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Hot Topic

Predicting the risk of bone metastasis in prostate cancer

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ABSTRACT

The ability to identify prostate cancer patients at 'high risk' for bone metastasis development could allow early selection of those most likely to benefit from interventions to prevent or delay bone metastasis. This review is aimed to identify potential predictors of risk for bone metastasis in newly diagnosed patients and in those who have already received treatment.

At diagnosis, established predictors of prostate cancer aggressiveness (e.g. PSA level, clinical stage, Gleason score) can identify patients at risk for bone metastasis. Following treatment of the disease, increasing evidence suggests that absolute PSA levels and other measures of PSA kinetics are useful to aid prediction of bone metastasis risk in patients both with and without a history of ADT. However, which PSA parameter most accurately predicts risk and the cut-off values that should be employed are unclear. *Inclusion of PSA parameters to identify a high risk population may be beneficial in whom bone-modifying treatments are being considered.* Other novel (but unvalidated) biomarkers that potentially predict the development of bone metastases have been identified, although it is unclear whether they will have value as independent markers or when combined with other parameters (e.g. measures of PSA kinetics). Further prospective studies of PSA kinetics and other predictive markers are, therefore, required to define the optimal criteria for identifying patients at high risk of bone metastases and those who are most likely to benefit from intensive monitoring and therapeutic intervention.

Introduction

In men, prostate cancer is the second most frequently diagnosed cancer and among the most common causes of cancer-related death world-wide [1,2]. As such, the disease imposes a considerable economic burden on both healthcare providers and society [3]. Although prostate-specific antigen (PSA)-based screening and diagnostic strategies mean that many patients with prostate cancer are now diagnosed relatively early, prior to metastasis of the disease [4], progression will still occur in many patients. Bone metastases were observed in approximately 3% of newly diagnosed patients in a Danish cohort study of 23,087 incident patients with prostate cancer, but developed during a median follow-up of 2.2 years in a further 11.5% of patients in whom there was no initial evidence of their presence [5,6]. Indeed, where metastasis does occur, bone is the single most dominant site (seen in 90% of patients with metastatic prostate cancer), and is in fact the only site of metastasis in the majority of patients (86%) [7].

The propensity of prostate cancer to metastasise preferentially to bone might be explained, at least in part, by the fact that the bone microenvironment provides a particularly fertile setting for the growth and aggressive development of tumour cells (the 'seed and soil' hypothesis first proposed by Paget in 1889) [8]. Bone-derived chemokines have been shown to act as chemoattractants for circulating prostate tumour cells which, on arrival in bone, are then exposed to factors within the bone microenvironment that support growth of metastases. The production of growth factors by the tumour cells can then directly stimulate osteoblast activity resulting in increased expression of RANK Ligand. This overproduction of RANK Ligand then mediates a vicious cycle of tumour growth and bone destruction, driving increased formation, function and survival of osteoclasts leading to excessive bone reabsorption, and release of growth factors from the bone matrix that may perpetuate tumour activity [9–11].

The disruptions in normal bone turnover associated with bone metastases lead to serious and debilitating skeletal consequences known as skeletal-related events (SREs). These include intractable pain necessitating palliative radiotherapy to bone, pathological

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fracture, spinal cord compression and surgery to bone [6,12]. Hypercalcaemia may also occur. Such events lead to decreased quality of life [6], are associated with high costs [13] and increased healthcare resource utilisation compared with non-metastatic disease [14], and have also been shown to predict poor prognosis in men with prostate cancer [5].

Diagnosis of bone metastasis currently relies primarily on technetium-99 m (^{99m}Tc) bone scanning and plain X-ray, although recent studies using modern imaging technologies such as positron emission tomography–computed tomography (PET–CT) and magnetic resonance imaging (MRI) demonstrate that bone scanning underestimates the true prevalence of bone involvement [15]. Even using modern imaging technologies, the specificity and sensitivity for identifying bone metastases range from 62% to 100% depending on the method, with no approach consistently reported to be 100% accurate [15]. Given that the occurrence of bone metastases significantly influences the choice of prostate cancer treatment [16], the ability to identify patients at 'high risk' for bone metastasis could allow early selection of those most likely to benefit from targeted therapy to prevent or delay bone metastasis, and/or intensive monitoring to optimise the likelihood of timely and successful intervention. Conversely, bone scans/intensive monitoring could be avoided in patients at low risk of metastasis. While various studies have attempted to identify predictors of progression (e.g. biochemical recurrence, hormone responsiveness), outcome (e.g. survival, SRE), or response to treatment in prostate cancer [16–19], there is, however, no standard definition of a patient at 'high risk' for bone metastases specifically.

Objectives and search strategy

The aim of this evidence-based review is to evaluate the level of support for potential predictors of risk for bone metastasis in patients with prostate cancer, in both newly diagnosed patients and in those who have already received treatment.

To ensure accuracy of data, articles published within the past 8 years were identified through comprehensive searches of PubMed using the terms 'prostate cancer' AND ('bone metastasis' OR 'bone metastases' OR 'bone metastatic') combined with general terms for risk (e.g. 'risk' OR 'prognosis' OR 'prognostic'). Given that historical data have indicated likely roles for PSA levels and Gleason score in predicting the presence of bone metastases, additional searches were carried out using 'prostate cancer' AND ('bone metastasis' OR 'bone metastases' OR 'bone metastatic') combined with these more specific terms (e.g. 'prostate specific antigen', 'Gleason'). The abstracts of the articles retrieved were then reviewed to identify those publications of relevance for further evaluation and inclusion.

Predictors of risk for bone metastasis in newly diagnosed patients

Although mostly cross-sectional and retrospective in design, multiple studies of patients with newly diagnosed prostate cancer are available that provide data on potential correlations between the outcome of bone scanning and patient characteristics such as PSA level and Gleason score. A systematic review published in 2004 pooled data from such studies in an attempt to define markers of risk for existing bone metastases, and thus help identify the most appropriate population for routine bone scanning at diagnosis. After analysis of data from 8644 patients in 23 studies, the authors concluded that the likelihood of a positive bone scan increases markedly in those patients with a PSA level $\geqslant$20 ng/mL, locally advanced disease, or a Gleason score $\geqslant$ 8; these patients should, therefore, be considered for a bone scan as part of baseline staging [20]. Multiple subsequent studies have also generally supported the concept of a risk threshold defined by prognostic factors such as PSA level and Gleason score below which patients are unlikely to have metastatic bone disease [21–24].

Criteria for the assessment of bone involvement in newly diagnosed patients (based on PSA level, Gleason score and tumour stage as described above) are reflected in many prostate cancer guidelines. However, there has been some debate about the exact parameters and cut-off levels that should be employed. As the guideline recommendations were initially based on limited and relatively old data, a study was performed in 2009 to externally validate the guideline recommendations in a large contemporary cohort of patients [25]. The guideline criteria used were those reported in the European Association of Urology (EAU), American Urological Association (AUA), National Comprehensive Cancer Network (NCCN) and American Joint Committee on Cancer (AJCC) guidelines at the time of the study. The results were also compared with those of a novel classification and regression tree model, which stratified patients into low risk (Gleason score $\leqslant$ 7, cT1–T3, and PSA < 10 ng/mL, with cT1 patients considered low risk regardless of PSA value), intermediate risk (Gleason score $\leqslant$ 7, cT2/T3, and PSA > 10 ng/mL), or high risk (Gleason > 7 score). While both this model and the guideline recommended criteria were associated with high degrees of accuracy for predicting bone metastases, the novel risk stratification tool was significantly more accurate (area under the curve [AUC]: 88%) than those used in the guidelines at the time (all $P \leqslant 0.002$) [25]. This model has since been incorporated into updated NCCN guidelines for prostate cancer [19]. A summary of the criteria for the assessment of bone involvement as reported in current guidelines is provided in Table 1.

Predictors of risk for bone metastasis in treated patients

Biochemical failure (rising PSA levels with no other evidence of disease recurrence) following initial treatment of localised prostate cancer may precede the development of bone metastases by many years, during which time there is the potential that patients at low risk of metastases undergo a series of unnecessary bone scans or other treatment, while patients at high risk could benefit from more aggressive therapeutic approaches. The identification of accurate predictors of risk in this population would therefore be beneficial for both low and high risk groups. As differing treatment approaches may be associated with significant changes in serum PSA and bone scan results [26,27], there is the potential that predictors of risk differ between those patients receiving local treatments with curative intent (radical prostatectomy or radiotherapy) compared with patients who receive androgen-deprivation therapy (ADT), and evidence for these groups should, therefore, be considered separately.

Predictors of risk for bone metastasis in patients with biochemical recurrence following radical prostatectomy or radiation therapy (with no history of ADT)

In a retrospective study evaluating the clinical and pathological predictors of bone metastases in men with detectable PSA following radical prostatectomy (n = 128), patients with a positive bone scan had a higher PSA level at the time of imaging (P < 0.001), shorter PSA doubling time (P = 0.007), greater incidence of extracapsular extension (P = 0.009), and a higher pathological stage (P = 0.042) [28]. Men with a PSA doubling time <6 months were found to be at increased risk of a positive bone scan relative to men with a longer PSA doubling time (incidence of 26% vs 3%, respectively). Among those men with PSA doubling time

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