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Diagnostic imaging to detect and evaluate response to therapy in bone metastases from prostate cancer: current modalities and new horizons

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Abstract Different therapeutic options for the management of prostate cancer (PC) have been developed, and some are successful in providing crucial improvement in both survival and quality of life, especially in patients with metastatic castration-resistant PC. In this scenario, diverse combinations of radiopharmaceuticals (for targeting bone, cancer cells and receptors) and nuclear medicine modalities (e.g. bone scan, SPECT, SPECT/CT, PET and PET/CT) are now available for imaging bone metastases. Some radiopharmaceuticals are approved, currently available and used in the routine clinical setting, while others are not registered and are still under evaluation, and should therefore be considered experimental. On the other hand, radiologists have other tools, in addition to CT, that can better visualize bone localization and medullary involvement, such as multimodal MRI. In this review, the authors provide an overview of current management of advanced PC and discuss the choice of diagnostic modality for the detection of metastatic skeletal lesions in different phases of the disease. In addition to detection of bone metastases, the evaluation of response to therapy is another critical issue, since it remains one of the most important open questions that a multidisciplinary team faces when optimizing the management of PC. The authors emphasize the role of nuclear modalities that can presently be used in clinical practice, and also look at future perspectives based on relevant clinical data with novel radiopharmaceuticals.

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Introduction

In recent years, prostate cancer (PC) has been an active field of research in terms of biology, diagnostic imaging and drug development. In particular, the widespread application of new diagnostic technologies is offering various strategies to detect bone metastases (BMT) and assess treatment response in patients with advanced disease. Therefore, the approach to the management of PC, particularly in patients with high-risk PC (i.e. at least one of the following characteristics: PSA >20 ng/mL, Gleason score (GS) ≥8, clinical stage T2c–3a in accordance with D'Amico classification) and with skeletal metastases, has rapidly changed. The relevance of skeletal metastases in patients affected by PC is well known, and their impact on survival, life expectancy and quality of life has been reported by many authors [1–6]. Until a few years ago, patients with skeletal metastases were treated only palliatively. Conversely, today the introduction of new drugs has provided both a delay in skeleton-related events (SREs) and a significant improvement in overall survival (OS) [7–18].

Knowledge of the number and the pattern of BMT is essential to choose the correct therapy and allow proper evaluation of tumour response. Several radiopharmaceutical agents are currently available and used in different diagnostic modalities, including bone scan (BS), SPECT, SPECT/CT, PET and PET/CT. The main challenges at present are to determine the best option to detect BMT in different phases of the disease and to measure changes in radiopharmaceutical uptake as an early sign of response to treatment or progression. National and international clinical guidelines still recommend traditional BS with 99mTc-phosphonates as the standard method for studying BMT, and only a few, in certain situations, suggest other nuclear medicine approaches, such as 18F-fluoride and 11C/18F-choline PET/CT, which have been validated in several clinical studies, and are registered and available for clinical use [19–21]. Thus, the time has come to stimulate open discussion about the role of different modalities based on bone-targeting agents

(99mTc-phosphonate BS, 99mTc-phosphonate SPECT/CT and 18F-fluoride PET/CT) and cancer-targeting agents (11C/18F-choline PET/CT, 18F-FDG PET/CT) compared with the diagnostic options offered by radiology (e.g. CT and MRI). In addition, rapid progress in radiopharmacy research has led to the development of new receptor-targeting radiopharmaceutical agents such as 68Ga/18F-PSMA, which has been the subject of intense clinical assessment in several European countries with very promising results. Therefore, this field is a fertile area of discussion and debate.
We review the current status regarding the management of BMT in PC patients by summarizing the most relevant achievements from pathogenesis to treatment. New scientific knowledge on the physiopathology of BMT formation, markers of bone remodelling, main diagnostic strategies and novel treatments for advanced disease are presented. Most discussion is focused on analysis of the advantages and disadvantages offered by currently available diagnostic tools in nuclear medicine and radiology, and their current position in the diagnostic work-up of patients with skeletal metastatic disease. 68Ga/18F-PSMA, 18F-FACBC and 18F-bombesin are still considered as experimental radiopharmaceutical agents, and therefore are not fully available in clinical practice or are already registeredby regulatory authorities.However, in the present manuscript, we will give more attention to 68Ga-PSMA that represents the most interesting tracers up to now. Pathogenesis of bone metastases BMT are observed in approximately 3 – 6 % of patients with newly diagnosed PC, and 11.5 % of patients who are metastasis-free at baseline develop BMT after about 2 years of follow-up [10, 22]. In advanced stage PC, skeletal involvement is present in about 90 % of patients with metastatic disease [23, 24]. From autopsy data, 35 % of patients with advanced PC will develop haematogenous metastases and, in 90 % of such patients, the metastases will be localized in the bone [25, 26]. However, there is a wide range in reported incidence (between 35 % and 70 %) that varies depending on the study characteristics, population and follow-up period [27–29]. Given the increasing sensitivity of imaging modalities such as PET/CT and improvement in survival using new therapies, the number of PC patients with metastases at diagnosis is likely to increase and the visceral/skeletal ratio is likely to change [30]. BMT is a multistep process and its complex pathogenesis is not yet fully clarified. High bone turnover induced by androgen ablation is a predisposing condition to the homing and dissemination of tumour cells to bone marrow [31]. In animal models, there is evidence that PC cells home to sites of osteoblast-rich niches at an early stage [32]. The osteoblastic lesion is the result of releasing osteoblast-promoting factors from PC cells, and it has recently been demonstrated that osteocytes are also critical mediators in the bone metastatic niches. Therefore, targeting bone turnover at an early stage may be a useful strategy for preventing BMT in PC patients. BMT in PC are usually defined as Bosteoblastic^ by conventional plain radiography. However, recent studies have shown a high heterogeneity of lesions with synchronous osteolysis and blastic lesions [33]. Histomorphometric studies have shown that blastic lesions are mixed in nature with increased activities of both osteoblasts and osteoclasts [34]. The under-mineralized woven bone and the osteopenic/osteolytic component of BMT may contribute to the skeletal frailty observed in PC patients with metastases, even in those with dense metastatic lesions [35].BMT most commonly affect the axial skeleton and pelvis, and patients with confined disease in the vertebrae have a better prognosis. Several authors have attempted to correlate the extent of skeletal metastatic involvement, number of metastases and distribution with survival of patients affected by advanced PC [8, 14, 16]. For example, patients with metastatic castration-resistant PC (mCRPC) with a higher number of BMT (more than five) showed shorter progression-free survival and OS than those with fewer than five lesions (HR 2.0, 95 % CI 1.7 – 2.4) [17]. Moreover, BMT can worsen the quality of life and survival through an increased risk of complications. The term SRE is a composite endpoint for research purposes used to group complications such as fractures and/or spinal cord compression that require radiotherapy and pre-emptive bone surgery. Pathological fractures are common, and the commonest sites for fractures are the vertebral bodies and long bones. The most serious complications are impingement of the spinal cord, impeded anabolism due to mandatory castration therapy, and deterioration of general status that are the leading causes of hospitalization and death.

In patients with mCRPC, the rate of SRE has been reported to be 44.2 % after 15 months in the placebo arm of a randomized clinical trial of zoledronic acid [7]. Oster et al. found that more than half (51.7 %) of PC patients experience an SRE during follow-up [13]. Interestingly, there are no differences in terms of incidence of SRE and median survival time after SRE between osteoblastic and osteolyticBMT. However, pathological fractures and hypercalcaemia are slightly more frequent in osteolytic than osteoblastic BMT (52 % vs. 25 %, respectively). Conversely, spinal cord compression is more frequent in osteoblastic than for lytic BMT (8 % vs. 3 %, respectively). Radiation or surgery to bone are used at similar rates for bothtypes of bone lesions [36]. Between 1998 and 2010, the rate of SRE in PC patients decreased from 18% to 15.4 %, and SREassociated mortality decreased from 8.5 % to 4.7 % [37]. The SEER-Medicare dataset (1999 – 2009) shows that the HR of PC-specific mortality associated with SRE ranges from 1.07 to 1.31, and is also associated with spinal cord compression and pathological fractures [10–12, 15]. More recently, other researchers have investigated whether novel molecular approaches might provide additional prognostic information in patients with BMT. Indeed, it has been shown that BMT in mCRPC patients express higher levels of androgen receptor (AR) splice variants, such as AR-V7 and AR567e, than BMT in hormone-naive patients. The overexpression of AR variants is usually correlated with poorer prognosis and resistance to endocrine therapies [38].

Current treatments

Nowadays, physicians can choose among several effective alternative treatments for mCRPC. Adequate management of patients with BMT should guarantee a correct balance of efficacy, symptom control and prevention of disease complications. Both chemotherapy with docetaxel and cabazitaxel [39–44], and novel endocrine therapies such as abiraterone acetate and enzalutamide [45–47] have been shown to have a favourable impact on survival in mCRPC. More recently, docetaxel has been shown to improve life expectancy of hormone-naive patients with high risk and high tumour burden when combined with androgen deprivation treatments [42]. Up to now, although several beta emitters are available for palliative treatment of BMT, only the alpha emitter 223Ra chloride has demonstrated a survival advantage in symptomatic mCRPC patients, with limited myelotoxicity [48]; this drug is now recommended in both chemonaive patients and patients who have received docetaxel when symptomatic bone disease is present [48, 49].

The appropriate algorithm for use of available drugs is still an area of open discussion. If palliation is the main purpose, bone-modifying agents including bisphosphonates and the inhibitor of the RANK/RANKL pathway, denosumab, can be used to reduce the risk of SRE and improve the bone pain control in symptomatic patients [50], although denosumab has been shown to be superior to zoledronic acid in delaying and preventing SREs. None of these agents, however, is associated with improvement in OS. External beam radiotherapy is also an effective palliative treatment for control of pain due to BMT. It can achieve significant clinical results in 60 – 80 % of patients, with up to half of patients obtaining complete pain relief at the treated site [51, 52]. Numerous prospective randomized trials, meta-analyses and systematic reviews have shown similar pain relief outcomes with single-fraction schedules (8 Gy) compared with longer courses of palliative radiotherapy in BMT from a variety of primary malignancies [52–54]. The available evidence supports the use of single-fraction radiotherapy as a standard for all uncomplicated BMT from PC, because of its positive effects on several types of endpoints (e.g. response rates, responseduration, re-treatment rates, toxicity, cost-effectiveness [55–57].

Methods to study bone metastases

Clinical evaluation and PSA

Pain is a common symptom in PC patients with skeletal metastases,with a prevalence of about 75 % [58]. Recognizing the cause of pain is a prerequisite for a correct and rational therapeutic approach to improve and/or preserve quality of life, avoid or delay SREs and, whenever possible, to prolong survival [59]. Patient examination and administration of appropriate questionnaires is needed using validated and standardized tools, such as the visual analogue scale and World Health Organization score [60]; a multidisciplinary approach to evaluate patients and establish the optimal approach should be implemented at the early stages of disease. At present, prostrate-specific antigen (PSA) is commonly used for detecting tumour presence, extension and growth. PSA is also considered for monitoring chemotherapy treatments, although for drugs targeting BMT it is reliable since it is a marker for tumour, and not bone remodelling. It is generally accepted that a 50 % decrease in PSA levels compared with initial values is predictive of good metabolic response, and is often associated with better survival [61]. However, even in this setting, changes in PSA can show unexpected trends [62]. Recent recommendations from the Prostate Cancer Clinical Trials Working Group (PCWG2 and PCWG3) of the American Society of Clinical Oncology define PSA progression, during or after therapy, as the date that a 25 % or greater increase and an absolute increase of 2 ng/mL or more from when nadir is documented and confirmed by a second value obtained ≥3 weeks later [30, 63].

Markers of bone turnover

Continuous skeletal remodelling by osteoclast bone resorption and osteoblast bone formation can be quantified using serum and urinary biochemical parameters, or so-called markers of bone turnover. BMT are characterized by high focal bone turnover with increased levels of osteolysis and/or osteogenesis. For this reason, biochemical markers of bone remodeling might be an ideal tool to monitor progression of osteolytic or osteoblastic metastasis and/or response to treatment. At present, serum procollagen type I N-propeptide, s-PINP, and serum C-terminal telopeptide of type I collagen, s-CTX, are recommended as gold standard markers of bone formation and bone resorption, respectively [12]. The clinical utility of bone markers as diagnostic indicators of bone metastatic disease and as prognostic indicators has been extensively examined. Several studies have revealed an association between bone turnover marker and presence or progression of skeletal metastases from PC [64–67]. Bone alkaline phosphatase (ALP) had the highest diagnostic accuracy (72 % sensitivity, 88 % specificity) and PINP the highest diagnostic specificity (92 %) [67]. Retrospective analyses of data from the phase III trials of zoledronic acid in patients with mCRPC and BMT showed that both baseline and on-study elevation in bone marker levels, in particular NTX and bone ALP, were associated with increased risks of SRE, disease progression and death [68–70]. A high baseline level of urinary NTX (>180 nmol/mmol creatinine) was associated with a more than 2.5-foldincrease in the risk of death (RR 2.58, 95 % CI 1.92 – 3.47) compared with a low baseline level of NTX (<55 nmol/ mmol creatinine), and an increase in baseline bone ALP was associated with a 4 % increase in the risk of death and SRE per 200 UI/L increase [68–70]. Recently, bone ALP velocity (>6.3 UI/L/year) has been found to be an independent predictor of OS in patients with mCRPC. A fivefold increase in the risk of death was observed among mCRPC patients with rapid bone ALP velocity (HR 5.11< 95 % CI 2.24 – 11.67) [71]. Moreover, CTX or NTX in association with PINP have prognostic significance as bone markers [72]. However, in cancer patients serum or urinary levels of bone turnover markers may be high for several concomitant causes such as age, vitamin D deficiency and adjuvant hormone therapy in addition to BMT, and it is impossible to distinguish the contribution of the different components that elevate the levels of bone markers [73].

In summary, the current clinical utilization of bone turnover markers for diagnosis, prognosis and monitoring therapy in PC patients with skeletal metastases remains of high interest, but cannot be recommended at present. There is, however, an objective need for harmonization, standardization

and common reference ranges for reproducible significance of bone biomarkers in routine practice [74–76].

Radiological imaging

Conventional plain radiography, often in association with 99mTc-diphosphonate BS, CT and MRI, can be used in the assessment of prostatic bone disease, with varying results, as confirmed by data in the literature (Table 1). Plain radiography was historically the first imaging modality available for assessing bone and BMT. Plain radiography is readily available and usually easy for the patient. Although not particularly sensitive (30 – 75 % of trabecular bone must be destroyed before osseous destruction is detectable on a conventional plain radiograph), plain radiography does give an overview of the status of a particular bone segment, and in the absence of Bred flag^ symptoms, it is a good preliminary investigation. In addition, it is simple and cost effective, especially in symptomatic patients, and allows the assessment of potential complications such as pathological fractures. However, neither systematic bone screening nor evaluation of treatment response of BMT by conventional plain radiography are currently used in clinical practice because of their low diagnostic accuracy; indeed, radiographic signs of therapeutic response of bone lesions (peripheral sclerosis, lesion filling, and condensation) are delayed by several months, ambiguous, or absent despite clinical improvement [86, 87]. Peripheral sclerosis is observed only in osteolytic lesions, which are observed in only 10 % of patients with bone metastatic PC. Conversely, condensation is more frequent in mixed or osteoblastic lesions. CT is well suited to bone imaging. The availability of CT has increased greatly in recent years and the speed and quality of image reconstruction has been substantially enhanced. CT allows finely detailed assessment of osseous architecture, including the cortex and trabecular framework, and detects much smaller areas of trabecular destruction/invasion than visible by plain radiography alone. CT is also particularly helpful in assessing areas that can be difficult to visualize by plain radiography, such as the sacrum. For evident radioprotection reasons, CT targets a particular portion of the body and is not used for whole-body (WB) bone screening in clinical applications, although in some situations it is routinely employed. Moreover, CT scans are limited in their ability to assess therapeutic response because bone structure rarely normalizes even with completely effective therapy. The appearance of new or worsening bone sclerosis on CT in patients is occasionally and erroneously classified as disease progression (CT flare response) by inexperienced radiologists. RECIST criteria (v. 1.1) allow individual osteolytic or mixed osteolytic/osteoblastic metastases to be measured if there is a soft-tissue component, but diffuse disease and osteoblastic BMT are considered non-evaluable [88, 89]. Furthermore, other observations (e.g. lack of change, appearance of new sclerotic areas) should be considered more cautiously and should not be taken into account in evaluation of response.

Plain radiography and CT detect neoplastic bone lesions at a late stage, i.e. weeks or months after the appearance of tumour cells within the bone marrow, because they rely on the activation of bone cells – osteoblasts and osteoclasts – to detect lesions. MRI is sensitive to early changes in bone marrow that precede the osteoclastic/osteoblastic response of the bone matrix to tumour infiltration before bone trabeculae or cortices are affected by disease. The superiority of MRI for detection of BMT over both plain radiography and CT (often as Baddons^ to bone scintigraphy) has been widely demonstrated (Table 1). The availability of the technique, its repeatability, lack of irradiation and its ability to provide WB evaluation have contributed to the development of MRI as the tool of choice for detection and follow-up of BMT. As an adjunct to conventional T1-weighted and STIR (short tau inversion recovery) acquisitions, diffusion-weighted imaging (DWI) sequences are also currently employed. DWI is able to detect changes in water diffusion that occur when normal fatty marrow is replaced with highly dense cellularity that restricts normal water movements among cell membranes. The advent of WB protocols with excellent image resolution and shortening of acquisition times, and the developmentWB DWIand Ball-organ^ capabilities, justify the increasing use of WB MRI at many centres [79, 90]. DWI provides morphological (qualitative)

and functional (quantitative) information on BMT. Qualitatively, reconstructed maximum intensity projection (MIP) or multi-parametric projection (MPR) images of DWI, covering the whole body or only the central skeleton, provide an easy Bat a glance^ qualitative evaluation of tumour burden, and focus attention on areas that are difficult to analyse on anatomic images. Several pitfalls in the visual analysis of DWI images must be recognized. As DWI not only reflects the cellular load but also the water content of tissues, benign conditions such as degenerative joint diseases, fractures, postirradiation changes and benign tumours (angiomas) may show high signal intensity on DWI images. The technique may also present false-negative findings, mainly in sclerotic or calcified metastases. These shortcomings underline the need for a systematic correlation of DWI images with conventional sequences. In this regard, T1-weighted images are the most helpful, in particular when acquired using the 3D protocol, which has been demonstrated to increase the sensitivity in detection of lesions [91].

The technique also shows great promise for assessment of response.DWI is able to detect changes in water diffusion that occur after therapy as a result of changes in cellular density and loss of membrane integrity. The impeded water mobility observed in tumour tissue will decrease or disappear in relation to the loss of cellular integrity in response to treatment, for example owing to cellular necrosis. Comparison of consecutive examinations provides a rapid and generally nonambiguous qualitative evaluation of disease response or progression during therapy. DWI also allows the measurement of the apparent diffusion coefficient (ADC, units $\times 10^{-3}$ mm2/s), which provides functional (quantitative) assessment of tumour lesions. Generally, a tumour focus shows decreased ADC values in relation to increased cellularity and restricted mobility of protons in water. DWI is able to detect an increase in ADC in PC metastases treated with antiandrogen therapy as early as 1 month after treatment initiation [92, 93]. The effectiveness of ADC monitoring to predict the response of BMT to therapy is, however, controversial. The interpretation of changes in ADC values is indeed complex, mainly because of heterogeneity of both the tumour and response to treatment. Newer analysis methods (ADC parametric response or functional diffusion map) taking into account spatial information and tumour heterogeneity enable careful voxel-by-voxel follow-up of treatment-induced changes and evaluation of the proportion of tumour tissues in which significant changes occur [94]. These approaches seem to be able to detect very early changes (such as an increase in ADC) after treatment initiation. However, ADC can be used routinely only after optimization of hardware, sequences, signal analysis and definitive standardization of the acquisition method to improve the reliability of the results. Evaluation of reproducibility of ADC measurements is also a priority [94].

In conclusion, MRI (especially with the use of WB and DWI acquisitions) has a well-established role for the detection of metastases, but evaluation of response to therapy is challenging due to the heterogeneity of disease and the mainly osteoblastic nature of metastases. Areas of sclerosis are often present at the time of diagnosis and may increase following treatment, even with other signs of response to treatment. When this occurs, neither DWI nor anatomic imaging appears to be useful in giving the correct response. In fact, the sclerotic lesion may actually appear larger and/or the evaluation of its diffusion coefficient may be controversial. MRI appears to be a more reliable tool for: confirming stable disease when the size of measurable bone lesions remains unchanged and no new lesions are found; corroborating progressive disease when new lesions are seen or if a sclerotic lesion shows a new peripheral halo (hypointense on T1-weighted imaging and hyperintense on DWI as signs of increased cellularity and restricted diffusion) [79]. Therefore, the potential of MRI in evaluation of treatment response is still being studied, and only a limited amount of data are currently available [95] .

Nuclear medicine imaging

Nuclear medicine offers several options for the detection of BMT in PC patients: (a) BS as planar or tomographic imaging (i.e. single photon emission tomography, SPET) and (b) PET/ CT with 18F-

fluoride or 18F-FDG, 11C/18F-choline or 11C-acetate, 68Ga-PSMA, or 18F-FACBC. Each imaging technique has a specific mechanism of action in the detection of BMT due to differences in uptake and metabolism among the radiopharmaceuticals. Therefore, each technique is associated with different diagnostic performance that is mainly based on the type of skeletal lesion (i.e. osteoblastic vs. osteolytic vs. bone marrow invasion) [96–98]. At present, 11C-acetate, 68Ga-PSMA and 18F-FACBC are still considered experimental radiopharmaceutical agents. These agents are not employed in routine clinical practice, and 11C-acetate, 68Ga-PSMA and 18F-FACBC are not discussed further in this review; however, the increasing data on 68Ga-PSMA in PC patients studied in several European countries has shown a promising role for this tracer in BMT detection, and this agent is discussed in the section New horizons in the detection of bone metastases and evaluation of response to treatment. Planar BS using 99mTc-diphosphonates is the standard technique for the detection of skeletal metastasis from PC as it is widely available, relatively inexpensive and highly sensitive. However, the mechanism of uptake of 99mTc to a suitable phosphonate that allows imaging of sites of blastic or mixed lesions, and not areas where a calcium deposit is lacking, limits the use of this radiopharmaceutical. For this reason, BS shows low specificity (falsely positive in benign lesions, prior trauma and arthritis) and flare phenomena. Therefore, an osteoblastic response that occurs as a result of bone healing/ flare response during systemic treatment can significantly alter its diagnostic performance and make clinical interpretation of scintigraphic findings very difficult. Moreover, in a large retrospective analysis, BMT were found in less than 1 % of patients with PSA <20 ng/mL, with a negative predictive value of 99.7 % [99]. Leucovet et al. found that in 100 patients with high-risk PC the sensitivity of BS increased from 80%to 86 % when it was added to targeted plain radiography [79]. However, although the introduction of tomographic imaging such as SPET and SPET/CT has overcome some of the limitations of BS, these modalities are not able to cover the entire body of the patient. An interesting possibility offered by BS is calculation of the BS index, which better reflects the extent of metastatic disease [100]. This approach is noteworthy since its measurement can be automated, although the technique has not shown value in routine clinical practice [101]. Even with persistently high costs, PET is an efficient modality for WB scanning in a reasonably short time.With the increasing availability of PET/ CT scanners and standardized acquisition protocols on different PET scanners, the possibility of obtaining more detailed and precise CT anatomic localizations of PET-directed metabolic abnormalities of tumour lesions, especially in skeletal diseases, has become a clinical reality. Moreover, PET is able to provide quantitative and semiquantitative information by May, 2012 October, 2012 February,2013 Fig. 2 A 68-year-old man with prostate cancer treated by radical prostatectomy (pT3aN0Mx, Gleason score 10; positive margins and extracapsular invasion) and adjuvant radiotherapy in 2010. May 2012 In 2012, for biochemical recurrence of disease (PSA 15.55 ng/mL), he was staged by 18F-choline PET/CT that showed metastatic bone recurrence of disease. He was started on bicalutamide and LHRH analogues. October 2012 Due to a further increase in PSA (141 ng/mL after 4 months), 18F-choline PET/CT was repeated that showed progression of metabolic disease. Therefore, the attending oncologist suggested switching the treatment from androgen deprivation therapy to chemotherapy (docetaxel + prednisone). February 2013 After 4 months, PSA had reduced to 33.6 ng/mL and 18F-choline PET/CTshowed a good response to chemotherapy Eur J Nucl Med Mol Imaging (2016) 43:1546–1562 1555 using reproducible standardized quantification methods [102] that are useful for comparing serial examinations, especially before, during and after therapy. Nowadays, many radiopharmaceutical agents are available for PET/CT imaging, especially for the detection of BMT. 18F-Fluoride, a hydroxyapatite stabilizer, has the desirable characteristics of high and rapid bone uptake accompanied by very rapid blood clearance, which results in a high bone-to-background ratio in a short time. 18F/11C-Choline is a substrate of phospholipid metabolism which is usually enhanced in PC that is able to identify the presence of viable cancer tissue; promising results, especially for early detection of bone marrow infiltration, have been obtained. 18F-FDG is mainly used for definition of osteolytic lesions [57], but seems to be able to identify the presence of viable cells in

osteoblastic ones, even if the majority of PC displays low glycolytic metabolic behaviour, which would suggest that its current use may not be optimal. Generally, high uptake of 18F-FDG is expected in prostate tumours that are poorly differentiated, hypoxic and have a high GS. However, it can be used to assess the extent of metabolically active castrate-resistant prostate disease.
Table 2 summarizes the performance of each imaging modality. As shown, the median sensitivity of 18F-fluoride PET/ CT is the highest in comparison to the other modalities for the detection of BMT in PC patients. However, it should be underlined that in many studies bone disease is often measured on follow-up imaging, such as CT, BS, or MRI, while histological assessment is not performed, mainly for ethical reasons. Conversely, both 11C-choline and 18F-choline PET/ CT show higher specificity than BS or 18F-fluoride PET/CT. This result can be linked to the different behaviour of 18F/11C-choline in osteoarticular disease. Moreover, as expected, 18F-FDG PET/CT has low sensitivity (between 56 % and 72 %) in the detection of BMT in patients with PC, although as suggested by several authors, and as mentioned above, it may occasionally be suitable for prostate imaging in a limited subset of selected patients with aggressive histology and poorly differentiated cancer [111, 117–119].
Considering the areas of assessment of response to therapy, all of the above-mentioned metabolic methods may have value since their uptake is linked to the phenomenon of bone remodelling or to the metabolic activity of neoplastic cells. Most of the available data relate to BS as for decades this has been the most widely used modality to study skeletal lesions and still remains the most common. There are limited data regarding other modalities, even if there is a progressive increase in their use. The most recent data available in the literature demonstrate a role for radiolabelled choline PET/ CT in assessment of new hormonal therapies, such as enzalutamide [120, 121] or abiraterone acetate [122], and chemotherapy (i.e. docetaxel) [123]. The findings of radiolabelled choline PET/CT have been compared to PSA changes in order to determine the response to therapy. Choline PET/CT findings agree with PSA changes in the majority of patients with progressive disease, during and after therapy; on the contrary, PET/CT is able to identify only a moderate number of patients with partial or complete response to therapy. However, the disappearance of uptake does not always correlate with the disappearance of the cancer lesion since it could be due to the effect of a stable or nonmetabolically active focus. In contrast, the appearance of new areas of uptake does not always correlate with certain progression due to the well-known phenomenon of flare reaction, whose correct interpretation in BS has been standardized. This issue is an open area of debate.

New horizons in the detection of bone metastases and evaluation of response to treatment

The majority of national and international guidelines for PC, such as EAU [20], AUA [124], ESMO [49] and NCCN [21], mainly recommend using PSA levels, BS and abdominopelvic CT to determine the presence of cancer and monitor treatment response. Moreover, in some recent clinical trials [41, 43, 46, 48, 90, 125], PSA, CT and BS have been used to evaluate tumour response to therapy in mCRPC patients. However, MRI has a greater ability to detect more skeletal lesions and earlier than CT; in addition, it is currently used as a Bproblemsolving^ technique when a lesion is reported as Bindeterminate^. However, MRI cannot be proposed as an alternative method for diagnosis of skeletal metastasis or for monitoring response to treatment because of its limited field of view (which can be overcome with WB MRI that is now available in a few centres) and restricted interpretation criteria when bone sclerosis is present at the metastatic site (such as RECIST).
Although CT remains the most widespread imaging technique for detection of cancer, it is important to underline that RECIST criteria can be used for assessment of visceral metastases, but cannot be employed for evaluation of response to therapy in BMT, considering their anatomic features and biological behaviour. Therefore, the integration of PSA, other appropriate bone biomarkers such as ALP and morphological imaging with metabolic techniques can provide

additional information that is reliable for monitoring changes occurring inside the tumour and bone structure. As already mentioned, BS continues to be used in clinical practice since it has advantages in terms of cost, availability and execution, even if it has low diagnostic specificity and cannot detect medullary and osteolytic lesions. The hybrid modality SPET/CTcan improve the accuracy of planar BS, but has a limited field of view like MRI and still suffers from the limitation of the poor specificity. 18F-Fluoride PET/CT can improve the sensitivity in detecting BMT, and also has other advantages, including better quality of images and shorter acquisition time. 18F/11CCholine and 18F-FDG PET/CTare able to visualize both skeletal and nonskeletal metastases. In some studies, both metabolic radiopharmaceutical agents have been used to assess response to therapy [120–123, 126, 127], but data are still preliminary. Table 3 summarizes the strengths and weaknesses of the currently employed radiological and nuclear medicine modalities in clinical practice for evaluation of bone lesions in patients with PC. The development of new receptor tracers, such as 68Ga-PSMA, has opened new approaches to the management of PC, although they are still experimental. The most significant advantages of 68Ga-PSMAPET/CTare the sensitive detection of lesions, even at low PSA levels (i.e. PSA <1 ng/mL), small lymph node metastases (primarily due to high radiotracer uptake) and central bone and liver metastases due to low background
signal. However, PSMA imaging should be approached with caution because of the limited information in the form of published data. From current data, the detection rate of BMT with 68Ga-PSMA is 37 % [96, 130–133] compared to 32.1 % with choline PET/CT [115, 134–138] (Tables 4 and 5). However, continuing research will probably soon provide more information on the use of 68Ga-PSMA (Figs. 1 and 2). Eur J Nucl Med Mol Imaging (2016) 43:1546–1562 1557 To date, on the basis of approved diagnostic instruments and radiopharmaceutical agents, we can summarize the evidence discussed above in a flow-chart to localize disease (BMT, monitor evolution and whenever possible obtain prognostic information). According to the site of recurrence, patients with PC can be classified as having bone-dominant (only skeletal involvement) or no bone-dominant disease (no skeletal, lymph node, visceral, or soft-tissue invasion; Fig. 3). Based on the extent of dissemination of disease, the most appropriate diagnostic tool to visualize BMT can be chosen based on disease grade (i.e. low grade, GS ≤7, or high grade, GS 8 – 10). Therefore, to detect lesions in bonedominant disease, all patients with PC who are candidates for bone-targeted therapies, such as 223Ra, could benefit from those techniques targeting bone modalities (BS and SPET or 18F-fluoride PET/CT). BS is still considered the standard method of choice, but could be replaced by 18F-fluoride PET/CT given its higher sensitivity. Moreover, since PET is always performed with CT (as PET/CT), the use of CT as a stand-alone examination for analysis of bone can be avoided. Additionally, MRI can be used to better characterize the structure of metastatic lesions and as a Bproblem-solving^ technique when an indeterminate lesion is found. In patients with bone-dominant disease and a GS ≥8 – 10, 18F-FDGPET/CTas a bone-targeting modality would be of value to obtain predictive information on both response to therapy and prognosis. Thus in patients with poorly differentiated disease, 18F-FDG PET/CT could be adopted. However, considering the limited utility of 18F-FDG PET/CTand the metabolic heterogeneity of PC, it should be considered together with other cancer or receptor-specific radiopharmaceutical agents such as radiolabelled choline and/or PSMA. Each imaging scan should be repeated, as suggested by the PCWG2, at the end of antitumour therapy unless more frequent assessments are required by the treatment protocol (2 – 3 months) or by the development of signs or symptoms suggesting tumour progression, or if a flare reaction is suspected. In these cases, it should be repeated after 3 months.
On the other hand, in patients with non-bone-dominant disease 18F/11C-choline PET/CT and CT should preferably be used for follow-up, since radiolabelled choline scan can visualize both visceral and skeletal lesions, while CT is adequate to follow visceral lesions, especially those in the liver. If more accurate skeletal evaluation is required, MRI or 18F-fluoride PET/CT can be substituted for CT. In this subset of patients, radiolabelled choline PET/CT should be used during therapy (every 3 – 6 months according to PCWG2 and the recent recommendations of the St. Gallen Consensus Conference [63, 139]) and at the end of therapy, or on the basis of changes in PSA level. 18F-

Choline PET/CT should be repeated within 3 months if a flare phenomenon is suspected (as described during abiraterone treatment). Lastly, there are two main advantages of including nuclear medicine imaging in monitoring the response to therapy in PC patients: to evaluate the effects of different targeting therapies on the metabolism of PC cells and to assess the state of the disease in relation to the timing of treatments.

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Table 1

Performance of radiological techniques in assessing the presence of bone metastases in patients with prostate cancer

Technique	Reference	No. of patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Plain radiography (add-on to bone scan)	[77]	66	63	64	100	70	–
	[78]	14	58.6	–	–	–	–
	[79]	100	86	98	98	87	–
	Weighted mean		75.4	84.5	98.8	80.2	NE
	Total	180					
CT (add-on to bone scan)	[80]	15	67	–	–	–	–
	[79]	66	100	88	100	100	–
MRI axial skeleton only	[80]	15	93	–	–	–	–
	Weighted mean		98.7	NE	NE	NE	NE
	Total	81					
Whole-body MRI with diffusion-weighted imaging	[80]	15	100	–	–	–	–
	[78]	14	96.4	–	–	–	–
	[81]	39	70	100	100	–	–
	[82]	49	100	87.2	–	–	–
	[83]	35	91	99	97	97	–
	[84]	49	100	98	83	100	98
	[79]	100	98	98	98	98	–
	[85]	23	80	98.2	–	–	–
	Weighted mean		93.2	96.6	94.9	98.3	NE
	Total	324					

– not reported, *NE* not evaluated

Table 2

Performance of nuclear imaging techniques in patients with prostate cancer

Technique	Reference	No. of patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Bone scan	[103]	91	65.4	38.5	86.4	15.6	61.5
	[104]	50	50.8	82.2	86.4	42.9	60.6
	[97]	44	57	57	59	55	–
	[105]	18	87.5	80	–	–	–
	[106]	72	96.9	41.2	75.6	87.5	77.5
	[107]	97	96.4	75.3	98.1	61.4	–
	[108]	10	66.7	81.6	53.3	88.6	78
	[109]	37	89.3	–	–	–	–
	Weighted mean		78.5	59.3	83.2	52.5	67.2
	Total	419					
SPET	[97]	44	78	67	72	74	–
	[107]	97	96.4	63.7	97.8	51.9	–
	Weighted mean		90.7	64.7	89.7	58.8	NE
	Total	141					
SPET/CT	[107]	97	96.4	94.2	98.5	87.1	
^{18}F-Fluoride PET/CT	[104]	50	93.1	54	81.8	77.9	81
	[97][a]	44	100	62	74	100	–
	[97][b]	44	100	100	100	100	–
	[110]	38	81	93	–	–	86
	[111]	42	91	83	–	–	88
	[105]	18	100	100	–	–	–
	[106]	72	100	70.6	86.5	100	65.4
	[108]	10	100	89.5	75	100	92
	Weighted mean		95.5	77.4	85.1	94.9	78.5
	Total	318					
^{18}F-FDG PET/CT	[105]	18	55.6	80	–	–	–
	[106]	72	71.9	100	100	65.4	81.6
	Weighted mean		68.6	96	NE	NE	NE
	Total	90					
^{18}F-Choline PET/CT	[110]	70	79	97	84	–	–
	[112]	26	96	100	–	–	–
	[104]	50	84.7	91.1	95	74.9	86.8
	[113]	38	74	99	–	–	88

Technique	Reference	No. of patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
^{11}C-Choline PET/CT	[111]	42	91	89	–	–	90
	[109]	37	82.7	–	–	–	–
	Weighted mean		83.5	94.9	88.6	NE	88.2
	Total	263					
	[114]	25	86	100	–	–	–
	[103]	91	96	92.3	98.7	80	95.6
	[115]	78	89	98	96	94	95
	[116]	95	81.3	98.7	–	–	95.8
	Weighted mean		88.4	96.6	97.5	86.5	95.5
	Total	289					

– not reported, *NE* not evaluated

[a]PET

[b]PET/CT

Table 3

Advantages and disadvantages of radiological and nuclear medicine techniques for detection and follow-up of bone metastases

Technique	Advantages	Disadvantages
Plain radiography	1. High availability 2. Low cost 3. Easy for the patient 4. Allows assessment of complications (e.g. fractures)	1. Low sensitivity and specificity 2. Not all bones can be screened 3. Does not allow assessment of therapeutic response
CT	1. High availability 2. Allows assessment of fine bone details and characterization smaller lesions 3. Allows detection of node and visceral metastases	1. High radiation dose 2. Not used for systematic bone screening 3. Not useful in assessment of therapy response
MRI axial skeleton only	1. Good availability 2. Earlier detection of tumour foci 3. Better diagnostic performance in detection and characterization of bone lesions	1. Bone metastases outside vertebral column or pelvic bones not detected 2. Not used for detection of node or visceral metastases 3. Not useful in assessment of therapy response
MRI with whole-body and diffusion-weighted acquisitions	1. Highest diagnostic performance in detection and characterization of bone lesions 2. Allows detection and assessment of therapeutic response of node and visceral metastases 3. Possible role of diffusion-weighted and anatomic imaging (3D T1-weighted) in assessment of therapeutic response	1. Advanced diagnostic techniques only available in specialist diagnostic imaging centres 2. Longer duration of examination 3. Higher cost
Bone scan	1. Low cost [104] 2. High availability [104] 3. Able to detect bone metastases several months before they are revealed by plain radiography	1. Low sensitivity for osteolytic lesions [97] 2. No detection of bone marrow disease 3. Poor sensitivity for osteolytic lesions without bone remodelling

Technique	Advantages	Disadvantages
		4. Low specificity (false-positive findings in case of degenerative changes, inflammatory processes, trauma, mechanical stress, and Paget's disease) [97]
		5. Bone reactive changes necessary for optimal sensitivity [104]
		6. Flare phenomenon due to some systemic treatments (also ^{223}Ra) [128]
SPET	1. Improves the sensitivity of planar images	1. Limited field of view [97] 2. Specificity not better than plain radiography 3. As bone scan (see above) [97]
SPET/CT	1. Improves the sensitivity of planar images 2. Improves the specificity of planar images [97]	1. Whole-body imaging not currently standard practice 2. Resource implications of increased cost, specialist equipment, and specialist manpower hours 3. Higher radiation dose than bone scan (3 – 5 mSv) 4. As bone scan (see above)
^{18}F-Fluoride PET/CT	1. Elimination of fluoride from the blood is rapid. First pass elimination is 100 % vs. 64 % for diphosphonates 2. Superior image quality and therefore high diagnostic accuracy [105] 3. Rapid acquisition protocol (15 or 60 min after injection) 4. As ^{99m}Tc-diphosphonate, is able to identify high bone turnover and remodelling 5. Quantitative and automatic semiquantitative analyses of uptake in lesions [102]	1. Very sensitive to minimal degenerative changes 2. Higher cost and radiation dose compared with bone scan (from 3 to 5 – 7 mSv) [97] 3. Uncertain clinical impact when used to monitor treatment response 4. Flare phenomenon due to some systemic treatments (also ^{223}Ra) [127]
^{18}F-FDG PET/CT	1. Can detect bone metastases at early stage of disease (bone marrow	1. Sclerotic metastases can be missed because of relatively small amount of

Technique	Advantages	Disadvantages
	involvement)	viable tumour tissue [126]
	2. In osteolytic lesions and in presence of aggressive prostatic cancer, accumulation of tracer is higher for an increase in glycolytic rate [106]	2. FDG uptake limited in moderately or well-differentiated prostate cancer by low metabolism of the tissue [126]
	3. Lack of FDG uptake in the osteoblastic lesion can be associated with the presence of quiescent cells	3. Higher cost and increased radiation dose compared with bone scan (from 3 to 5 – 7 mSv)
	4. Superior image quality and therefore high diagnostic accuracy	
	5. Prognostic information [129]	
	6. Quantitative and automatic semiquantitative analyses of uptake in lesions [102]	
$^{11}C/^{18}F$-Choline PET/CT	1. More specific for prostate cancer	1. Flare phenomena reported during administration of abiraterone acetate and granulocyte-colony stimulating factor [121]
	2. Able to identify three patterns of bone disease (bone marrow involvement, osteoblastic lesions, no active tumour) [110]	2. ^{11}C-Choline not available in centres without on-site cyclotron
	3. No uptake in chronic degenerative disease	3. High cost and increased radiation dose compared with bone scan (from 3 to 5 – 7 mSv)
	4. Quantitative and automatic semiquantitative analyses of uptake in lesions [102]	

Table 4

Performance of ^{68}Ga-PSMA PET in the detection of bone metastases

Reference	No. patients	PSA level[a] (ng/mL)	Bone metastasis detection	
			Detection rate	Sensitivity (%)
[132]	5	–	–	Not available
[130]	319	4.59 (0.01 – 41,395)	359/901	Not available
[96]	37	4.0 (0.01 – 116)	23/78	Not available
[133]	38	1.72 ± 2.54	10/59	Not available
[131]	20	2.62 (0.51 – 73.6)	23/75	Not available
All	419	–	415/1,113 (37 %)[b]	–

[a]Expressed as median (range) or mean ± standard deviation, in accordance with available data

[b]A lesion-based analysis was available in all studies

Table 5

Performance of radiolabelled choline PET in the detection of bone metastases

Reference	No. of patients	PSA level[a] (ng/mL)	Bone metastasis detection	
			Detection rate	Sensitivity (%)
[137]	48	12.71[b] (2.80 – 581)	14	100
[134]	102	0.93 (0.67 – 1.10)	13	100
[138]	132	7.2 (2.2 – 1028)	26	Not available
[115]	78	2.4 (0.2 – 500)	24	89
[135]	140	4.9 (0.2 – 92)	70	Not available
[136]	1,000	3.30 (0.2 – 10,960)	335	80 (in 235 patients)
All	1,500	–	482 (32.1 %)[c]	–

[a]Expressed as median (range) or mean ± standard deviation, in accordance with available data

[b]The study was performed at initial staging of disease

[c]A patient-based analysis was available in all studies

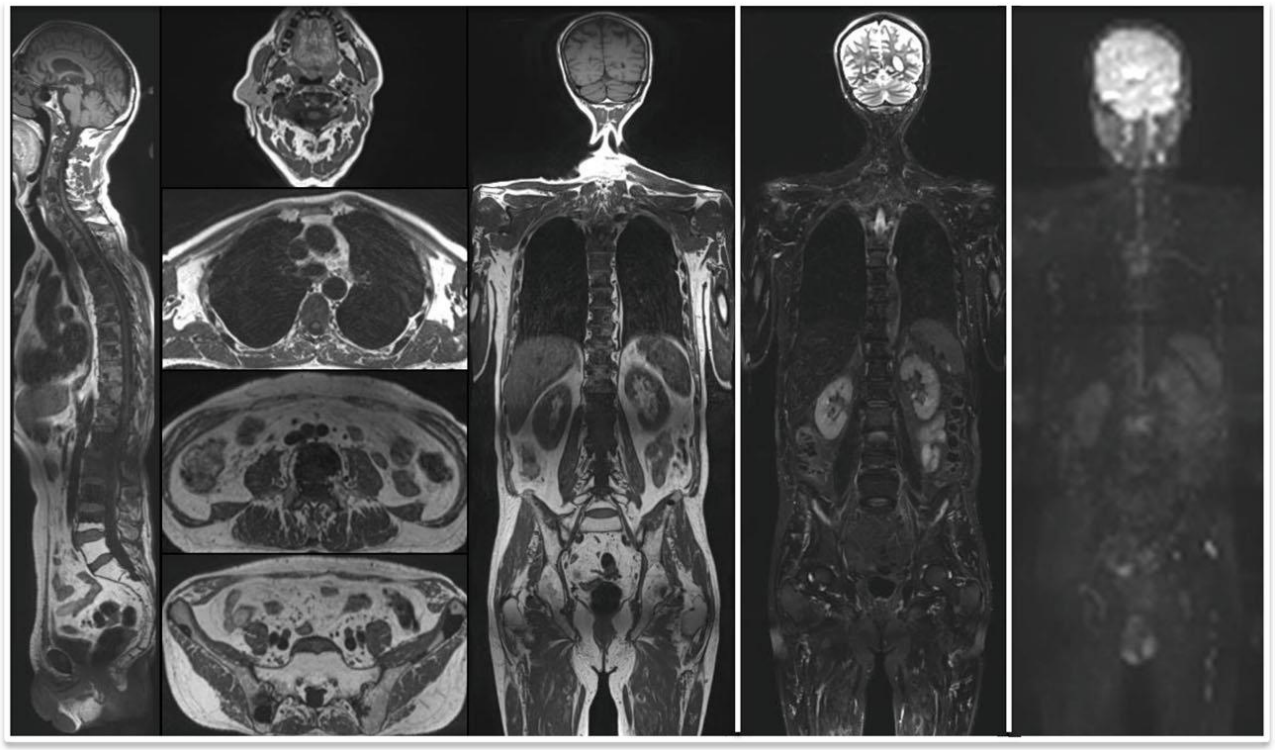

Fig. 1 Whole-body MR images in a 69-year-old man with diffuse metastatic bone disease and signs of progression during antiandrogenic therapy. MR protocol corresponding whole-body 3D T1-weighted, STIR (short-tau inversion recovery) and diffusion-weighted images. Total scan time 54 min. a 3D coronal T1-weighted images with reconstructed sagittal and axial planes showing bone metastases as multiple hypointense foci involving vertebrae, ribs, hip, sternum and femurs. Early progression of disease is represented by the appearance of low signal intensity tissue adjacent to some of these foci (e.g. L2 and right iliac bone). b Corresponding STIR images confirm the predominantly osteosclerotic nature of the metastases which appear mostly hypointense; early progression of metastatic involvement is represented by the appearance of moderately high signal intensity bone changes. C DW images with 3D maximum intensity projection reconstruction identify early progression of disease as appearance of hyperintense bone foci representing tissue with restricted diffusion due to high cellularity. The remaining bone metastases are not clearly seen on the DW images, representing false-negative findings due to advanced sclerotic changes inside the lesions

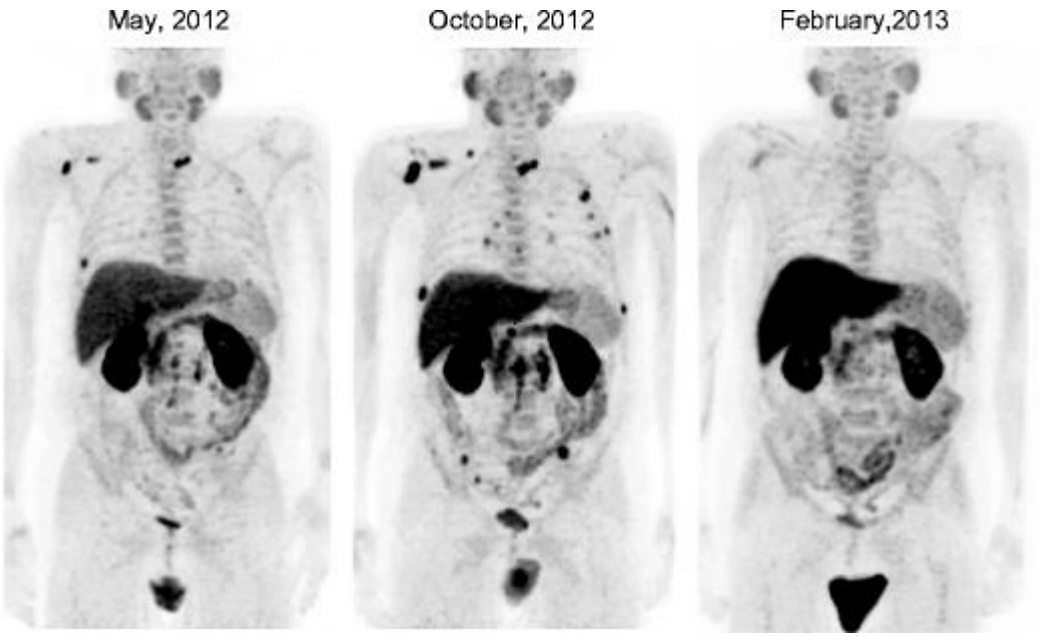

Fig. 2

A 68-year-old man with prostate cancer treated by radical prostatectomy (pT3aN0Mx, Gleason score 10; positive margins and extracapsular invasion) and adjuvant radiotherapy in 2010. *May 2012* In 2012, for biochemical recurrence of disease (PSA 15.55 ng/mL), he was staged by ^{18}F-choline PET/CT that showed metastatic bone recurrence of disease. He was started on bicalutamide and LHRH analogues. *October 2012* Due to a further increase in PSA (141 ng/mL after 4 months), ^{18}F-choline PET/CT was repeated that showed progression of metabolic disease. Therefore, the attending oncologist suggested switching the treatment from androgen deprivation therapy to chemotherapy (docetaxel + prednisone). *February 2013* After 4 months, PSA had reduced to 33.6 ng/mL and ^{18}F-choline PET/CT showed a good response to chemotherapy

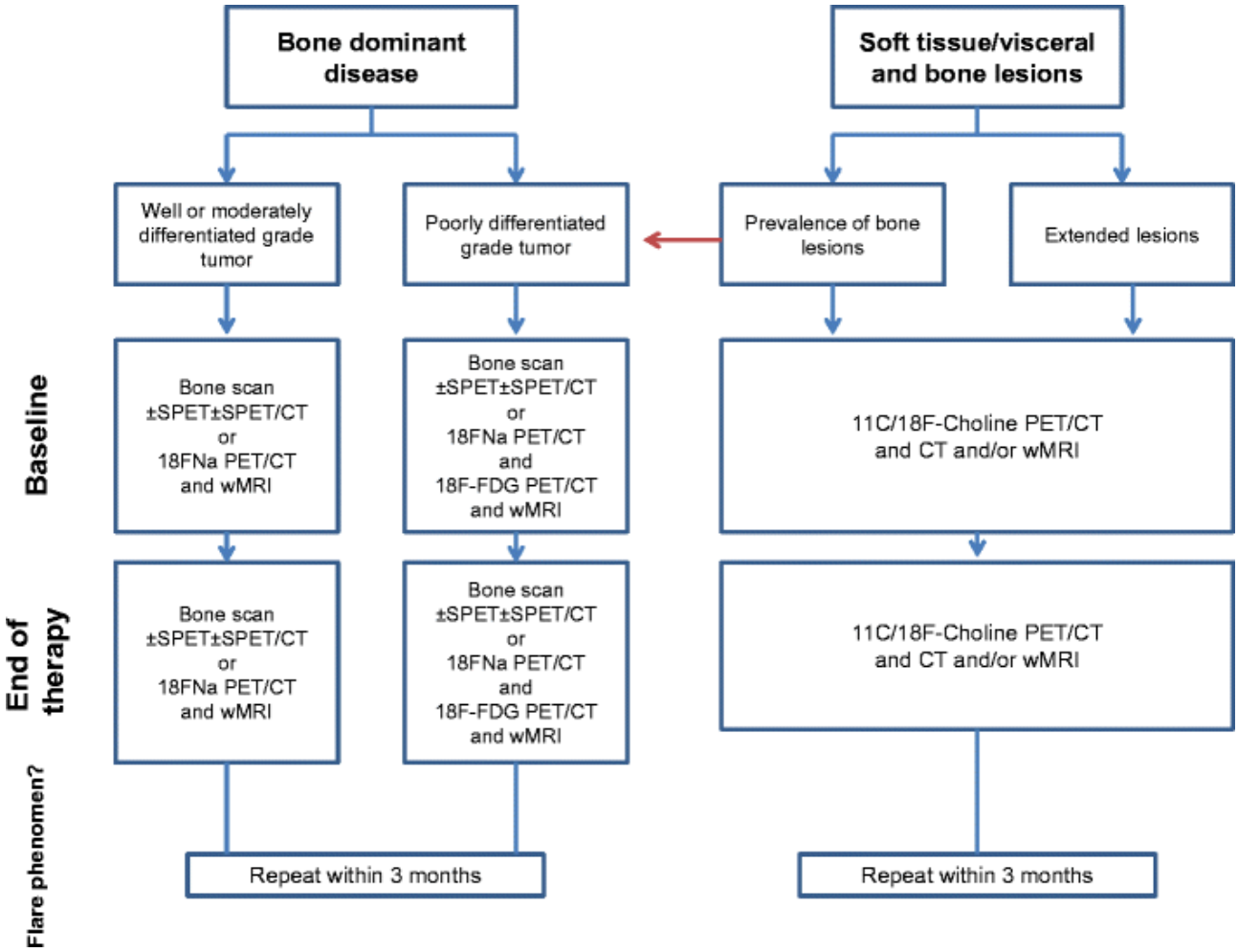

Fig. 3
Diagnostic algorithm proposed for assessment of response to therapy in patients with metastatic prostate cancer (well-differentiated or low-risk prostate cancer is considered to be present in patients with a Gleason score of 6, moderately differentiated or intermediate-risk prostate cancer in patients with a Gleason score of 7, and poorly differentiated or high-risk prostate cancer in patients with a Gleason score of between 8 and 10) *wMRI* whole-body MRI