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Vertebroplasty in patients with prostate cancer raises skeletal morbidity characterized by bone loss

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Abstract

Background: Prostate cancer (PCa) is associated with high skeletal morbidity especially vertebral compression fractures (VCF) occurring on bone loss. We aimed to characterize benign (bVCF) versus malignant VCF (mVCF), in PCa patients who underwent vertebroplasty, and describe respective populations. **Methods:** An observational retrospective study was conducted in two French cancer centers. Characterization of VCF was made using a composite criterion (bone scan, CT scan, MRI +/- bone biopsy). **Results:** From 2008 to 2016, 100 patients, mean age 73.5 (45-94) and 128 VCFs were reported: 66 (52%) mVCF and 62 (48%) bVCF. Among bVCF, 17 (27%) occured in bone metastatic patients. Among mVCF, 28 (42%) of bone metastases were purely osteolytic and 38 (58%) with osteolytic component. Regarding bVCF, continuous androgen deprivation therapy and high doses of corticosteroids (> 6 months, ≥7.5 mg/day prednisone equivalent) were given in respectively 85% and 24% of cases. Dual X-ray Absorptiometry was performed in 13% of pts. Vitamin D supplementation was prescribed in 38% of patients. **Conclusion:** These data suggest the necessary prevention of bVCF even in patients with bone metastases with consequences on patient

management, while studies for bone targeted agents approval used skeletal related events with no definition of the cause, i.e. benign or malignant. Occurrence of bVCF is a rising concern since these pts are experiencing longer survival. Malignant VCF were mostly with osteolytic component, which constitutes one feature of rising dedifferentiated phenotype. Vertebroplasty may play a major role in these newly defined populations.

Key words: prostate cancer – bone - osteoporosis – skeletal related events – vertebral compression fracture

Introduction

Prostate cancer (PCa) is associated with high skeletal morbidity [1, 2]. In patients with bone metastases, events are usually defined in clinical trials as Skeletal Related Events (SRE) or Skeletal Symptomatic Events (SSE), when associated with symptoms [3]. Skeletal morbidity is in contrast mostly related to osteoporotic complications in patients with no bone metastases [4]. While PCa is well known for "osteoblastic" metastases, scarcer is skeletal morbidity characterized by "bone loss" irrespective to the cause (on bone metastasis or not). These events affect quality of life and even mortality in older patients [5, 6], especially when occurring on spine, responsible of vertebral compression fracture (VCF) [7, 8]. Since recently, patients with PCa experience longer survival with frequent and longer prescription of treatment responsible of bone loss, such as androgen deprivation therapy (ADT) [4], glucocorticoids [9] and new generation of hormone therapy. Corticosteroids are not only used in association with treatments (abiraterone acetate, docetaxel and cabazitaxel) in patients with metastatic castration resistant prostate cancer (mCRPC), but also prescribed for symptoms relief, such as

anorexia, nausea, pain and fatigue [10]. Furthermore, while they contributed to dramatically increase overall survival in mCRPC, new androgen receptor targeted agents such as abiraterone acetate and enzalutamide may promote the emergence of dedifferentiated phenotypes of PCa, in part defined by predominant osteolytic metastasis [11]. For these reasons, we assume that VCF occurring on bone loss may be a rising concern in PCa patients.

Vertebroplasty is an interventional radiology technique, offering a minimally invasive treatment, with a short time procedure as well as a rapid achievement on pain control. This approach represents an appropriate option to prevent or treat VCF [12]. Therefore, we assume that vertebroplasty could select a population of patients presenting with PCa and VCF secondary to bone loss.

We carried out a bicentric retrospective study aiming to characterize VCF in PCa patients who underwent vertebroplasty.

Methods

Patients

This bicentric retrospective study was approved by a national ethic board (Commission National Informatique et Liberté), and included all patients with histologically proven prostate cancer, who underwent one or several vertebroplasties between December 2008 and December 2016, at Bergonie Institute in Bordeaux and at University Hospital Center in Strasbourg. Patients with another primary tumour were excluded. Patients with cementoplasty of the acetabulum or the iliac wings were excluded, since these procedures are exclusively dedicated for pathological fractures.

Data from clinical records were retrospectively collected regarding population and disease and treatments characteristics at the time of VCF, as well as levels and number of levels of vertebroplasty. Follow-up elements i.e. new VCF in the next year, date of last follow-up or death were also collected.

Characterization of Vertebral Compression Fractures (VCF)

Vertebral compression fractures (VCF) were classified in two categories: benign VCF related to osteoporotic complication (bVCF) *versus* malignant VCF occurring on bone metastasis (mVCF).

A composite criterion was used including both imaging (bone scan, Computer-Tomography scan (CT-scan) and/or Magnetic Resonance Imaging (MRI)) and histologic data, when available.

Published criteria were used to characterize bVCF *versus* mVCF on imaging. Arguments for benign VCF were as follows on CT-scan: cortical fractures of the vertebral body without cortical bone destruction, a retropulsed posterior bone fragment with angular margins and absence of pedicle involvement, fracture lines within the cancellous bone of the vertebral body (intravertebral cleft formation), an intravertebral vacuum phenomenon, and a thin diffuse paraspinal soft-tissue mass (PSTM). Conversely, destruction of the anterolateral or posterior cortical bone of the vertebral body, destruction of the cancellous bone of the vertebral body, destruction of a vertebral pedicle, the presence of a focal paraspinal

mass and/or an epidural mass were the elements associated with malignant VCF [13].

On MRI, retropulsion of a bone fragment, preservation of normal signal intensity on T1-weighted images, normal signal intensity after gadolinium injection with horizontal bandlike patterns, and isointense vertebrae on T2-weighted images were suggestive of benign VCF. In opposition, convex posterior cortex, epidural mass, diffuse low signal intensity within the vertebral body on T1-weighted images and in the pedicles, high or inhomogeneous signal intensity after gadolinium injection and on T2-weighted images were in favour of malignant VCF [14, 15].

Interpretations were made by three (XB, JP and RLC) expert radiologists in vertebroplasty and cancer. Moreover, osteoblastic or lytic features of a given metastasis were reported. Histologic data were obtained from bone biopsies performed during procedure, and in case of equivocal imaging features.

Vertebroplasty procedure

Vertebroplasty required a short hospitalization and was performed by an interventional radiologist. Under imaging guidance, a large calibre bone trocar was inserted into the affected vertebral body usually *via* a transpedicular route and bone cement, polymethylmethacrylate (PMMA), was injected. Indications were vertebral compression fracture whatever the cause, with the aim to consolidate and to induce a quick analgesic effect. If needed, vertebroplasty could be associated with other focal treatments (surgery and/or radiotherapy).

Population description

Following data were collected from medical records. These data included osteoporosis risk factors such as Body Mass Index (BMI), continuous castration, duration of castration before vertebroplasty, corticosteroid treatment (high cumulated dose corresponding to ≥ 7.5mg/jour of equivalent prednisone, along more than 6 months) [16] and prior radiotherapy at VCF zone (the occurrence of pelvic radiotherapy was

taken into account for sacral vertebroplasties). Also, parameters regarding bone health management were reported i.e. Dual X-Absorptiometry (DXA), vitamin D and/or calcium supplementation and data relative to bone targeted agents (bisphosphonates or denosumab) at the time of VCF.

Statistical analysis

Median duration of castration was calculated from the sum of all the periods of castration before vertebroplasty. Duration of each period was calculated from the initiation date of castration to the end date.

If patient was still receiving chemical castration (LH-RH agonist or antagonist) at the time of the procedure of vertebroplasty, corresponding date was noted for the end date.

Corticosteroid dose was calculated by adding daily doses and reported in equivalent prednisone dose. For these two types of treatment, each intervention was analysed independently.

Overall survival was estimated using the Kaplan-Meier method and median follow-up duration with inversed Kaplan-Meier method.

These parameters concerned patients and no procedures, and for patients who underwent several interventions, participation time was calculated from first vertebroplasty to date of last follow-up. SAS software, version 9.4, was used.

Results

Patients

Patients and disease characteristics are presented in Table I. One hundred patients with PCa who underwent 128 vertebroplasties were included. Seventy-eight, 17, 4 and 1 patients had one, 2, 3 and 4 procedures respectively. Mean age at the time of vertebroplasty was 73.5 years (45-94 years). Eastern Cooperative Organization Group (ECOG) Performans Status (PS) score was 0 or 1 in 52 (41%) and ≥ 2 in 41 (32%) cases. Thirty-eight (30%) procedures were performed on patients free of bone metastases. In the population with bone metastases, 19 (23%) and 56 (67%) procedures were carried out in castration sensitive and castration resistant patients, respectively. For a median follow-up duration of 21.6

months (CI95% 17.0-29.3), 31 (24%) procedures were followed by a new VCF in the year.

Characterization of Vertebral Compression Fractures

MRI alone was realized in 27 (21%) cases, CT scan alone in 34 (26%) cases and both in 47 (37%) cases. Forty-one bone biopsies were performed, 26 for bVCF and 15 for mVCF. Among bVCF, all biopsies were negative, free of carcinomatous proliferation, while eight bone biopsies in mVCF exhibited malignant proliferation (53%). Elements for VCF characterization are summarized in table 2.

Sixty-six (52%) mVCF and 62 (48%) bVCF were assessed after 2 interpretations on imaging. Among bVCF, 17 (27%) occurred in bone metastatic patients (Figure 1).

Regarding mVCF, 28 (42%) were purely osteolytic and the remaining 38 (58%) cases had an osteolytic component (Figure 2) (Table 3).

No symptomatic complication of vertebroplasty, particularly no epidural cement leakage even if rupture of posterior wall was reported.

Population description

Almost all patients had received ADT: continuous ADT was prescribed in 107 cases (83%) while high cumulated dose of corticosteroids (> 6 months ≥ 7.5mg/day equivalent prednisone [17] was given in 38 cases (30%) before VCF. The median time duration of ADT was 3 years (range 0-17) in bVCF group and 1.1 year (range 0-12) in mVCF before vertebroplasty. We reported a history of radiotherapy at the location of VCF in 19 (15%) cases, among them 8 (6%) occurring on bVCF. Risk factors of osteoporosis are summarized in table 4.

A DXA was performed in 17 (13%) cases, all in bVCF group. Vitamin D supplementation was prescribed in 49 (38%) and calcium supplementation in 36 (28%) cases, while a bone-targeted therapy was used in 56 (44%) cases.

VCF (59) occurred in 59 (46%) patients ≥ 75 year-old: 39 (30%) in bVCF and 20 (16%) in mVCF group.

Discussion

This observational retrospective study aimed to select a population who presented with prostate cancer and vertebral compression fracture (VCF) characterized by spinal bone loss, requiring consolidation with vertebroplasty. These results raise at the first place the importance of benign VCF in terms of incidence and management. Vertebroplasty has been performed in 48% of cases for VCF without evidence of bone metastasis. Such event may be related to osteoporotic complications. These data are consistent with studies that reported a high rate of osteoporosis in PCa patients [4, 18]. This proportion of bVCF reflects a rising concern in daily practice since these patients, and especially those with bone metastasis are experiencing longer survival and thereby are more exposed to osteoporosis and its complications. These events are also favoured by longer exposure to corticosteroids and continuous ADT [19]. The prevalence of osteoporosis in men with PCa treated with ADT increases with time and reaches 80% after 10 years of treatment [20]. This bone loss is associated with an increased risk of fractures, such as VCF [21]. Furthermore, glucocorticoids used at a minimum dose of 7.5

mg per day during more than 6 months constitute a risk factor of fracture by loss of Bone Mineral Density (BMD) [19]. Corticosteroids are currently prescribed in patients with mCRPC and more recently with metastatic castration-sensitive prostate cancer (mCSPC) in association with approved chemotherapies (docetaxel, cabazitaxel) or abiraterone acetate [22-26], in order to prevent from adverse reactions and toxicities as well as to manage symptoms such as pain, anorexia or spinal cord compression [10]. While the impact of corticosteroids associated with abiraterone in mCRPC have been recently nuanced by a study suggesting that a long-term prescription of prednisone was not highly associated with glucocorticoids side effects [27], physicians are now encouraged to start prescription of abiraterone with 5mg daily prednisolone instead of 10mg in mCSPC patients, revealing a concern in this setting.

Besides, 17 (27%) of bVCF occured in bone metastatic patients. To our knowledge, this observation constitutes a real novelty, since the Skeletal Related Event used as a primary endpoint for bone-targeted agents approval in mCRPC [28, 29] was not defined according to its causality i.e. malignant *versus* benign. Thereby, the proportion of benign events in mCRPC patients with bone metastases remains unknown. Only one recent

study reported 74% of fractures outside of metastatic site including 17% of osteoporotic fractures in abiraterone – prednisone arm and are consistent with our results [30]. For the same arguments related to therapeutic advances and longer survival discussed above, this kind of benign events may also be a rising clinical concern for which physicians have to be aware, as shown in figure 2. Even if the efficacy of bone targeted agents was demonstrated for both setting (malignant or benign), ignoring that may then lead to focally mistreat patients. A striking example may be to give radiation therapy on a new symptomatic linear bone scan hyperfixation, in a patient with known bone metastases, while this picture corresponds to a benign VCF.

Recommendations were made in order to help physicians to maintain bone health in their patients with cancer. Those recommend assessing clinical risk factors and measuring BMD by dual X-ray absorptiometry (DXA) in patients with PCa and treated with ADT [19]. Among our population, only 17 DXA were performed before VCF, showing osteopenia in 8 cases and osteoporosis in 6 cases. While prescription of vitamin D and calcium is needed in all patients with ADT [17, 31], only 38 and 28% respectively received this treatment. These results are consistent with

underutilization of DXA and therapies currently reported [32, 33]. Furthermore, the relevance of DXA may be discussed since it assesses only quantity or bone density and does not provide information about the quality of the bone [34]. Of note, about 40% of patients experience osteoporotic fractures while DXA is normal. Fracture Risk Assessment Tool score (FRAX score), consisting in several clinical risk factors of osteoporosis (DXA facultative) may be a better tool to predict risk of fracture [35].

The fact that bone loss can occur within the first year following ADT initiation, strongly argues for an early caution about bone management. Indeed, men treated with ADT exhibit bone loss of 2–4% at the lumbar spine and hip and 5.3% at the distal radius in the first year of treatment [18]. Besides, effects of ADT may persist a long time, even after stopping this treatment [35] meaning that detection and management of bone morbidity should be included in normal follow-up of patients in complete remission or with a past history of ADT.

Among bVCF, 13% (8/62) of prior radiotherapy was noted in the area of fracture. Since radiation therapy is a standard treatment for symptomatic bone metastasis and no cut-off for side effects to the bone was clearly

defined [36], it is difficult to discuss its effect on adjacent healthy bone. However, it has been described an increase of pelvic fractures in patients with gynecologic cancers [37]. A retrospective study showed an incidence of 6.8% of symptomatic fracture after pelvic radiation for PCa with a median time of occurrence of 20 months [38]. Advances made in the definition of target volume will help to prevent from this potential side effect especially when such a treatment is given using high dose in early stages of the disease.

While most bone metastases in Pca patients are osteoblastic, resulting in rigid bone structure, they do not represent a common indication for vertebroplasty. In this study, all bone metastases exhibit at least an osteolytic component and 42% were purely osteolytic. A subset of patients with advanced castration-resistance disease who evolve into an androgen receptor (AR)–independent phenotype was described, with increasing incidence in part explained by a potential selection using new AR-targeting agents [11]. Terms of anaplastic or neuroendocrine prostate cancer are currently used and associated with the development of rapidly progressive disease. Seven clinical criteria were prospectively assessed

including the occurrence of radiographically predominant lytic bone metastases [39] to define this subgroup. Since these osteolytic metastases - most of malignant VCF in our study - represents one feature of rising dedifferentiated phenotype of PCa, vertebroplasty may play a more important role in their management.

Our study had some limitations inherent to any retrospective study, such as missing data, heterogeneity of imaging needed to characterize the type of VCF and size of the population. Of note, we did not prospectively collect elements for diagnosis and risk factors of osteoporosis, as well as elements included in FRAX score [40]. The primary endpoint was to characterize the VCF, using a composite criterion (imaging and bone biopsy). Few patients underwent DXA and biopsies, however these elements were somewhat useless compared to the robustness of imaging criteria [13-15]. Furthermore, biopsies are not necessary in routine practice for diagnosis except in some doubtful cases. Main difficulty consisted of classify multifactorial VCF in one category. Indeed, the same VCF may be the result of a double mechanism (VCF on lytic metastases

occurring on bone insufficiency). In these cases, predominant lesion was considered but this assessment may have been subjective.

In conclusion, this study from daily practice draws a recent picture of skeletal morbidity, mainly characterized by bone loss in patients with prostate cancer. Important rate of osteoporosis complications, under diagnosis and under treatment in this population have been highlighted. These data also emphasize the need of growing awareness of early management of bone loss, even in patients with bone metastases. Finally, VCF on lytic metastasis also represent a rising concern since this dedifferentiation may be favoured by therapeutic pressure caused by new AR-targeted agents. Vertebroplasty should play a major role in this new era of PCa management, with evolution of bone morbidity.

Abbreviations

ADT: Androgen Deprivation Therapy

AR: Androgen Receptor

BMD: Bone Mineral Density

bVCF: benign Vertebral Compression Fracture

CT-scan: Computer-Tomography scan

DXA: Dual X-ray Absorptiometry

ECOG PS: Eastern Cooperative Organization Group Performans Status

FRAX score: Fracture Risk Assessment Tool score

mCRPC: metastatic Castration Resistant Prostate Cancer

mCSPC: metastatic Castration Sensitive Prostate Cancer

MRI: Magnetic Resonance Imaging

mVCF: malignant Vertebral Compression Fracture

PCa: Prostate Cancer

PSTM: paraspinal soft-tissue mass

SSE: Symptomatic Skeletal Event

SRE: Skeletal Related Event

VCF: Vertebral Compression Fracture

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Informed consent was not required for this retrospective study. Ethics approval was given by the Institutional National Ethics Review Board (Commission Nationale Informatique et Liberté CNIL).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

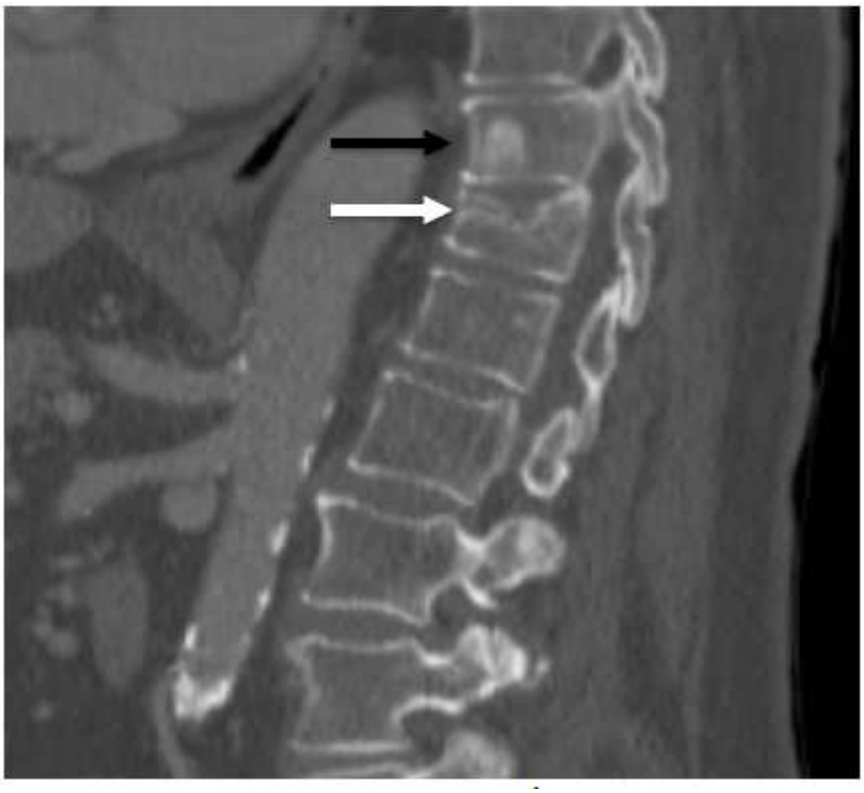

Figure 1

Benign VCF in bone metastatic patient: CT scan shows an osteoblastic metastasis (black arrow) and a benign VCF (white arrow) with fracture line parallel to the end plates, intravertebral cleft

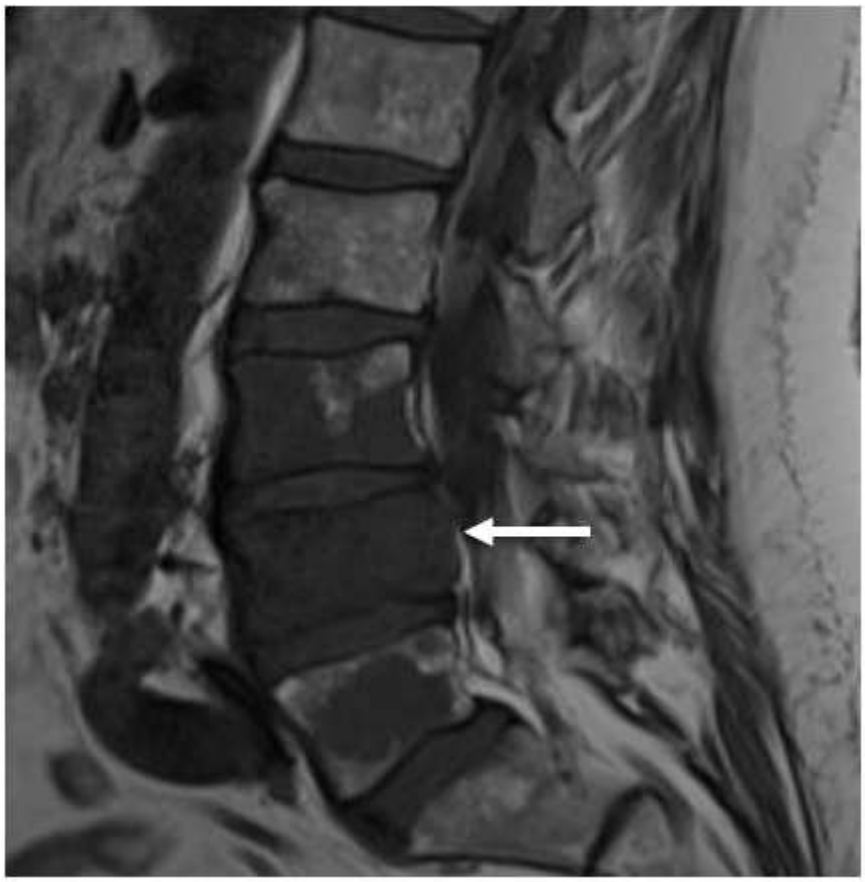

Figure 2

Osteolytic malignant VCF: MRI shows multiple lumbar lytic zones and posterior wall bulge at L4 level (white arrow)

Supplementary Files

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