatments were the biggest cost-driver (36%) whereas this only represents 10.95% in our study. With docetaxel's patent having expired in 2010, the majority of drugs used in the treatment of metastatic prostate cancer patients were generic. One patient in our cohort received any of the novel therapeutics described above, (abiraterone acetate) costing €8690 and accounting for 0.36% of total costs of all patients.

A previous cost of illness study of metastatic prostate cancer performed by de Groot *et al.*, showed an average cost of €13,051 in their cohort of 28 patients with a median survival of 24 months [7]. SREs were found to contribute to more than 50% of total costs at an average of €6973 per patient. The base year of the study was 1998, a 15-year difference with our study. With an annual inflation rate in The Netherlands of ~1.5% during this period, the total cost calculated by de Groot and coworkers is roughly comparable with the €17,931 established by our research [26].

Table 4. Skeletal-related events.

SRE specification	Costs and frequency
SRE with inpatient days (n = 53)	
RNT (n = 26):	
– Median total costs, € (range)	2.039 (1.599–11.560)
– RNT (%)	34.0
– Imaging and diagnostics (%)	7.4
– Inpatient days (%)	49.2
EBRT (n = 18):	
– Median total costs, € (range)	9.346 (3.558–30.170)
– EBRT (%)	23.7
– Imaging and diagnostics (%)	5.7
– Inpatient days (%)	59.5
Surgery (n = 10):	
– Median total costs, € (range)	5.762 (3.437–21.920)
– Treatment (%)	20.9
– Imaging and diagnostics (%)	4.6
– Inpatient days (%)	64.9
Others (n = 2):	
– Median total costs (range)	6.307 (6.268–6.347)
– Treatment (%)	4.7
– Laboratory analysis (%)	4.0
– Inpatient days (%)	82.3
SRE without inpatient days (n = 165)	
RNT (n = 75):	
– Median total costs, € (range)	1.159 (1.159–2.852)
– RNT (%)	93.0
– Imaging and diagnostics (%)	5.7
– Daycare treatments (%)	0.5
EBRT (n = 83):	
– Median total costs, € (range)	1.912 (1.912–3.824)
– EBRT (%)	99.5
Others (n = 7):	
– Median total costs, € (range)	200 (132–633)
– Treatments (%)	51.6
– Emergency department visits (%)	17.9
– Imaging and diagnostics (%)	16.5

EBRT: External beam radiotherapy; RNT: Radionuclide therapy; SRE: Skeletal-related event.

Skeletal-related events

As can be seen in Table 4, a total of 218 events were recorded of which 53 included an inpatient stay. In these cases, all resource used during this inpatient stay were incorporated into that specific SRE. For the 165 SREs that did not require an inpatient stay, all resource used on the day the SRE occurred were used to assess the costs of these episodes. Inpatient days were the biggest cost driver of SREs featuring inpatient days and were less costly than SREs that did not require hospitalization. SREs featuring inpatient days and EBRT were costlier than SREs featuring inpatient days and RNT at a median of €2039 and €9346, respectively. This was according to our expectations regarding the more acute nature of the indications for EBRT such as spinal cord compression, whereas RNT is mainly used for nonacute pain relief. Because of these differing indications, a direct comparison between costs of RNT and EBRT cannot be made. Surgery to bone always required inpatient days and was costlier than the RNT equivalent. This can be explained by the more invasive nature of the intervention. Policy aimed at actively preventing SREs could potentially reduce costs. Ideally, prevention of SREs is performed as early in treatment as

possible. However, since only a limited fraction of patients with prostate cancer progresses to metastatic disease early prediction and prevention of SREs might not be feasible.

Conclusion

In our study, the mean intramural cost of illness of prostate cancer, metastatic to bone, was €17,931. Costs of SREs with or without hospitalization, with the former having a particularly significant impact on total costs, differed substantially. SREs that required hospitalization were, at median costs of €2039–9346 depending on care required, more costly than SREs without hospitalization. These SREs had median costs of €200–1912, depending on care required. The impact of SREs on total costs and quality of life could justify policy aimed at actively preventing SREs, for example, with RNT, possibly resulting in better healthcare at a lower cost.

Novel therapeutic treatment options for prostate cancer will dramatically increase costs resulting in a large budget impact on our healthcare budgets [28]. To keep European healthcare affordable, of high quality and available for every patient, proper head-to-head cost–effectiveness studies of all treatment modalities are necessary.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Summary points

- The mean intramural cost of illness of prostate cancer, metastatic to bone, was €17,931.
- Skeletal related are major cost drivers in metastatic prostate cancer.
- Prostate cancer treatment costs have remained constant until the introduction of novel treatment options in the last few years.
- Our analysis can be used as a solid basis for cost–effectiveness studies of new treatment options.

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