REVIEW ARTICLE

Factors that predict the development of bone metastases due to prostate cancer: Recommendations for follow-up and therapeutic options

A. Rodriguez-Antolín a,*, F. Gómez-Veiga b, J.K. Álvarez-Osorio c, J. Carballido-Rodriguez d, J. Palou-Redorta e, E. Solsona-Narbón f, E. Sánchez-Sánchez g, M. Unda h

a Departamento de Urología, Hospital Universitario 12 de Octubre, Madrid, Spain
b Departamento de Urología, Complexo Hospitalario Hospital A Coruña Juan Canalejo, A Coruña, Spain
c Departamento de Urología, Hospital Puerta del Mar, Cádiz, Spain
d Departamento de Urología, Hospital Universitario Puerta de Hierro, Madrid, Spain
e Departamento de Urología, Fundació Puigvert, Barcelona, Spain
f Departamento de Urología, Instituto Valenciano de Oncología, Valencia, Spain
g Departamento de Urología, Hospital Virgen de la Macarena, Sevilla, Spain
h Departamento de Urología, Hospital de Basurto, Bilbao, Spain

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KEYWORDS
Prostate cancer; Bone metastasis; Prognostic factors; Local disease; Follow-up; Hormone therapy

Abstract
Context: Prostate cancer is a public health problem in Spain and in the Western world. Bone involvement, associated to significant morbidity, is practically constant in the advanced stages of the disease. This work aims to review the prognostic factors used in the usual clinical practice that predict the development of bone metastases and to analyze the follow-up and treatment option in these patient profiles.

Acquiring of evidence: We performed a review of the literature on the useful factors in the context of therapy with intention to cure. We included the classical clinical values in the diagnosis (PSA, clinical stage, Gleason score on the biopsy) pathological factors (pT stage, margins, bladder invasion, tumor volume, lymph node involvement) and PSA kinetics in their different contexts and the histological and molecular parameters.

Synthesis of evidence: The tumor differentiation “Gleason” score and PSA are the most important predictive factors in the prediction of bone metastases in patients with intention to cure. Kinetic factors such as PSA doubling time (TDPSA) < 8 months or PSA > 10 ng/ml in the case...
of castration-resistant prostate cancer (CPRC) are predictive factors for the development of metastasis. Zoledronic acid and denosumab have demonstrated their effectiveness for the treatment of bone disease in randomized studies.

Conclusions: There are predictive factors within the usual clinical practice that make it possible to recognize the "patient at risk" to develop bone metastatic disease. The currently available treatments, zoledronic acid or denosumab, can help us in the management of the patient at risk of developing metastasis or metastatic patient, increasing the quality of life and decreasing skeletal events.

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PALABRAS CLAVE
Cancer de próstata; Metástasis óseas; Factores pronósticos; Enfermedad local; Seguimiento; Hormonoterapia

Factores que predicen el desarrollo de metástasis óseas por cáncer de próstata: recomendaciones de seguimiento y opciones terapéuticas

Resumen

Contexto: El cáncer de próstata representa un problema de salud pública en España y en el mundo occidental. En las fases avanzadas de la enfermedad la afectación ósea es prácticamente constante, asociada a una notable morbidad. El objetivo de este trabajo es realizar una revisión de los factores pronósticos utilizados en la práctica clínica habitual que predicen el desarrollo de metástasis óseas y analizar las opciones de seguimiento y tratamiento en estos perfiles de pacientes.

Adquisición de evidencia: Realizamos una revisión de la literatura sobre los factores útiles en el contexto de terapia de intención curativa; incluimos los valores clínicos clásicos al diagnóstico (PSA, estado clínico, Gleason de la biopsia) factores patológicos (estadio Tp, márgenes, invasión de vesículas, volumen tumoral, afectación ganglionar) y la cinética de PSA en sus diferentes contextos, así como parámetros histológicos y moleculares.

Síntesis de evidencia: El grado de diferenciación tumoral «Gleason» y el PSA son los factores predictivos más importantes en la predicción de metástasis óseas en pacientes con intención curativa. Factores cinéticos como TdPSA < 8 meses o PSA > 10 ng/ml en la situación de CPRC son factores predictivos de desarrollo de metástasis. El ácido zoledrónico y el denosumab han demostrado su efectividad para el tratamiento de la enfermedad ósea en estudios aleatorizados.

Conclusiones: Existen factores predictivos dentro de la práctica clínica habitual que permiten reconocer el «paciente riesgo» para el desarrollo de enfermedad metastásica ósea. Los tratamientos actualmente disponibles, ácido zoledrónico o denosumab, pueden ayudarnos en el manejo del paciente con riesgo de desarrollo de metástasis o metastásico, aumentando la calidad de vida y disminuyendo los eventos esqueléticos.

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Introduction

The importance of prostate cancer (PCa) in social and health terms is indisputable. With 12% of new cancer diagnoses made in Europe,1 data for 2010 in our country from the Registro Español de Cáncer de Próstata (Spanish Registry of Prostate Cancer) show a standardized incidence rate among the Spanish population of 82.27 for every 100,000 men, with 90% of tumors diagnosed at a limited stage (28.6% of high-risk tumors according to D’Amico criteria)2 and only 3.8% of them at a metastatic stage.3

The presence of bone involvement is nevertheless practically constant; 70% of cases of the disease at advanced stages will develop bone metastases.4

The development of bone metastases is associated with significant morbidity which includes intermittent or continuous pain in bony areas, an increased risk of fractures, need for radiotherapy (RT) or orthopedic surgery, and hypercalcemia.3 The association between these events and the significant deterioration of quality-of-life parameters, as well as an increase in the economic cost and a significant increase in mortality associated with pathological fractures,5 have been widely demonstrated.

The identification of prognostic factors which may help clinicians determine which patients are at risk for bone metastases after curative therapy or after hormone-blocking therapy is of great value when establishing different treatment and monitoring protocols, possible multimodal treatment schemes, or when selecting those patients for whom inclusion in a clinical trial is appropriate.

This study involves a bibliographic review of the articles registered on Medline during the last 10 years on clinical, pathological and laboratory prognostic factors used in routine clinical practice, which predict disease progression and which are in many cases associated with the development of bone metastases. The search terms were prostate neoplasm, neoplasm metastases, bone neoplasm, disease progression, prognosis, hormonal antineoplastic agents, zoledronic acid, denosumab, and radiopharmaceuticals. The prognostic factors were analyzed in 2 contexts: patients with curative-intended radical therapy and patients on hormone-deprivation therapy. The secondary aim of this
review was to summarize the diagnostic, monitoring, and therapeutic indications for these patients in accordance with the main clinical practice guidelines.

Factors predicting the occurrence of bone metastases in patients treated with a curative intent

Biological progression of the disease occurs in approximately 30% of patients on long-term follow-up after radical prostatectomy (RP). External RT and brachytherapy show similar or higher recurrence parameters in selected cases. The development of bone metastases after radical treatment with curative intent (both with RP and RT) is rare. Recent data from the PIVOT study have shown a significant decrease in the incidence of bone metastases (4.7 versus 10.6; hazard ratio [HR] 0.40; 95% confidence interval [CI]: 0.22–0.70) in prostatectomy patients when compared to the observation group, although there are no differences in cancer-specific mortality in the low-risk group.

Traditionally, the estimated median time to metastasis after biochemical recurrence has been 8 years, and time to death has been estimated at 5 more years. A Gleason score ≥ 8, a prostate-specific antigen (PSA) doubling time (PSADT) ≤ 10 months and early recurrence (<2 years) are significantly associated with the onset of bone metastases and lower cancer-specific survival.

The most analyzed prognostic factors for progression in the literature include the classical clinical values in the diagnosis (PSA, clinical stage, Gleason score on the biopsy), pathological factors (pT stage, margins, lymph node involvement, bladder invasion) and PSA kinetics in their different contexts. Other histological and molecular parameters, with a lower weight of evidence, include histological subtype, ploidy, PNI, lymphovascular invasion, neuroendocrine differentiation, cellular proliferation markers, and genetic markers.

The importance of PSA as a significant predictor of biological failure has been well-known for more than 15 years in RP and RT series. More recently, it has also been confirmed that it is an independent predictor, though not the most important one, of metastasis development and survival in the multivariate analysis, when its pre-treatment value is ≥ 20 ng/ml in patients treated with RT. Clinical stage and biopsy Gleason score show good correlation with the development of bone metastases. Patients with stage T1/T2 and T3/T4 tumors develop metastasis within 10 years in 3–41% and 12–55% of cases, respectively. Patients with well, moderately, or poorly differentiated tumors develop bone metastases within 10 years in 2.7–10%, 13–57% and 42–80% of cases, respectively.

As regards histological parameters of surgical specimens, primary and secondary Gleason grades and seminal vesicle invasion are the 2 major prognostic factors for 15-year cancer-specific mortality, according to a multicenter series of 23,910 radical prostatectomies of localized tumors performed between 1987 and 2005. 15-year cancer-specific mortality was 0.8–1.5%, 2.9–10%, 15–27%, and 22–30% for those patients with organ-limited tumors, extraprostatic extension, vesicle invasion, and lymphatic infiltration, respectively.

The occurrence of bone metastases after RT was documented in 6% of cases in the study carried out by Zagars, with 14,938 patients and a median follow-up time of around 4 years. The risk factors for the development of these metastases were a Gleason score ≥ 8, pre-treatment PSA level > 20 ng/ml, T3/T4 stage, N+ or a minimum nadir PSA level after therapy > 4 ng/ml.

The association between PSA velocity (PSAV) during the year before diagnosis and the risk for cancer-specific mortality (CSM) were examined by D’Amico et al. in a cohort of 1,095 patients treated with RP due to T1c-T2 PCa. In the multivariate analysis, a PSAV > 2 ng/ml/year prior to surgery was associated with an increase in CSM (relative risk [RR] 9.8, p < 0.001) and a higher pathologic stage and Gleason score. This author examined this association in 358 patients treated with RT due to localized PCa, with an average follow-up of 4 years. Those patients with a PSAV > 2 ng/ml/year showed a significantly higher CSM rate (HR 12; p = 0.001). These studies imply that low-risk patients (Gleason score ≤ 6, PSA ≤ 10 ng/ml and T1c-2a) and a PSAV > 2 ng/ml/year behave more like high-risk patients than low-risk ones, which suggests a possible presence of micrometastases at the time of diagnosis.

The prognostic significance of pre-diagnostic PSAV in relation to biochemical disease-free survival (BDFS) has been validated in other cohorts of patients with radio- or brachytherapy, although not all the studies concluded that it is a prognostic factor of response to therapy. PSAV is still not considered standard in therapeutic decision-making and will require future validation.

PSADT before primary treatment, as well as PSAV, has been studied as a predictive factor for progression in PCa, and has shown a significant association with CSM.

Awareness of PSADT in patient follow-up after radical treatment has been significantly associated with the risk of progression, metastasis, and death. PSADT < 1 months is the highest predictor of CSM. The presence of PSADT < 3 months, along with a Gleason score > 8 and biological recurrence within < 3 years, is associated with a median patient survival of only 3 years. The series provided by D’Amico of 8,699 patients (5,918 RP and 2,751 RT) confirms that those patients with PSADT < 3 months have a median survival of 6 years, and that their risk of dying from PCa is multiplied by 20.

It has been observed both in patients treated with surgery and in those treated with RT that the information on the number of cylinders affected at the time of biopsy is a prognostic factor for BDFS. Patients in the intermediate- and high-risk groups with <34% of positive cylinders have a 4-year probability of biochemical control of 86% versus 11% of those patients with >50% of affected cylinders. However, it does not seem to have a prognostic value in the low-risk group.

As regards tumor volume of the prostatectomy specimen, the information is controversial and some authors consider its exact quantification unnecessary.

Nomograms for prediction of biochemical failure after surgery and RT are available, although PSA is not a good surrogate marker for metastases and disease-specific mortality. The only nomogram predicting 15-year CSM, based on clinical information, provides information of little value in this context.
Another step in prediction consists of the estimation of bone metastases and CSM in localized prostate tumors. The Cancer of the Prostate Risk Assessment (CAPRA) score, which uses the CaPSURE database with a total of 10,627 patients, combined PSA value, biopsy Gleason score, age, clinical stage, and the percentage of positive cylinders at the time of biopsy in patients who had undergone radical treatment (RP or RT), hormone-deprivation monotherapy or expectant management/active surveillance as therapy options. 2.9% of them developed bone metastases. Each single-point increase in the CAPRA score was associated with increased bone metastases (HR for bone metastases = 1.47, 95% CI = 1.39 to 1.56). Basal PSA levels >10 ng/ml and elevated PSAV were also associated with a higher risk of metastases.26

Factors predicting the occurrence of bone metastases in patients with hormonal therapy and at the castration-resistant stage

Current indications for hormonal therapy in PCa include those for metastatic patients, with node involvement, certain patients with locally advanced M0 tumors, and a progressively increasing contingent of patients with biological recurrence after curative therapy which has determined a lead-time bias in the natural history of this stage. As known, the natural history of the disease will end up in a castration-resistant stage, metastasis development, mainly bone metastases, and finally death after a median of approximately 40–68 months since the onset of hormone resistance.27

Few studies provide precise information on natural history until the occurrence of metastases at the castration-resistant stage. A clinical trial, which was concluded prematurely, of zoledronic acid versus placebo in patients with castration-resistant PCa (CRPCa), which aimed at assessing the efficacy of the drug in delaying the time to the first metastasis, was the first contribution to natural evolutionary history in this regard. The study determined a median of 30 months for metastasis-free survival time. In two years, 33% of patients develop one or more bone metastases. A PSA higher than 10 ng/ml (RR: 3.18) and PSAV (RR: 4.34 for each 0.01 increase) independently predicted the early occurrence of bone deposits, as well as overall metastasis-free survival.28 In the univariate analysis, a Gleason score >7 was associated with lower metastasis-free survival rates (RR: 1.62; 95% CI: 0.96–2.75; p = 0.07). The Kaplan–Meier curves for estimating the time to metastasis or death showed that a PSA level >24 ng/ml and a PSADT >6.3 months were also associated with lower metastasis-free survival. Once metastases have occurred, PSA parameters seem to have a limited utility in predicting the risk of skeletal-related events (SRE).

Another recent contribution in relation to natural history at the M0 stage of the disease is that resulting from the placebo group of a clinical study conducted on 1,432 men with non-metastatic CRPCa, though with a high risk of progression defined by PSA >10 ng/ml and/or PSADT <8 months in the 3 months before random allocation. The median bone metastasis-free survival was 25.2 months with placebo. The average time to the occurrence of the first metastasis was 29.5 months (22.4–33.1). PSADT behaved as a strong predictor of bone disease, in such a way that the median time was 22.4 months in those patients with PSADT ≤10 months (≈80% of the population), 18.7 months in patients with PSADT ≤6 months (≈60% of the population), and 18.3 months in patients with PSADT ≤4 months (≈40% of the population).29

Data from population studies, such as the CaPSURE series, with over 4,000 patients under androgen deprivation therapy and without metastasis, show an occurrence of bone metastases in 4.8% of patients after a median of 18 months (1–139) from start of blockade. In the multivariate analysis, the risk factors for the occurrence of metastases were the percentage of positive biopsies at diagnosis (>33% versus <33%) with a HR of 3.36 (1.53–7.38; p < 0.001), risk category (high versus low or intermediate) with a HR of 2.57 (1.60–4.15; p < 0.0001), age at diagnosis (>65 versus >65 years) with a HR of 2.11 (1.36–3.28, p < 0.001) and PSAV with a HR of 1.04 (1.02–1.06; p < 0.0001).30

As there is a possibility that an early start of hormonal treatment in patients with biological recurrence after RP may delay the occurrence of bone metastases, it seems that only those patients with a Gleason score >7 and PSADT <12 months would benefit from it.31

The serum concentration of tartrate-resistant acid phosphatase (TRAP) may be regarded as a useful predictor of bone metastases in PCa. It has been suggested that a combination of TRAP, alkaline phosphatase (ALP), and PSA levels may avoid the need for a bone scan (BS) in 70% of cases. The effects of bone metastases can be indirectly inferred from measuring bone turnover markers, mainly N-telopeptide-NTx (a marker of osteolysis along with carboxyterminal telopeptide of type I collagen (ICTP) and TRAP (type 5b) and bone ALP (a formation marker). Despite the data cited above indicating the usefulness of the combination of ALP, PSA, and TRAP to predict metastases, its clinical use as a substitute for BS is not sufficiently supported.32

Although markers are not used as predictors of bone metastases, preclinical and clinical studies on castration-resistant patients, conducted with docetaxel, bisphosphonates, denosumab, endothelin inhibitors, Src inhibitors (dasatinib) and radium-223 have shown a modulation of bone markers in any of the cases with an associated prognostic impact.33

Follow-up recommendations in patients at a high risk of developing bone metastases

The general follow-up for those patients undergoing radical surgery or RT techniques is properly defined both in European guidelines and American NCCN guidelines, and it is based on the use of PSA, digital rectal exam, and an adequate clinical history.34,35 BS is the diagnostic technique of choice for determining the presence or distribution of bone metastases. BS is not systematically recommended in the follow-up of asymptomatic patients, and may be omitted when PSA is <20 ng/ml, although it may be indicated for patients with elevated PSA which could affect treatment outcome.36 Furthermore, in the case of bone pain a BS should be performed regardless of PSA values, since metastases may even occur with undetectable values (level of recommendation B).33 Routinely performing BS is not
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recommended in the follow-up of asymptomatic patients with stable PSA levels either.\(^{25}\)

No specific diagnostic or follow-up scheme has been clearly defined in patients at the castration-resistant stage.\(^{34,35,37,38}\) The Prostate Cancer Working Group (PCWG2) defined bone progression in the event of 2 new deposits on the BS. The recommendations of the Group for the development of clinical trials with drugs at this stage of the disease suggest the performance of a BS at the beginning and every 12 weeks.

In the cases of osteolytic predominance, as it happens in well-differentiated tumors or with neuroendocrine differentiation, this technique is rather insensitive and it becomes necessary to resort to other techniques such as computed tomography scan (CT) or magnetic resonance (MR). MR shows greater sensitivity and specificity than BS, although its limited availability and its high cost limit its use, and it has not displaced BS as a first diagnostic step.\(^39\) The use of positron emission tomography (PET) with 18-fluoro-2-deoxyglucose (FDG) seems to have a limited usefulness, given the poor glucose uptake by prostate cells. Its usefulness is higher when detecting local recurrence.\(^35\)

**Therapeutic options for the management of bone metastases**

Treatment of bone metastases in men with PCa is a palliative one. The goals of treatment are pain control, improving mobility, and the prevention of complications such as pathological fractures, cord compression, or the need for RT. The approved treatment choices include bisphosphonates, denosumab, RT, radiopharmaceuticals, treatment with surgery, use of analgesics, and support measures.

**Zoledronic acid**

Zoledronic acid (currently the most potent bisphosphonate available) is a potent inhibitor of osteoclasts through inhibition of mevalonate pathway enzymes. This drug, whose first approved indication was tumor hypercalcemia, has shown beneficial effects on skeletal complications and pain control in breast tumors, myeloma, lung tumors, and other solid neoplasms.\(^36,40\) At a dose of 4 mg IV/4 weeks, along with administration of calcium and oral vitamin D, it has been approved by the United States Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of patients with castration-resistant PCs and bone metastases, since, in comparison to placebo, it showed a 36% decrease in SRES, a concept including hypercalcemia, pathological fractures, cord compression, and the need for surgery or RT. The use of zoledronic acid showed in the study a delay of up to 5 months until the occurrence of bone events.\(^41,42\) This reduction in skeletal events has also been identified, beyond clinical trials, in large population studies,\(^23\) with a greater potential benefit having been identified in patients with no pain, which suggests the convenience of early start of therapy in this context.\(^43\)

A decrease in urinary excretion of markers of bone resorption has also been shown with zoledronic acid, as well as in pain parameters, mobility limitation and analgesic consumption, and no significant differences in disease progression have been observed.\(^44\) Treatment with zoledronic acid at a single annual dose has led to a significant benefit in terms of reducing fractures in patients with primary osteoporosis or those associated with hypogonadism.\(^45\)

The EAU guidelines recommend its use (grade A) and warn of the potential risk of osteonecrosis of the jaw described in 1.3% of patients in combined studies.

**Denosumab**

Denosumab is a completely human monoclonal antibody, obtained by genetic engineering, which inhibits the activity of RANK-L, a cytokine released by activated T cells that stimulates the formation, activation, adherence and survival of osteoclasts. It has been proved that it delays the first and subsequent SRES, and also that it reduces skeletal morbidity in comparative studies with placebo in PCa, breast and other solid tumors.\(^46\) The FDA and the EMA have approved its use for this indication.\(^47\)

SC administration of denosumab 120 mg every 4 weeks in patients with CRPCa and bone metastases in comparison to zoledronic acid IV 4 mg/month has shown a 18% relative reduction in the time to the first SRE (20.7 versus 17.1 months) and lesser evidence of new skeletal events. Differences were observed neither in overall survival nor in time to progression.\(^48\)

The European Urology Guidelines recommend (grade A) the use of denosumab in metastatic CRPCa, and assessment of side effects is advisable, basically of osteonecrosis of the jaw (2.3%).\(^35\)

**Radiopharmaceuticals**

IV use of radiopharmaceuticals has shown clinical usefulness in the management of patients with multiple painful metastases and with persistent pain despite treatment with RT, and its use is advisable before pain becomes intractable. Agents such as samarium-153 (\(^{153}\)Sm), strontium-89 (\(^{89}\)Sr), rhenium-186 (\(^{186}\)Re) and radium-223 (\(^{223}\)Ra) are capable of attaching themselves to areas of osteoblastic activity, thus radiating tumor cells and cytokine-releasing cells measuring bone pain with variable percentages of analgesic response. Myelosuppression is its most important toxic effect, and it is more prominent with strontium than with samarium. A systematic review carried out regarding \(^{89}\)Sr showed a complete response to \(^{89}\)Sr in 32% of patients and some degree of response in 44% of cases.\(^49\) \(^{223}\)Ra has shown, in a recently published study, a 30% decrease in mortality with respect to placebo in patients previously treated with docetaxel or not subsidiary to this drug.\(^50\)

**Conclusion**

PSA and Gleason biopsy score are the 2 most important predictive factors with respect to the occurrence of bone metastases and with respect to cancer-specific mortality in patients with localized PCs receiving radical therapy with surgery or RT, whereas PSADT after treatment is the most unfavorable marker indicating metastatic progression and death in a context where tools such as CAPRA score may
be useful for the urologist to determine the risk of bone metastases.

In patients at a castration-resistant stage, PSA > 10 ng/ml and PSADT < 8 months behave as adequate predictors of bone disease. The use of zoledronic acid and denosumab has proven to be effective and these drugs are approved to reduce SREs. Zoledronic acid has shown improvements in terms of pain and functional mobility, with a decrease in the markers of bone resorption.

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Conflict of interest

The authors declare that they have no conflict of interest.

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