



Research Paper

A real-world study assessing the use of bone-targeted agents and their impact on bone metastases in patients with prostate cancer treated in clinical practice in Europe

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ABSTRACT

Background: Bone metastases (BMs) are common in patients with prostate cancer and can lead to skeletal-related events (SREs), which are associated with increased pain and reduced quality of life (QoL). Bone-targeted agents (BTAs), such as zoledronic acid and denosumab, reduce the incidence of SREs and delay progression of bone pain.

Methods: We evaluated the management of BMs and pain in six European countries (Belgium, France, Germany, Italy, Spain and the UK) using the Adelphi Prostate Cancer Disease Specific Programme. Patient-reported outcomes (PROs) were used to assess the impact of BMs on pain and QoL.

Results: In total, 358 physicians completed Patient Record Forms, of whom 246 were oncologists and 112 were urologists. Data were collected on 3667 patients with prostate cancer, including 1971 with BMs and 551 with metastases at sites other than bone (non-BMs). PROs were assessed in 573 patients with BMs and 220 with non-BMs. Most patients with BMs (74%) received a BTA and 53% received treatment within 3 months of BM diagnosis. Patients treated by oncologists were more likely than those treated by urologists to receive a BTA (78% vs. 60%) and to have treatment initiated within 3 months of BM diagnosis (56% vs. 43%). For patients who did not receive a BTA, the main reasons for not treating were very recent BM diagnosis and a perceived low risk of bone complications. Data collected by physicians showed that most patients with BMs (97%) were taking analgesics, with 30% receiving strong opioids. Despite this, 70% were currently experiencing bone pain and 28% were experiencing moderate to severe pain. PRO pain measures showed that 70% of patients with BMs were experiencing moderate to extreme pain, suggesting a disparity between pain levels reported by physicians and by patients.

Conclusions: Although most patients with BMs receive a BTA, there remain a proportion of patients who are not receiving adequate treatment to prevent SREs or manage pain. Oncologists are more likely to adhere to clinical guidelines than urologists for the prescription of BTAs. Bone pain is common and undertreated. Increasing awareness of SRE prevention and bone pain management might improve patient care.

Abbreviations: AAP, abiraterone acetate with prednisone/prednisolone; AQA, Analgesic Quantification Algorithm; BMs, bone metastases; BPI, Brief Pain Inventory; BTA, bone-targeted agent; DSP, Disease Specific Programme; EQ-5D-3L, 5-dimension 3-level EuroQol questionnaire; EU5, France, Germany, Italy, Spain and the UK; FACT-P, Functional Assessment of Cancer Therapy – Prostate questionnaire; mCRPC, metastatic castration-resistant prostate cancer; ONJ, osteonecrosis of the jaw; PRF, Patient Record Form; PRO, patient-reported outcome; PSCF, Patient Self-Completion Form; QoL, quality of life; SRE, skeletal-related event

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1. Introduction

Bone is a common site of metastasis in patients with prostate cancer; up to 90% of those with advanced disease have bone metastases (BMs) [1,2]. BMs often cause pain and lead to bone complications such as skeletal-related events (SREs), commonly defined as radiation or surgery to bone, pathologic fracture, spinal cord compression or hypercalcemia of malignancy [3]. SREs are associated with increased pain, reduced quality of life (QoL) and poor survival [4–6]. Without treatment, the time to first SRE in patients with prostate cancer is approximately 10 months [7]; moreover, patients may experience several SREs during the course of their disease [8]. Besides having a significant impact on patients' pain and QoL, bone complications are additionally associated with high healthcare resource utilization and costs [9–12].

The management of patients with BMs focuses on pain palliation and prevention of SREs [13]. The anti-resorptive bone-targeted agents (BTAs) zoledronic acid (a bisphosphonate) and denosumab (a receptor activator of nuclear factor kappa B ligand inhibitor) delay the time to first and subsequent SREs in patients with prostate cancer and BMs [7,14,15]. In a randomized phase 3 clinical trial, in the absence of treatment to prevent SREs, almost half of those with prostate cancer and BMs developed an SRE; treatment with zoledronic acid provided a relative risk reduction of 36% in this study [7]. Denosumab, a more potent BTA, can delay time to first SRE by an additional 18% when compared with zoledronic acid [14]. Both agents are also effective in reducing pain levels in patients with moderate to severe pain, however, denosumab is also more effective than zoledronic acid at delaying the onset of pain or progression of pain severity and delaying the requirement for strong opioids [14,16]. For the prevention of SREs, zoledronic acid is recommended as a 4 mg intravenous infusion given every 3–4 weeks [17]. Denosumab is administered as a 120 mg subcutaneous injection every 4 weeks [18]. Both therapies are recommended in patients with BMs whether they are symptomatic or not [3].

Several agents have recently been approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), including abiraterone acetate [19], enzalutamide [20] and radium-223 dichloride [21]. These agents have been shown to improve survival and pain palliation, and reduce the incidence of SREs when given alongside standard of care in patients with mCRPC [1,22–24].

Currently, few data exist on the utilization pattern of BTAs and the impact of BMs in real-world practice. This study aimed to describe the real-world BTA treatment pattern across Europe in patients with prostate cancer and BMs, including reasons guiding treatment decisions, the timing of treatment following diagnosis of BMs, and how BTAs are being combined with recently approved therapies for mCRPC. Furthermore, by using validated instruments to collect patient-reported outcomes (PROs), we aimed to understand the impact of BMs on patients' experiences of pain and QoL.

2. Methods

2.1. Physicians and patients

Data were collected using the Adelphi Prostate Cancer Disease Specific Programme (DSP), an independent, multi-country, cross-sectional survey. Details of the full DSP methodology have previously been described [25–27]. The Adelphi DSPs do not have any academic or pharmaceutical affiliations. The DSP fieldwork materials are designed by, and the DSP data are owned by, Adelphi Real World. Pharmaceutical companies may choose to subscribe to the data as an independent data source; however, such companies will never own the data themselves. No employees of Adelphi Real World have any affiliations with pharmaceutical companies or academic institutions. The study was conducted between February and April 2015 in six European countries: Belgium, France, Germany, Italy, Spain and the UK. Physicians were selected from publicly available lists of healthcare professionals and

approached by field investigators to take part in this study. Physicians were financially compensated for their participation in the study at a fair market rate for their time involved. The study aimed to gain participation from 365 physicians (75 in each of France, Germany, Italy and Spain, 50 in the UK and 15 in Belgium). To be eligible for inclusion in the study, physicians must: have qualified as an oncologist or urologist between 1978 and 2011; be seeing a minimum of five patients with prostate cancer per week; and be personally responsible for prescribing decisions for patients with prostate cancer.

Participating physicians reported data on their next eight consecutive adult patients (aged ≥ 18 years) who had diagnoses of prostate cancer and who were not currently enrolled in a clinical trial. Physicians also collected data from a further two patients with the additional criterion of a diagnosis of BMs. Physicians captured data using a detailed Patient Record Form (PRF) (Supplementary material) for each of the 10 eligible patients; data were included regardless of the number of patients physicians had completed a PRF for. All patients for whom a physician completed a PRF were invited to complete a Patient Self-Completion Form (PSCF). Informed consent was obtained from patients before they completed this form. Patient involvement was voluntary.

2.2. Study variables

In this cross-sectional survey, data on patient baseline characteristics were extracted from all the PRFs. For patients with BMs the following data were also collected from the PRFs: presence of bone pain (at initial diagnosis of BMs and at time of data collection – pain was classified as mild, moderate or severe according to the Brief Pain Inventory [BPI]) [28]; analgesic use (measured using the modified Analgesic Quantification Algorithm [AQA] [29], which scored analgesic use from 0 for no analgesic to 7 for strong opioid [> 600 mg/day oral morphine equivalent]); whether a BTA was prescribed; time from diagnosis of BMs to BTA treatment initiation; which BTA was prescribed; dose of BTA; discontinuation of a BTA; and switching from one BTA to another.

Physicians were asked to rank up to three reasons from a predefined list (see PRF, Supplementary material) on: why patients were treated or not treated with a BTA; reasons for choosing one BTA over another; reasons for a change in BTA treatment dose; reasons for discontinuing BTA treatment or switching from one BTA to another. To understand whether BTA treatment was initiated immediately after BM diagnosis or not, a cutoff period of 3 months from diagnosis of BMs to treatment initiation was used. Physicians were asked to rank their reasons for initiating BTA treatment early (≤ 3 months following diagnosis of BMs) or for delaying treatment (> 3 months after diagnosis of BMs).

The PSCFs incorporated three instruments to facilitate the collection of PRO data on pain and QoL from patients with BMs and from those with metastases located at sites other than the bone (non-BMs), which included the BPI [28], the 5-dimension 3-level EuroQol questionnaire (EQ-5D-3L) [30] and the Functional Assessment of Cancer Therapy – Prostate questionnaire (FACT-P) [31].

2.3. Statistical analysis

Patient characteristics and outcome variables were analyzed using descriptive statistics. Frequencies (%) were calculated for categorical or ordinal variables, and medians (interquartile ranges) were calculated for continuous variables. PROs (EQ-5D-3L, BPI and FACT-P) for patients with BMs were compared with those with non-BMs using univariate Mann–Whitney tests and multivariate linear regression analysis. Regression analysis included covariates for presence of BMs, age, smoking status, time since diagnosis of prostate cancer and number of additional underlying comorbidities. Standard errors in regressions were adjusted to allow for intragroup correlation within reporting physician, relaxing the usual assumption that observations are

independent.

3. Results

3.1. Physician characteristics

In total, 358 physicians (comprising 79 in Spain, 76 in Germany, 76 in Italy, 69 in France, 42 in the UK and 16 in Belgium) provided data via PRFs. Of these, 246 (69%) were oncologists and 112 (31%) were urologists. Most physicians worked for a public healthcare provider (82%; $n = 294$), were based in a university or teaching hospital (55%; $n = 177$) and had less than 15 years' experience (53%; $n = 188$). Participating physicians were personally responsible for the care of a mean number of 76 patients with prostate cancer at the time of the study (Supplementary Table 1).

3.2. Patient characteristics

In total, physician-reported data were collected for 3667 patients with prostate cancer, of whom 2614 (71%) were treated by oncologists and 1053 (29%) by urologists. Patient demographics and clinical characteristics are presented in Supplementary Table 2. Among these patients there were 2522 patients with metastatic (stage IV) cancer, comprising 1971 patients with BMs (1319 patients had BMs only) and 551 with non-BMs. Of those with BMs, 1533 (78%) were treated by an oncologist and 438 (22%) were treated by a urologist. The proportions of patients with prostate cancer and BMs who were treated by a urologist were similar across France, Germany, Italy and Spain (21–26% of patients), but were lower in the UK (9%) and higher in Belgium (48%). Approximately one-third of patients with BMs were receiving a recently approved anti-tumor therapy; 23% ($n = 449$) received abiraterone acetate, 8% ($n = 148$) enzalutamide and 1% ($n = 10$) radium-223.

3.3. BTA treatment patterns

Most patients with BMs were receiving a BTA (74%; $n = 1454$) and 53% ($n = 1048$) had BTA treatment initiated during the 3 months following diagnosis of BMs (early initiation). Among patients with BMs who were treated by an oncologist ($n = 1533$), 78% ($n = 1191$) received a BTA with 56% ($n = 861$) of patients initiating treatment early. Of patients with BMs who were treated by a urologist ($n = 438$), 60% ($n = 263$) received a BTA and 43% ($n = 187$) had treatment initiated early.

Across all physicians, the main reasons for initiating BTA treatment were bone pain (40% of patients; $n = 422$) and a perceived high risk of bone complications (28%; $n = 297$). Data were broadly similar across the six countries studied (Table 1). For patients who had a delay in the initiation of BTA treatment (> 3 months from BMs; $n = 406$), the main reasons were: a perceived low risk of bone complications (22%; $n = 89$); waiting to see if there was a response to antineoplastic treatment (14%; $n = 56$); and a very recent diagnosis of BMs (so not had time to initiate) (13%; $n = 54$). There were some differences across the six countries studied (Table 2). Of the 517 patients who did not receive a BTA, the top two reasons for not prescribing were very recent

diagnosis of BMs (so not had time to initiate) (35%; $n = 182$) and a perceived low risk of bone complications (22%; $n = 115$). Very few physicians implicated the cost impact on the patient, hospital or healthcare system in their decision whether to treat with a BTA (4%; $n = 21$).

Of those treated with BTAs, most patients received zoledronic acid (56%; $n = 820$) or denosumab (41%; $n = 601$) as a first-line BTA (Fig. 1). The main reasons physicians gave for choosing zoledronic acid were clinical efficacy in delaying the onset of SREs (35%; $n = 285$) and long-term safety (16%; $n = 131$). Among physicians choosing to use denosumab as the first BTA, the main reasons were: clinical efficacy in delaying SREs (34%; $n = 207$); lower risk of renal toxicity (13%; $n = 80$); and reducing the risk of SREs (13%; $n = 78$). Most patients prescribed zoledronic acid were receiving it every 3–4 weeks (98%; $n = 800$), and most patients prescribed denosumab were receiving it every 4 weeks (98%; $n = 586$). Only 6% ($n = 45$) of patients receiving zoledronic acid and 2% ($n = 9$) of those receiving denosumab required a change in dose frequency. Discontinuation was more common in patients receiving zoledronic acid (20%; $n = 165$) than in those receiving denosumab (5%; $n = 28$). Of those discontinuing zoledronic acid, 27% ($n = 45$) switched to another BTA, with most (91%; $n = 41$) receiving denosumab as their second BTA. The main reasons for switching from zoledronic acid to another BTA were disease progression of primary tumor ($n = 12$) and decreased renal function ($n = 10$). Among patients discontinuing denosumab, 11% ($n = 3$) switched to another BTA. The main reason leading to discontinuation of both zoledronic acid and denosumab among those who did not then receive a second BTA ($n = 120$) was patients ending the treatment as planned (25%; $n = 30$ for zoledronic acid; 16%; $n = 4$ for denosumab).

Most patients (76%; $n = 341$) with BMs receiving a recently approved treatment for mCRPC were concurrently treated with a BTA (Table 3). Among patients treated with abiraterone acetate, a higher proportion of those treated by an oncologist received concurrent BTA treatment compared with those treated by a urologist. However, the reverse was observed among patients receiving enzalutamide (Table 3).

3.4. Patient pain and analgesic use

At the time of BM diagnosis, 73% ($n = 1437$) of patients were experiencing bone pain, which was estimated to be mild in 34% ($n = 663$) of patients, moderate in 31% ($n = 605$) and severe in 9% ($n = 169$), as reported by their physician. Also, at this time, 9% ($n = 181$) of patients with BMs had already experienced a bone complication. Physicians reported that at the time of data collection, 70% of patients with BMs ($n = 1372$) were currently experiencing bone pain, which was mild in 41% ($n = 813$) of patients, moderate in 25% ($n = 488$) and severe in 4% ($n = 71$). Almost all of these patients, 97% ($n = 1325$), were taking analgesics to manage pain; 30% ($n = 392$) were receiving strong opioids as classified by the AQA scale (Table 4). Of the 1325 patients with BMs taking analgesic drugs, 70% were treated with BTAs. A higher proportion of patients who were receiving a BTA were also receiving strong analgesics (32%; $n = 303$) compared with those not receiving a BTA (23%; $n = 89$).

Table 1

Top four reasons for physicians deciding to initiate a bone-targeted agent treatment early (≤ 3 months following diagnosis of BMs).

<i>n</i> (%)	Overall (<i>n</i> = 1048)	Belgium (<i>n</i> = 85)	France (<i>n</i> = 196)	Germany (<i>n</i> = 302)	Italy (<i>n</i> = 161)	Spain (<i>n</i> = 197)	UK (<i>n</i> = 107)
Bone pain	422 (40)	28 (33)	58 (30)	134 (44)	88 (55)	70 (36)	44 (41)
High risk of bone complications	297 (28)	31 (36)	65 (33)	89 (29)	23 (14)	68 (35)	21 (20)
Number of BMs	114 (11)	11 (13)	27 (14)	27 (9)	21 (13)	17 (9)	11 (10)
Location of BMs	83 (8)	8 (9)	23 (12)	17 (6)	15 (9)	18 (9)	2 (2)

Physicians were asked to rank up to three reasons from a predefined list. High risk of bone complications was determined as per the treating physician's clinical opinion.

BM, bone metastases.

Table 2
Top four reasons for physicians delaying the initiation of bone-targeted agent treatment (> 3 months following diagnosis of BMs).

n (%)	Overall (n = 406)	Belgium (n = 24)	France (n = 89)	Germany (n = 52)	Italy (n = 45)	Spain (n = 87)	UK (n = 109)
Low risk of bone complications	89 (22)	6 (25)	15 (17)	17 (33)	9 (20)	19 (22)	23 (21)
Wait until I know there is an absence of response to the first line of antineoplastic treatment	56 (14)	6 (25)	16 (18)	3 (6)	0 (0)	16 (18)	15 (14)
Very recent diagnosis of BMs, so not had time to initiate	54 (13)	0 (0)	9 (10)	6 (12)	8 (18)	13 (15)	18 (17)
Risk of ONJ	38 (9)	4 (17)	19 (21)	7 (13)	5 (11)	3 (3)	0 (0)

Physicians were asked to rank up to three reasons from a predefined list. High risk of bone complications was determined as per the treating physician's clinical opinion.

BM, bone metastases; ONJ, osteonecrosis of the jaw.

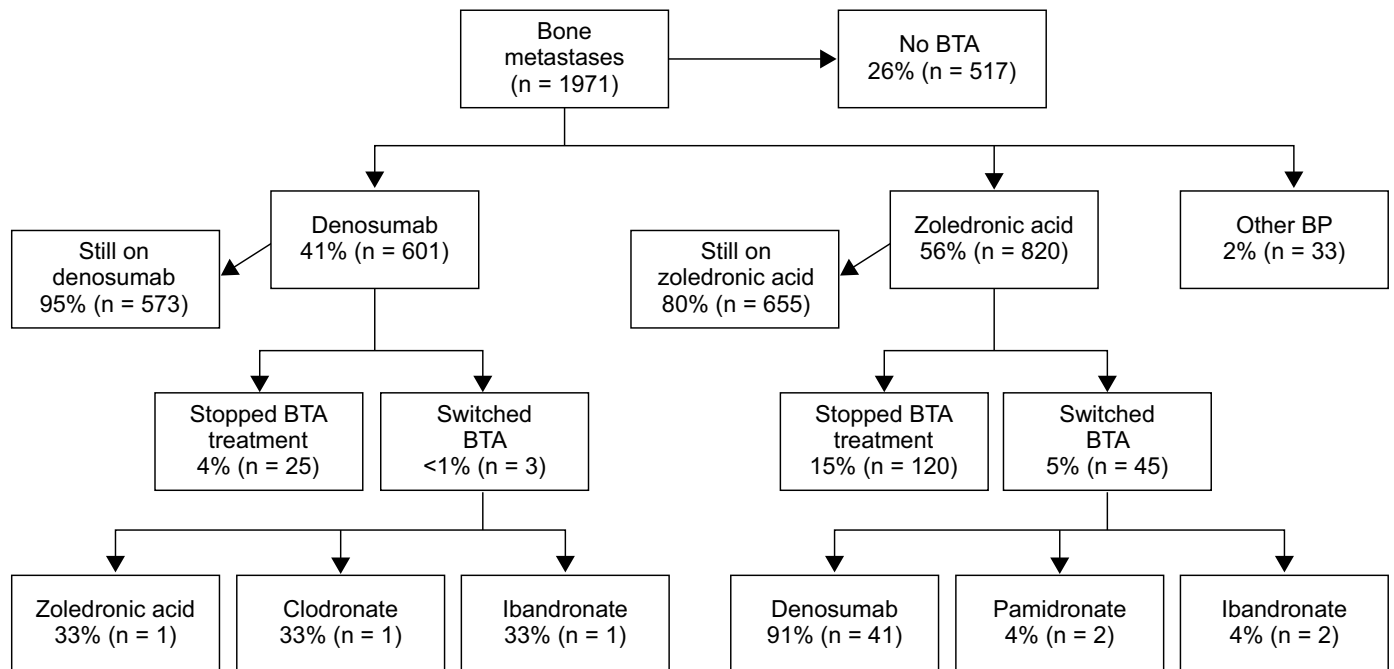


Fig. 1. Bone-targeted agent treatment patterns for patients with prostate cancer and bone metastases. BP, bisphosphonate; BTA, bone-targeted agent.

3.5. Patient-reported outcomes

Of the 1971 patients with BMs, 29% completed a PSCF (n = 573) and of the 551 patients with non-BMs, 40% completed a PSCF (n = 220). Demographic and clinical characteristics of patients who completed a PSCF are shown in Supplementary Table 3. Among those completing a PSCF, the main metastatic sites in these patients with non-BMs were lymph nodes (78%; n = 171), lung (27%; n = 60) and liver (13%; n = 28). Results from the BPI and the EQ-5D-3L showed that patients with BMs reported higher worst and average pain scores than those with non-BMs, and that 70% of patients with BMs, compared with 46% of patients with non-BMs, reported experiencing moderate or extreme pain (p < 0.001) (Table 5). Patients with BMs reported significantly lower well-being scores in the FACT-P overall index and for most FACT-P domain scores than patients with non-BMs (Fig. 2).

Table 3
Concurrent treatment with bone-targeted agents and recently approved anti-cancer therapeutics for patients with prostate cancer and BMs.

Concurrent BTA	All patients			Patients treated by an oncologist			Patients treated by a urologist		
	AA (n = 449)	ENZ (n = 148)	Ra-223 (n = 10)	AA (n = 387)	ENZ (n = 115)	Ra-223 (n = 5)	AA (n = 62)	ENZ (n = 33)	Ra-223 (n = 5)
Any BTA, n (%)	341 (76)	98 (66)	7 (70)	301 (78)	71 (62)	4 (80)	40 (65)	27 (82)	3 (60)
Denosumab, n (%)	175 (39)	37 (25)	3 (30)	152 (39)	23 (20)	1 (20)	23 (37)	14 (42)	2 (40)
Zoledronic acid, n (%)	159 (35)	61 (41)	3 (30)	142 (37)	48 (42)	2 (40)	17 (27)	13 (39)	1 (20)

AA, abiraterone acetate; BMs, bone metastases; BTA, bone-targeted agent; ENZ, enzalutamide; Ra-223, radium-223.

Multivariate linear regression analysis, adjusting for confounding factors (age, smoking status, time since diagnosis of prostate cancer and number of additional underlying conditions), confirmed that patients with BMs reported a poorer QoL, poorer overall health, worse function and more pain than patients with non-BMs (Fig. 2).

4. Discussion

This multi-country, cross-sectional study revealed important data on real-world BTA treatment patterns and PROs in patients with metastatic prostate cancer. Encouragingly, most patients (74%) with BMs were treated with BTAs. This figure is substantially higher than those previously reported [13,32]. This may reflect selection bias, because physicians agreeing to participate in this study were likely to be aware of the high prevalence of BMs and SREs in this patient population.

Table 4
Use of analgesic medications in patients with prostate cancer and BMs currently experiencing bone pain.

Patients currently experiencing mild, moderate or severe bone pain							
AQA score, n (%)	Overall (n = 1372)	Belgium (n = 82)	France (n = 263)	Germany (n = 279)	Italy (n = 204)	Spain (n = 271)	UK (n = 273)
0 = no analgesic	47 (3)	8 (10)	3 (1)	20 (7)	7 (3)	2 (1)	7 (3)
1 = non-opioid analgesics	481 (35)	40 (49)	92 (35)	100 (36)	60 (29)	112 (41)	77 (28)
2 = weak opioids ^a	452 (33)	16 (20)	91 (35)	81 (29)	53 (26)	94 (35)	117 (43)
3 = strong opioids (≤ 75 mg OME/day)	277 (20)	10 (12)	56 (21)	54 (19)	70 (34)	37 (14)	50 (18)
4 = strong opioids (> 75–150 mg OME/day)	87 (6)	6 (7)	17 (6)	17 (6)	10 (5)	18 (7)	19 (7)
5 = strong opioids (> 150–300 mg OME/day)	23 (2)	1 (1)	4 (2)	6 (2)	4 (2)	5 (2)	3 (1)
6 = strong opioids (> 300–600 mg OME/day)	4 (< 1)	0 (0)	0 (0)	1 (< 1)	0 (0)	3 (1)	0 (0)
7 = strong opioids (> 600 mg OME/day)	1 (< 1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients currently experiencing moderate to severe bone pain							
AQA score, n (%)	Overall (n = 559)	Belgium (n = 35)	France (n = 113)	Germany (n = 109)	Italy (n = 114)	Spain (n = 97)	UK (n = 91)
0 = no analgesic	4 (1)	2 (6)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
1 = non-opioid analgesics	82 (15)	9 (26)	17 (15)	12 (11)	17 (15)	21 (22)	6 (7)
2 = weak opioids ^a	185 (33)	7 (20)	41 (36)	42 (39)	28 (25)	33 (34)	34 (37)
3 = strong opioids (≤ 75 mg OME/day)	195 (35)	10 (29)	37 (33)	40 (37)	54 (47)	22 (23)	32 (35)
4 = strong opioids (> 75–150 mg OME/day)	71 (13)	5 (14)	14 (12)	9 (8)	10 (9)	17 (18)	16 (18)
5 = strong opioids (> 150–300 mg OME/day)	19 (3)	1 (3)	4 (4)	5 (5)	3 (3)	3 (3)	3 (3)
6 = strong opioids (> 300–600 mg OME/day)	2 (< 1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
7 = strong opioids (> 600 mg OME/day)	1 (< 1)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

^a For example, codeine and tramadol. AQA, Analgesic Quantification Algorithm; BMs, bone metastases; OME, oral morphine equivalent.

Therefore, these results may not be directly comparable to secondary database studies. Alternatively, the high BTA treatment rate reported here may reflect improvements in the real-world management of bone disease. A similarly high rate of BTA treatment was reported in a recent chart audit of BTA use in five European countries (EU5; France, Germany, Italy, Spain and the UK), in which 68% of patients with BMs from solid tumors received a BTA [33]. Further improvements in the treatment of individuals with BMs might be expected considering updates to guidelines, such as the European Society for Medical Oncology clinical practice guidelines, that occurred just before this study was conducted, which recommend initiating BTAs as soon as BMs are diagnosed [3].

Interestingly, patients treated by an oncologist were more likely to receive a BTA and to have treatment initiated early than those treated by a urologist. Low rates of BTA treatment and long delays between diagnosis of BMs and treatment initiation have previously been reported in a chart audit of BTA use in patients with prostate cancer and BMs treated in urology centers in the USA [34]. These results suggest a notable gap between guidelines and current clinical practice, particularly among urologists. Given that early BTA initiation is associated with positive clinical outcomes [32], physician education on the importance of BTA treatment and the timing of BTA initiation is required to ensure optimum patient care in the real-world setting.

All patients with BMs are at risk of developing bone complications [35]; however, almost one-half of patients had either a delay in receiving a BTA or received no BTA treatment. Aside from a very recent diagnosis of BMs, a low perceived risk of bone complications and wanting to wait until first-line antineoplastic treatment had failed before initiating BTA treatment were frequently cited as main reasons for delaying treatment or not treating patients with BTAs. In this study, bone complication risk was determined by the investigator using their clinical judgment; indeed, there are no clinically validated guidelines that can be used to assess SRE risk accurately [3]. This study shows that perceived SRE risk influences physicians' treatment decisions, and that increased awareness of current guidelines is required so that all patients with BMs receive appropriate treatment. The role of BTAs in the management of advanced prostate cancer may require further clarification following the approval of novel therapies for mCRPC

(abiraterone acetate, enzalutamide and radium-223), which have shown efficacy in delaying SREs and improving pain palliation [1,22,23]. Although data are limited, *post-hoc* analysis of phase 3 studies of these therapies show that combination treatment of novel therapies with BTAs may provide patients with additional benefits in terms of reducing SREs and increasing overall survival [1,36,37]. A recent randomized phase 3 trial (ERA 223) of concurrent abiraterone acetate with prednisone/prednisolone (AAP) plus radium-223 versus AAP plus placebo in men with asymptomatic or mildly symptomatic mCRPC and BMs, investigated symptomatic skeletal event-free survival. The study showed an increased number of fractures and deaths in the AAP plus radium-223 group versus the placebo-controlled group leading to a protocol amendment allowing the initiation of BTAs. At baseline, approximately 40% of patients were receiving BTAs and, importantly, the use of BTAs was associated with lower fracture rates in both treatment groups; highlighting the importance of BTAs for the management of bone health in patients with mCRPC and BMs [38]. Data from this real-world study show that, in current clinical practice, BTAs are being used in combination with novel mCRPC therapies and, furthermore, that the pattern of BTA use was not altered in patients receiving emerging therapies. It is unlikely that the introduction of novel therapies into clinical practice explains why a large proportion of patients either did not receive a BTA or had a delay in treatment initiation. Improved awareness among physicians of the benefits of BTA therapy, whether in combination with emerging therapies for mCRPC or with traditional therapies for prostate cancer, may help to ensure that treatment to prevent SREs is prioritized.

Most patients in this study (73%) had bone pain at diagnosis of BMs and bone pain was a main reason for initiating BTA treatment. The recent EU5 chart audit (discussed earlier) identified differences in the detection of BMs across the countries studied. In patients with solid tumors, BMs were diagnosed in more than one-third as a result of bone pain. This was not the case in Germany, where BMs were diagnosed in 20% of patients as a result of bone pain; routine screening during follow-up was the main method of BM detection (41%) [33]. This has consequences for the management of BMs and bone pain because evidence suggests that early detection and treatment of BMs, before the

Table 5
Univariate Mann–Whitney tests comparing patient-reported outcomes in patients with BMs and those with non-BMs.

	BMs	Non-BMs	p value
BPI, mean (95% CI)	n = 570	n = 220	
Worst	3.6 (3.5–3.8)	2.6 (2.3–2.9)	<0.001
Average	2.8 (2.7–3.0)	2.0 (1.7–2.2)	<0.001
Interference	3.2 (3.0–3.4)	2.4 (2.1–2.7)	<0.001
EQ-5D-3L	n = 570	n = 215	
EQ-5D overall index score, mean (95% CI)	0.65 (0.62–0.68)	0.81 (0.78–0.84)	<0.001
Mobility, n (%)	n = 572	n = 217	<0.001
No problems	286 (50)	147 (68)	
Some problems	270 (47)	67 (31)	
Confined to bed	16 (3)	3 (1)	
Self-care, n (%)	n = 572	n = 216	0.007
No problems	368 (64)	160 (74)	
Some problems	180 (32)	52 (24)	
Unable to wash or dress self	24 (4)	4 (2)	
Usual care activities, n (%)	n = 571	n = 217	<0.001
No problems	253 (44)	142 (65)	
Some problems	266 (47)	71 (33)	
Unable to perform normal activities	52 (9)	4 (2)	
Pain/discomfort, n (%)	n = 572	n = 216	<0.001
No pain	169 (30)	116 (54)	
Moderate pain	358 (63)	96 (44)	
Extreme pain	45 (8)	4 (2)	
Anxiety/depression, n (%)	n = 573	n = 217	0.001
No anxiety/depression	226 (39)	111 (51)	
Moderate anxiety/depression	303 (53)	98 (45)	
Extreme anxiety/depression	44 (8)	8 (4)	
EQ-VAS	n = 567	n = 218	<0.001
EQ-VAS overall index score, mean (95% CI)	59.6 (57.9–61.2)	70.1 (67.5–72.7)	
FACT-P, mean (95% CI)	n = 573	n = 219	
Physical well-being	18.5 (18.0–18.9)	20.7 (20.0–21.4)	<0.001
Social well-being	17.1 (16.6–17.6)	16.6 (15.9–17.4)	0.160
Emotional well-being	13.8 (13.4–14.2)	15.0 (14.4–15.7)	0.001
Functional well-being	12.7 (12.2–13.2)	13.9 (13.1–14.8)	0.005
Prostate cancer subscale	27.9 (27.3–28.5)	31.2 (30.2–32.1)	<0.001
Trial outcome index	59.0 (57.7–60.3)	65.6 (63.4–67.9)	<0.001
FACT-G	62.0 (60.6–63.3)	66.2 (63.7–68.6)	0.003
FACT-P	89.9 (88.0–91.7)	97.2 (93.9–100.5)	<0.001

BMs, bone metastases; BPI, Brief Pain Inventory; CI, confidence interval; EQ-5D-3L, 5-dimensions 3-level EuroQol questionnaire; EQ-VAS, EuroQol visual analog scale; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy – Prostate; non-BMs, metastases at sites other than bone.

onset of pain, could prevent or delay pain and provide protection from SREs [33,39,40]. Improved detection methods and guidelines for the diagnosis of BMs are required to support early diagnosis and treatment.

Most patients in this study (70%) were reported to be experiencing pain by their physicians. Patients with BMs reported significantly worse pain, pain interference and health status than those with non-BMs. Almost all individuals (97%) who were experiencing bone pain were taking analgesics; however, approximately half of all patients with moderate to severe pain were not receiving strong opioids. In line with previous data [41–43], these results suggest under-treatment in the management of pain in patients with advanced cancer. Furthermore, the extent of under-treatment is likely to be even higher given that PROs showed that 71% of patients with BMs were experiencing moderate or extreme pain, in contrast to the 29% that physicians reported to be experiencing this level of pain. This highlights a disparity between

physicians' perception of pain and patients' experience of pain. It is also possible that patients do not report pain to physicians, or that the current methods employed by physicians to assess patients' pain are insufficient. Time without moderate or severe pain has been associated with increased functionality and QoL [44], thus underlying the importance of appropriate pain management. Although several guidelines on the management of cancer pain are available [40,45,46], further physician education may be required to raise awareness of patient pain and to ensure that current guidelines are reflected in real-world practice. Given the high patient burden associated with BMs, there is much value in treatment that may delay or prevent BMs. Data in patients with early stage prostate cancer suggest that BTA treatment could delay the development of BMs [47]. Further studies assessing the role of BTAs in early prostate cancer are warranted.

This study has some limitations. First, data were self-reported by physicians and patients and, as such, no measures were clinically verified. Secondly, results may be biased by physician selection, because physicians who are more aware of the issues related to BMs and SREs may be more likely to participate in the study. The study design does, however, benefit from the fact that the Adelphi DSP is a recognized and consistent methodology that can be applied across multiple countries, enabling valid comparisons to be made. Additionally, because no tests or investigations were undertaken as part of the research, treatment decisions were unbiased and can be assumed to reflect real-world practice. Furthermore, in contrast to clinical trials in which strict inclusion criteria limit the patient population under study, DSPs provide data on treatment decisions in the wider patient population encountered in real-world clinical practice [25].

5. Conclusions

Our data suggest that under-treatment in the management of pain in patients with prostate cancer and BMs is common and may, in part, reflect a disparity between physician-recorded pain and patients' experience of pain. A proportion of patients did not receive a BTA and delays in treatment initiation were common. Patients treated by a urologist were more likely than those treated by an oncologist not to receive BTA treatment or to have a delay in BTA initiation. Common reasons for not treating or delaying treatment were a low perceived risk of complications or to initiate BTAs only once antineoplastic therapies had failed. There remains an educational need to improve understanding of the role of BTAs and the importance of early treatment following BMs diagnosis, particularly among urologists. This is especially important in light of the emergence of novel therapies for mCRPC.

Declarations

Ethics approval and consent to participate

The DSP adheres to Good Pharmacoepidemiology Practice (GPP) and the European Pharmaceutical Market Research Association (EphMRA) Code of Conduct. The EphMRA Code of Conduct states that research that meets the definition relating to market or consumer behavior of the sort that pharmaceutical companies routinely commission, whether involving healthcare professionals, patients, carers or members of the public, does not require Clinical Research Ethics Committee or Independent Review Board approval.

All data collection from the DSP is undertaken through third-party fieldwork agencies, ensuring that the identity of healthcare professionals and patients is not known to Adelphi or any subscribers to the data. Furthermore, data are analyzed and provided to subscribers in an aggregated format. The EphMRA Code of Conduct states that once all identifiers linking data to the subject have been removed, it is anonymized and is no longer personal data and, therefore, not covered by the European Union Data Protection Directive. Patients who

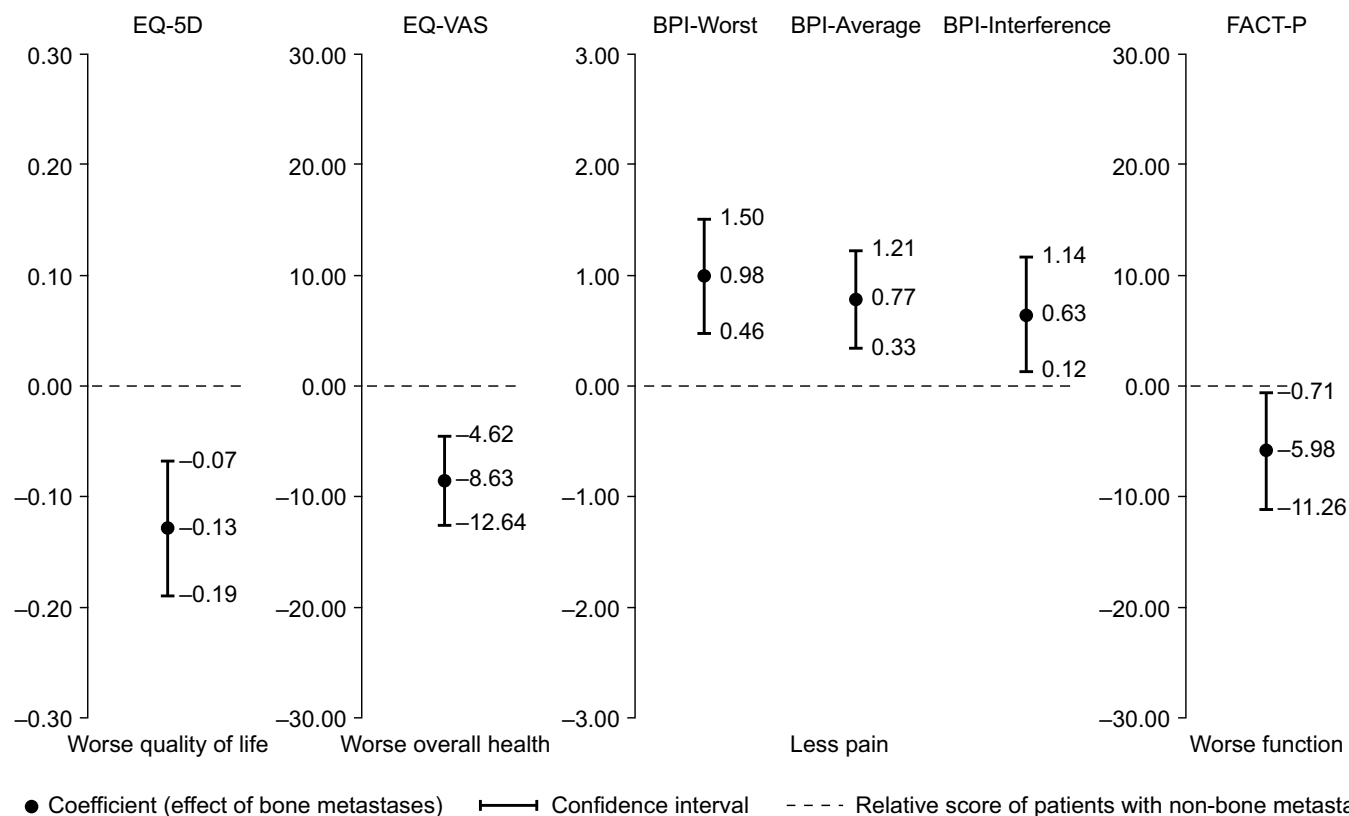


Fig. 2. Multivariate linear regression analyses of patient-reported outcomes for patients with bone metastases compared with those with non-bone metastases. Error bars show 95% confidence intervals. BMs, bone metastases; BPI, Brief Pain Inventory; EQ-5D, 5-dimensions 3-level EuroQol questionnaire; EQ-VAS, EuroQol visual analog scale; FACT-P, Functional Assessment of Cancer Therapy – Prostate.

participated in the study provided consent for their self-completion data to be used by selecting a check box on the PSCF and by returning the PSCF for use. Physicians provided written consent for their data to be used via the online survey they completed. Physicians were paid a fair market rate for their time involved in completing the survey.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from Adelphi Real World, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Adelphi Real World.

Conflicts of interest

Jean-Jacques Body has received speaker and consulting fees from Amgen.

Roger von Moos has received research grants from Amgen and Bayer, has consulted for Amgen, Bayer, GlaxoSmithKline, Roche, BMS, MSD and Novartis, and has received honoraria from Amgen, Bayer and GlaxoSmithKline.

Alex Rider and Pamela Hallworth are employees of Adelphi Real World.

Debajyoti Bhowmik, Guy Hechmati and Yi Qian are employees of Amgen and own stock.

Francesca Gatta was an employee of Amgen at the time the study was conducted.

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Authors' contributions

J.-J.B., R. v M., G.H. and Y.Q. conceived and designed the study, interpreted data and critically revised the manuscript. A.R. and P.H. acquired and analyzed data, and critically revised the manuscript. D.B. and F.G. interpreted data and critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.100212.

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