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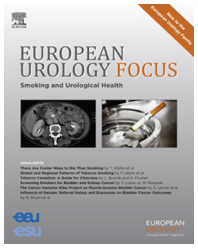

Platinum Priority – Review – Prostate Cancer
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Rationale for Modernising Imaging in Advanced Prostate Cancer

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Article info

Article history:
Accepted June 29, 2016

Associate Editor:
James Catto

Keywords:
Advanced prostate cancer
Metastatic castrate-resistant prostate cancer
Bone scans
PET/CT scans
Whole-body MRI
Diffusion MRI
Response assessment
Metastasis detection

Abstract

Context: To effectively manage patients with advanced prostate cancer (APC), it is essential to have accurate, reproducible, and validated methods for detecting and quantifying the burden of bone and soft tissue metastases and for assessing their response to therapy. Current standard of care imaging with bone and computed tomography (CT) scans have significant limitations for the assessment of bone metastases in particular.
Objective: We aimed to undertake a critical comparative review of imaging methods used for diagnosis and disease monitoring of metastatic APC from the perspective of their availability and ability to assess disease presence, extent, and response of bone and soft tissue disease.
Evidence acquisition: An expert panel of radiologists, nuclear medicine physicians, and medical physicists with the greatest experience of imaging in advanced prostate cancer prepared a review of the practicalities, performance, merits, and limitations of currently available imaging methods.
Evidence synthesis: Meta-analyses showed that positron emission tomography (PET)/CT with different radiotracers and whole-body magnetic resonance imaging (WB-MRI) are more accurate for bone lesion detection than CT and bone scans (BSs). At a patient level, the pooled sensitivities for bone disease by using choline (CH)–PET/CT, WB-MRI, and BS were 91% (95% confidence interval [CI], 83–96%), 97% (95% CI, 91–99%), and 79% (95% CI, 73–83%), respectively. The pooled specificities for bone metastases detection using CH-PET/CT, WB-MRI, and BS were 99% (95% CI, 93–100%), 95% (95% CI, 90–97%), and 82% (95% CI, 78–85%), respectively. The ability of PET/CT and WB-MRI to assess therapeutic benefits is promising but has not been comprehensively evaluated. There is variability in the cost, availability, and quality of PET/CT and WB-MRI.
Conclusions: Standardisation of acquisition, interpretation, and reporting of WB-MRI and PET/CT scans is required to assess the performance of these techniques in clinical trials of treatment approaches in APC.
Patient summary: PET/CT and whole-body MRI scans have the potential to improve detection and to assess response to treatment of all types of advanced prostate cancer. Consensus recommendations on quality standards, interpretation, and reporting are needed but will require validation in clinical trials of established and new treatment approaches.

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http://dx.doi.org/10.1016/j.euf.2016.06.018

Please cite this article in press as: Padhani AR, et al. Rationale for Modernising Imaging in Advanced Prostate Cancer. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.06.018

1. Introduction

Advanced prostate cancer (APC) patients who present with metastatic disease at the time of diagnosis or after failed attempts at curative therapy almost always respond to androgen deprivation therapy (ADT). However, ADT initiation inevitably leads to the development of the castration-resistant disease state, which occurs within 1–3 yr in most patients [1,2]. More than 80% of patients with metastatic castrate-resistant prostate cancer (mCRPC) have bone metastases, which produce significant morbidity and are associated with increased mortality [3–5]. Data from older studies suggest that overall survival (OS) is approximately 30–36 mo from the appearance of metastases, with a median OS of approximately 18 mo once the metastatic castrate-resistant state is established [6–8]. More contemporary data confirm that OS remains poor, approximately 30–42 mo [9–11], even with the increased number of active treatments available for mCRPC. These data emphasise the continued need for improvements in the diagnosis and treatment of APC.

With the increasing availability of therapies that prolong survival for metastatic castrate-naive prostate cancer (PCa) and mCRPC and the increasing use of prostate-specific antigen (PSA) testing after definitive therapy, imaging detection of the metastatic state is occurring for lower disease burdens. Recent data on patients who developed metastatic disease indicated that most have bone-only disease (62%), with bone and soft tissue metastases occurring in an additional 12% [9]. Soft tissue metastases occur mostly in lymph nodes outside the true pelvis, possibly because many patients receive pelvic radiotherapy for biochemical recurrence (BCR). Visceral metastases (liver, lungs, and other sites) occur infrequently at initial relapse (2%) [9], but prevalence increases with advancing disease (15–21% in mCRPC) [12,13]. The prevalence of visceral metastases also increases after multiple lines of treatment and with the emergence of aggressive histologic variants; antemortem, visceral disease can be observed in up to half of the patients [14].

APC patients with bone metastases have a greater risk of skeletal morbidity, which can impair quality of life (QoL) [15]. Bone disease causes pain, pathologic fractures, hypercalcaemia, anaemia, and spinal cord and nerve compression. Delaying symptoms from bone metastases as APC progresses is central to therapeutic management [16]. Treatments for bone metastases are generally systemic but often include local radiotherapy and/or surgery; all are currently given with palliative intent. The treatment of APC with bone metastases has significant health economic implications including the costs of systemic therapy (endocrine therapy, chemotherapy, radioisotope treatments, bisphosphonates, other supportive care medications); imaging; hospital admissions for the treatment of fractures, hypercalcaemia, and cord compression; and the costs of palliative radiotherapy [5,17].

To effectively manage patients with metastatic disease, it is essential to have accurate, reproducible, and validated methods for detecting and assessing response to therapy. These methods include clinical reviews, the use of serum PSA as a tumour marker, circulating tumour cell counts, blood and urinary markers of bone health, and imaging assessments [18,19].

1.1. Need for comprehensive metastatic imaging assessments

Imaging helps define the clinical groups for drug development [20] and clarifies the APC state for therapy recommendations [21] because the presence, volume, and distribution of metastatic disease has profound implications for the curability of PCa, greatly affecting therapy choices. At initial staging or in the setting of initial BCR, for example, the presence of metastatic disease often precludes the use of curative and local salvage options. The time to metastasis development in BCR is also highly prognostic, with a shorter interval to radiographically depicted metastasis associated with poor OS [22]. The presence and volume of metastatic skeletal disease is also highly prognostic, regardless of the imaging method used for metastatic volume estimation [12,23–26].

Imaging can also identify patients with metastatic disease patterns who have poorer prognosis. Subgroup analysis of major clinical trials has shown that imaging features contribute strongly to prognostic models that predict for survival for docetaxel-treated patients [27]. In mCRPC, the location of metastases, particularly the presence of visceral disease and the number of skeletal metastases, are highly prognostic [13,28–30]. A recent meta-analysis showed varying OS according to the anatomic location of metastases in men with mCRPC treated with docetaxel, with increased lethality for lung and liver metastases compared with bone and lymph nodal involvement [13].

Patients with poorer prognosis and higher tumour volumes appear to benefit from intensified combination treatments [12,31,32]. In the CHAARTED study, "high volume" disease was defined by the imaging presence of visceral disease and/or more than four bone metastases with at least one metastasis beyond vertebral bodies or the pelvic skeleton [12]. In mCRPC, the presence of visceral or symptomatic disease is often used as a reason for initiating chemotherapy in fit patients [21,33].

Patients are deemed to have "anaplastic features" based on clinical, biochemical, or imaging results. Imaging features used include exclusively visceral or predominantly lytic bone metastases, bulky tumour masses, low PSA levels relative to tumour burden, and short responses to ADT. Patients defined in this way may benefit more from combination docetaxel and platinum chemotherapy compared with docetaxel alone [31], although this remains controversial.

Well-powered clinical studies have shown that that abiraterone and enzalutamide therapy of asymptomatic or mildly symptomatic chemotherapy-naive mCRPC patients can be helpful for delaying clinical decline and death [10,34]. In this group, lower volume disease such as fewer than four bone metastases [30] and better performance status [11,35] seem to indicate improved OS. Note, however, that the presence of visceral disease and/or large-volume

Please cite this article in press as: Padhani AR, et al. Rationale for Modernising Imaging in Advanced Prostate Cancer. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.06.018