Oligometastatic Disease in Prostate Cancer:

Use of modern imaging methods to facilitate trials of metastasis-directed therapy.

A Consensus Recommendation from the EORTC Imaging Group

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Key words: Cancer, Prostate, Staging, Metastasis, Oligometastasis, Treatment, Imaging, Molecular

Abstract

Oligometastatic disease (OMD) represents a clinical and anatomical manifestation between localized and polymetastatic disease. In prostate cancer, as with other cancers, recognition of OMD enables focal, metastases-directed therapies. These therapies potentially shorten or postpone the use of systemic treatment and may delay further metastatic progression, thus increasing overall survival. To validate their efficacy, metastases-directed therapies require imaging methods that definitively recognize OMD and reliably monitor response, particularly to avoid morbidity of inappropriately treating disease subsequently recognized as polymetastatic.

This paper reviews current imaging methods used for identifying metastatic prostate cancer at first diagnosis, at biochemical recurrence (BCR), or at the castration resistant stage. Standard imaging methods recommended by current guidelines have insufficient diagnostic accuracy for reliably diagnosing OMD. Modern imaging methods using positron emission tomography /computed tomography (PET/CT) with tumour specific radiotracers (choline or PSMA ligand), and increasingly even whole-body magnetic resonance imaging (WB-MRI) with diffusion-weighted imaging (DWI), allow earlier and more precise identification of metastases.

The EORTC Imaging Group suggests clinical algorithms for integrating modern imaging methods into the care pathway at the various stages of prostate cancer in order to identify OMD. Clinical trials utilizing modern imaging methods are proposed for evaluating the benefits of metastasis-directed therapies.

INTRODUCTION:

Oligometastatic disease (OMD) represents a clinical and anatomical manifestation between localized and polymetastatic disease, and is recognized in prostate cancer (PCa) [1,2]. Its importance is increasingly acknowledged, as evidence grows for treating limited metastatic lesions with focal ablative therapies such as stereotactic body radiation therapy (SBRT), surgery, or focal thermal ablation [3, 4] rather than with systemic therapies. In OMD, these metastasis-directed therapies (MDT) potentially shorten or postpone the use of systemic treatment and alter the course of the disease by delaying further metastatic progression, potentially increasing overall survival. However, although MDTs have become increasingly popular amongst physicians, their delivery relies more on conventional wisdom that on robust evidence [5]. Implementing these treatments in patients in whom the underlying disease is polymetastatic is undesirable, (a particular problem in PCa where there is a long lead time in metastasis development) as it merely results in unnecessary morbidity. If disease is polymetastatic, stereotactic radiotherapy and salvage surgery may cause specific toxicity (e.g. increased femoral fracture rate [6] and vertebral compression fracture rate [7] after focal radiation therapy), delay systemic treatment, and in rapidly progressing patients may even be counterproductive. MDTs in PCa therefore, remain largely investigational; only one phase II trial has shown that MDTs delay the onset of androgen deprivation therapy (ADT) in patients with biochemical recurrence (BCR) after local treatment [8]. Demonstration of the efficacy of MDTs crucially relies on a definitive diagnosis of OMD at the outset.

Imaging plays a critical role in identifying metastases at various points in the PCa care pathway, *i.e.* at new diagnosis (ND), biochemical recurrence (BCR), or in castration resistant prostate cancer (CRPC). There is no standard definition of OMD and experts still debate on the maximum number of metastatic deposits and their locations. In the latest APCCC consensus meeting, OMD was defined as the presence of ≤ 3 bone or lymph node metastases [9]. Such an anatomical definition implies that the imaging technique used to define lesions is accurate for metastasis detection. For PCa, the standard imaging methods (SIMs) are 99mTc-MDP bone scintigraphy (BS) to detect bone metastases and contrast-enhanced thoraco-abdomino-pelvic (TAP) computed tomography (CT) or morphologic magnetic resonance imaging (MRI) for

identifying malignant nodes and visceral lesions[10]. Although recommended by most guidelines, these techniques have poor diagnostic accuracy, underestimating the number of metastatic deposits [11]. Modern imaging methods (MIMs), i.e. positron emission tomography (PET)/CT with tumour specific tracers and increasingly even whole-body magnetic resonance imaging (WB-MRI) with diffusion-weighted sequences (DWI) allow earlier and more precise identification of metastases [12,13].

To date, there is no consensus regarding the use of MIMs in PCa, nor are there comprehensive recommendations on clinical trials that should be conducted to evaluate the benefits of treating OMD recognized using these MIMs. . This article first aims at reviewing the evidence for using MIMs to identify OMD in PCa patients at the various stages of the disease pathway. It then outlines several clinical trial designs for evaluating the potential benefit of delivering MDT to OMD, based on the use of MIMs. It does not address specific drug or ablative technologies, sample size or endpoints for these trials. Figure 1 illustrates the methodology, participants and procedures used for agreeing the imaging recommendations for diagnosis of OMD in PCa. : definition of OMD and MDT, review of guidelines and of evidence for the use of MIMs, determination of the stages of PCa to consider. At each structured round, results of the findings were submitted to controlled feedback, re-iteration and validation of content, finally integrating them into our trial designs.

VALIDITY OF IMAGING METHODS

The main imaging requirements for efficient OMD screening include high sensitivity, specificity, but also high negative predictive value at the patient, region, and lesion levels. It is also critical to have standardized acquisition, validated repeatability and reproducibility, reading recommendations and response measurement criteria[14]. Comparisons of SIMs and MIMs have repeatedly shown the superiority of MIMs, and in particular the deficiency of SIMs to meet the requirements for precision medicine [15,16]. MIMs are therefore preferred for optimal diagnosis and therapeutic planning in OMD. Some MIMs may only partially meet the requisite criteria for detecting OMD, so that a combinatorial

approach may be required [17]. Despite their cost implications, therefore, MIMs may help rethink the care pathways of patients with PCa, by providing information that facilitates selection of targeted curative therapy in the presence of a limited metastatic burden [16]. Nevertheless, MIMs are poorly represented in current guidelines. **Tables 1-3** highlight the specific imaging strategies currently recommended by international and national authorities to be used at new diagnosis of PCa, at BCR and at progression to CRPC.

Standard Imaging Methods (SIMs) (Table A1)

Computed Tomography (CT) and **^{99m}Tc- MDP Bone Scintigraphy** (BS) have a low sensitivity to detect OMD [15,16] based on current evidence. CT allows whole-body imaging. It is widely availability at relatively low cost, but has limited sensitivity and specificity for detection of lymph nodes metastases and is suboptimal for the detection of bone metastases [18,19]. BS offers reader consistency for classification of M1 versus M0 disease in PCa, but clearly misses metastatic lesions [20,21,22]. Using standardized reporting tools, the classification of progression versus non-progression with these SIMs is excellent, but responses are not readily detected [23]. BS suffers from the need for time intervals between examinations and from the "flare" phenomenon [24], therefore requiring additional confirmatory examinations and increasing diagnostic delay [22,25]. Computer-aided analysis has been proposed to improve classification of the presence and extent of M1-status, but to-date evaluation of the diagnostic performance of the software with blinded experts shows notable variation [26].

Modern Imaging Methods (MIMs) (Table A1)

^{18}F-natriumfluoride (^{18}F-NaF) PET, like 99mTc-MDP largely reflects regional bone blood flow and osteoblastic activity so that its specificity and sensitivity for lytic metastases and soft tissue disease is limited [27]. ^{18}F-NaF PET/CT does not offer a substantial clinical benefit compared to BS (including SPECT/CT) [27].

PET with **^{18}F- or ^{11}C radiolabeled choline** images cell membrane phospholipid synthesis and accordingly cell growth. ^{18}F-labelling is more widely available and more convenient because of its longer half-life (110 versus 20 minutes) and better spatial resolution (shorter positron range of

^{18}F) [27]. ^{18}F-choline PET/CT is mainly used for restaging patients at BCR (**Figure A1**). Choline PET use is acknowledged by guidelines when prostate-specific antigen (PSA) levels are > 1 ng/mL [28,10].

PET with **^{68}Ga-PSMA-ligand** matches well known cellular expression of PSMA across organs [29,30]. ^{18}F-labeled PSMA-targeting imaging compounds, such as ^{18}F-DCFBC, (a first generation low-molecular-weight inhibitor of PSMA), ^{18}F-DCFPyL (2nd generation 18F-labeled small molecule PSMA inhibitor, with superior tissue binding ability, improving the detection of metastases adjacent to large blood vessels), or ^{18}F-PSMA-1007 (little or no bladder excretion) are also being developed [31,32,33]. Metastases usually appear as focally increased tracer uptake contrasting with the background. High background liver activity obscures disease detection in this organ and is compounded by the loss of PSMA-expression in advanced liver metastases [34,35,36]. Absent or low expression of PSMA on the tumour cells may result in false negatives, although the exact proportion of patients is not known, so that strict criteria for visual interpretation remain to be established [37]. Maurer et al comparing PSMA-ligand PET/CT with pelvic lymph node dissection found that 8.4% of the patients had no/very faint PSMA uptake in the primary tumour [38]. ^{68}Ga-PSMA-ligand PET is recommended at BCR in patients with PSA levels >1 ng/mL [10](**Figure A2**). A high level of inter-observer agreement has been shown with ^{68}Ga-PSMA PET/CT imaging, particularly for the diagnosis of lymph node and bone metastases. Both high and intermediate experienced observers emphasize the potential added value of ^{68}Ga-PSMA-ligand PET/CT for primary staging and for BCR detection with a PSA value < 1 ng/ml [39 40 41,42].

Whole body MRI (using T1, T2, short tau inversion recovery (STIR) and diffusion weighted imaging (DWI) sequences) allows mapping of the full extent of the disease and additionally identifies spinal lesions at risk or responsible for neurologic complications [43,44]. "Interobserver agreement for reading of WB-MRI images including DWI has been tested in detail in a small patient cohort and shown to be 0.98 (0.89-0.99) and 0.97 (0.83-0.99) for median and mean global apparent diffusion coefficient (ADC) respectively [45]. In other studies, whole body MRI has outperformed BS (K = 0.87 [0.66; 1.00] for ADC, K = 0.60 [0.26; 0.78 for BS)"[46,47]. The variability of ADC measurements is <15%, making it sensitive to treatment-induced changes, so that response is quantifiable and measurable [48,49,50]. This is particularly helpful in late stage disease

(CRPC) [44]. International guidelines have been published for harmonization in acquisition, interpretation and reporting of whole body MRI, and response assessment criteria have been defined [51].

DATA COLLECTION

Search strategy and selection criteria

We searched PubMed and MEDLINE, for relevant articles published between Jan 1, 1995, and March 31, 2018, using the search terms: "metastasis", "oligometastasis", "oligorecurrence", "prostate cancer", "guidelines" and "imaging". The No language restrictions were imposed. We excluded preclinical and animal studies. The type of study, source of data, and important findings were noted.

Methodology for reaching consensus recommendations for imaging metastases in prostate cancer

The imaging group of the EORTC comprises radiologists and nuclear medicine physicians from trial centres throughout Europe who actively participate in multicenter, EORTC sponsored trials. There are strong links to the EORTC disease-oriented groups who run these trials. Participants for this consensus working group comprised all interested parties by open invitation from the imaging and prostate cancer groups. We discussed the potential recommendations over an 18-month period, during which there were 3 face-to-face meetings at the main Imaging Group meetings and 2 teleconferences to refine the final recommendations, thus following a procedure of discussion and re-iteration between experts that considered the relevant published literature and currently accepted clinical practice to achieve unanimous consensus (**Figure 1**).

FINDINGS

Optimal methods for imaging metastases in newly diagnosed patients (Table 1).

In countries where PSA testing is available, less than 10% of the newly diagnosed (ND) PCa are metastatic[52]. Based on five randomized controlled trials, the standard treatment of patients metastatic at diagnosis has shifted from androgen deprivation therapy (ADT) alone to ADT plus chemotherapy or abiraterone [53,54]. These drugs have demonstrated a clear benefit in patients with high-volume disease (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis), but their benefit is still unclear for lower volume disease. For patients with OMD, intense research is ongoing to assess the potential benefit of combining ADT with loco-regional MDT. Imaging at ND therefore should include recognition of metastatic disease in high-risk patients.

SIMs detect abnormal lymph nodes based on a size threshold. According to RECIST 1.1, nodes with short axis ≥ 10mm but <15 mm are considered pathological, although non-target lesions [55]. Nodes > 15mm in short axis are considered pathologic and measurable by both RECIST and Prostate Cancer Working Group 3 (PCWG3) criteria [55,25]. Despite its high spatial resolution and even when using additional contrast agents, CT has poor soft tissue contrast resolution, resulting in inferior performance compared to MRI [56]. Lack of ability to detect architectural changes in lymph nodes < 10 mm results in very low sensitivity (40%) for CT, while reactive or inflammatory changes explain may result in false positive observations, which explains its limited specificity (80%). Although widely used for bone metastases screening at staging of PCa [10,57,58], the proportion of equivocal planar BS in large trials ranges from 15 to 25%[20,59]. The proportion of falsely negative examinations is even more problematic as it is likely that radical treatments to the prostate are ultimately futile. At a lesion level, a polymetastatic patient may be falsely identified as OMD. For BS, recent meta-analyses show a sensitivity ranging from 79 to 88% and a specificity ranging from 75 to 82%, respectively [60 61]. The use of SPECT/CT reduces the proportion of equivocal findings [62,63].

MIMs: ^{18}F-NaF PET is superior to BS but is similarly limited to bone screening alone. In a recent review of 318 patients from 8 studies, sensitivity, specificity, PPV, NPV and accuracy (range) were 95.5% (81-100), 77.4% (54-100), 85.2% (74-100), 94.9% (77.9-100) and 78.5% (65.4-

100) [64]. Sensitivity to minimal degenerative changes impacts its specificity [64]. Higher cost and lower availability mean that it has not replaced BS.

Radiolabelled choline PET/CT offers the advantage of being tumour specific. For bone metastases, ^{18}F-choline PET/CT has a sensitivity, specificity and diagnostic accuracy of 79%, 97% and 84%, respectively, compared with a consensus definition of bone metastases based on conventional imaging and clinical endpoints [65]. For lymph node staging the sensitivity of ^{18}F-choline PET/CT ranges between 33-100% and the specificity between 95-100% [28]. In 912 lymph nodes sampled in high risk patients, ^{18}F-choline PET/CT proved better than CT, particularly for metastases > 5 mm in size (sensitivity, specificity, positive and negative predictive values of 66%, 96%, 82%, and 92%, respectively) [66]. Tumour specificity is further improved by use of ^{68}Ga-PSMA PET/CT, where sensitivities of 33% and 66% and specificities of 100% and 99% against histological gold standard have been reported for nodal disease [67,68]. Low patient-based sensitivity (64%) and high specificity (95%) is described in both single-centre studies[69] and in literature reviews [40]. Furthermore, comparative data suggests that ^{68}Ga-PSMA PET/CT is more accurate than BS and CT for the detection of bone and visceral metastases [70,71]. Formal prospective assessment is needed prior to translation into clinical routine.

Another validated approach to detect both bone and lymph node metastases at staging of first diagnosed PCa is the use of WB-MRI. A meta-analysis study on bone metastasis showed a pooled sensitivity, specificity, and area under the curve for DWI of 95% (95% CI, 90–97), 92% (88–95), and 0.98, respectively on both a per patient and per lesion basis and on per-lesion basis [72]. Meta-analyses have confirmed its superior diagnostic accuracy over ^{18}F-choline PET/CT, CT and BS in PCa [61,73].

Optimal methods for imaging metastases in patients with biochemical recurrence after radical treatment (Table 2)

Approximately 30% of patients treated radically for high or very-high risk PCa experience BCR [74]. In those with previous radical prostatectomy, salvage external beam radiotherapy is recommended [74]. After previous external beam or interstitial radiotherapy, salvage surgery, high-intensity focused ultrasound (HIFU), or cryotherapy can be used [74]. These treatment modalities assume that the initial pathology, the time interval between the local treatment and the PSA recurrence, and the PSA kinetics are sufficient to distinguish local relapse from early metastatic spread.

The role of imaging in these cases is critical. Imaging firstly should be to **rule-out** poly-metastatic disease not amenable to cure by local treatment alone, and to detect OMD that could benefit from regional salvage therapies [75,76,77]. The detection of OMD at BCR is important since at least one trial has demonstrated that MDT could delay initiation of ADT [8]. Secondly and separately, imaging at BCR also can **rule-in** and confirm loco-regional recurrence in order to plan salvage local treatment. mpMRI is the technique of choice here[78,77]. However, even where imaging is negative, pelvic bed EBRT is administered on the assumption that local recurrence is undetected at imaging, a strategy supported by several trials of salvage EBRT. Imaging is recommended in BCR when PSA levels are > 0.2-1 ng/mL after surgery and >2ng/mL above the nadir after radiotherapy [79] **(Table 2)**

SIMs: CT and BS are not recommended in these patients, although the latter may be used if the PSA has reached a level of 10 ng/mL or higher [80, 81] **(Table 2)**

MIMs: A meta-analysis of 12 studies in 1055 patients with BCR showed that ^{18}F-/^{11}C-choline PET/CT on a per-patient basis had a pooled sensitivity, specificity, and diagnostic odd ratio (DOR) of 85% (95% CI, 79–89%), 88% (73–95%), and 41.4 (19.7–86.8%), respectively [82]. Comparable results were also described in a meta-analysis of 19 studies in 1555 patients and showed that the pooled sensitivity for all sites of disease (prostatic fossa, lymph nodes, and bone) including ^{11}C- and ^{18}F-Choline PET/CT was 85.6% (95% CI: 82.9–88.1%) and 92.6% (90.1–94.6%), respectively [83]. However, another meta-analysis of 14 studies in 1869 patients, reported a pooled detection rate of 58% for ^{18}F-/^{11}C-choline PET/CT in restaging setting [84]. A PSA doubling time (DT) < 6 months and PSA velocity > 1 ng/mL/y or > 2 ng/mL/y proved to be relevant

factors in predicting a positive result. However, none of the meta-analyses have reported the performance of Choline-PET in relation to the PSA level.

The most studied MIM in the setting of BCR is with ^{68}Ga-PSMA-ligand PET/CT [29,85,86,87]. Detection rates of 90% at BCR after radical prostatectomy are reported, with at least one lesion in 83% of cases [85,86] A meta-analysis showed that the rate of positive ^{68}Ga-PSMA-ligand PET/CT scans increases with pre-PET PSA (42%, 58%, 76%, and 95% positive scans for the PSA categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml, respectively)[41]. Shorter PSA doubling time also increases detection rate of ^{68}Ga-PSMA-ligand PET/CT on per-patient and per- lesion analysis [41]. The limitations of the previous studies must however be emphasized: lack of strong histologic proof for tumoural involvement in detected foci, heterogeneity in patient populations, and uneven validation weaken the results. False positive PET scans, mostly PSMA based, showed no lymph node involvement on pathology in 32% at salvage surgery and only 30% of patients experienced a PSA drop [88]. However, as no post-surgery imaging was performed, it is also possible that the wrong lymph node was taken out underlining the need for PSMA-directed radioguided surgery [89]. A recent case report study also emphasized the problem of false negative findings of MIMs where both PSMA PET/CT and USPIO-MRI underestimated the number of involved nodes [90].

WB-MRI can detect metastases at BCR even at (very) low PSA values (median 0.36 ng/ml) [76](**Figure A2**). A WB-MRI based study evaluating the distribution of bone and node recurrence showed that metastatic disease was often distant, located beyond usual surgical and radiotherapeutic boundaries for treating BCR [12]. Although it is potentially a reliable alternative to choline PET/CT in these patients [91], a single-centre study where a direct comparison was made between WB-MRI (done with the suboptimal high b value of 600 mm2/s as per ESUR guidelines) with 68Ga-PSMA PET/CT showed WB-MRI to be inferior [92].

Optimal methods for imaging metastases in early castration-resistant prostate cancer (CRPC) (Table 3)

Castration resistance is defined by a PSA rise or a radiological progression in a patient with a testosterone in the castrate level[74]. Registration of drugs for metastatic CRPC in the last ten years (two androgen-receptor pathways inhibitors (ARpI)- abiraterone and enzalutamide, two chemotherapies- docetaxel and cabazitaxel, three bone targeted agents- RA223, denosumab and zoledronic acid, and one vaccine, sipuleucel-T [74]) demand imaging to justify their use and to monitor treatment response. ARpI are the treatment of choice where available [93] The progression to metastatic CRPC (mCRPC, identifiable lesions on imaging) from non-metastatic CRPC (nmCRPC, PSA increase without detectable metastases on SIMs) is usually slow, except in patients with a short PSA doubling time ≤ 6 months [94] in those with a PSA doubling time ≤10 months, the ARpI apalutamide and enzalutamide have been shown to significantly extend metastatic free survival [95,96]. In CRPC patients therefore, MIMs can help identify early metastatic progression resulting in an earlier initiation of abiraterone and enzalutamide. In particular, as up to 30% of progressing patients have OMD, addition of MTD to further increase metastasis-free survival may be warranted [97].

SIMs: BS is the reference diagnostic tool **(Table 3)** for defining progression of bone metastases, as defined by the PCWG3 criteria.[25]. The bone scan index (BSI) carries a prognostic value for estimating survival and the PCWG 3 criteria (two new confirmed lesions = progressive disease (PD)) predict overall survival [98,99,100,101,102,103]. The lack of sensitivity of BS to treatment response, however, exposes patients with short life expectancy to futile and potentially toxic treatment.

Contrast-enhanced CT and MRI are recommended (PCWG 3) for nodal staging and visceral lesion detection (M1a and M1c) **(Table 3)**. Locations of nodal disease are recorded separately (up to five nodes in total) and visceral lesions are reported as per RECIST [55]. A > 5 mm increase in the short axis from baseline or nadir in a previously normal lymph node to >10 mm is considered progressive for RECIST. For PCWG3, nodes between 10 and 15 mm in short axis are considered pathological subject to clinical discretion but non-measurable; increase in size to >15 mm short axis is considered progressive and measurable [25].

MIMs: Choline PET/CT has been suggested to assess treatment response in patients treated with Docetaxel and decreasing PSA levels but with clinical signs of disease progression [104]. As a change in choline uptake does not significantly correlate with PSA response [105], its use in CRPC

patients is limited to the detection of resistant tumour lesions during the course of treatment (positive predictive and negative predictive values, 99% and 81% respectively) [104]. Furthermore, in CRPC undergoing dedicated therapy with abiraterone, enzalutamide, or ^{223}radium [106,107,108], early ^{18}F-Choline PET/CT might predict clinical outcome beyond PSA response, although standardised uptake value measurement is not routinely used in interpretation [109,110]. In contrast to its value in BCR, PSMA PET/CT is not currently used for response assessment due to the lack of knowledge on the temporal relationship (early overexpression and later decrease) between treatment and PSMA expression [111].

WB-MRI has potential to allow early categorization of lesions into response categories to define disease response, stability or progression. Examination protocols and both qualitative (e.g. lesion signal, soft tissue extension) and quantitative (e.g. number, size, average diffusion coefficients, ADC) response criteria have been defined, harmonized and reported in the literature [49,50,44]. The volume of target lesions, the total metastatic volume assessed by DWI and the median ADC values have been shown to be reliable markers of response, showing correlation with PSA levels and circulating tumoral cell counts [112]. The available data is derived from single-centre, non-randomized studies with small patient numbers, so should be interpreted with caution. Larger-scale multicenter trials are necessary.

PROPOSED CLINICAL TRIAL DESIGNS INCORPORATING MIMs TO VALIDATE CARE PATHWAYS IN PCa

The study of MIMs to date has focused primarily on assessing their diagnostic performance, not their impact on care pathways. A study where patients are stratified by MIMs vs. SIMs for subsequent care would demonstrate the difference between a MIM and a SIM-driven care pathway. We anticipate that the detection of OMD on MIMs would trigger MDT whenever deliverable. The alternative would be to test a care pathway in which everybody receives MIMs and a decision is taken to use or ignore the results. Based on this, the EORTC Imaging Group has proposed clinical trial designs to validate the use of MIMs for treating OMD at various stages of PCa, namely at ND, at BCR, and at the CRPC stage. Trials of MDT to the prostate itself in these cases are not included. Endpoints and sample-size are not addressed in these simulated

trials. MIMs are referred to generically. Each study could therefore use the most appropriate MIM, i.e. choline *vs.* PSMA-ligand PET/CT, *or* WB-MRI.

Newly diagnosed PCa (Figure 2).

In patients with a Gleason score > 7(4+3), a T stage ≥T3, a PSA > 20ng/ml, or in presence of symptoms, current guidelines recommend BS and CT/MRI for the detection of bone, lymph node, and visceral metastases [74] (Table 1). In patients with a negative metastatic workup on these SIMs, MIMs have been shown to identify metastatic deposits in a substantial proportion of patients, potentially altering treatment by triggering a radiation plan for lymph node treatment or replacing/ complementing radical treatment with ADT and/or MDT where metastatic disease is low-volume. In patients with low-volume metastatic disease on SIMs, MIMs also may be useful to exclude poly-metastases. MIMs have no role in patients designated poly-metastatic on SIMs.

High-risk patients with ND PCa with a negative SIM should be randomized to receive a MIM or not. The standard of care when MIM is not performed is local treatment of the prostate and the pelvic lymph nodes and ADT for 18 to 36 months. If MIM is negative, the standard of care remains unchanged. If MIM reveals OMD, patients additionally could receive MDT, the duration of which in that setting being investigational. Poly-metastatic patients on MIM could be treated by ADT ± docetaxel or abiraterone, local treatment being investigational.

Based on the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group, endpoints are Metastasis Free Survival (MFS) for patients with localized disease on SIMs [113]. For metastatic patients, there is no other validated endpoint than overall survival (OS). Time to CRPC (tCRPC) could be captured for early reading.

BCR after radical treatment without loco-regional salvage options (Figure 3)

Patients with BCR can be stratified in two categories, those at low- or at high-risk of metastasis and death. The latter are candidates for early ADT (indicated if PSA-DT < 6-12 months, or a high initial Gleason score (> 7), and a long-life expectancy) [10]. EAU guidelines already recommend choline-PET/CT and PSMA-PET/CT at BCR at a PSA threshold > 1 ng/ml. The latter is preferred, if available, based on numerous studies proving its superiority over choline-PET and because of lower production costs [114,115]. Based on individual studies and meta-analyses, WB-MRI also appears superior to ^{18}F-choline PET/CT and may be considered at this stage [61,44].

In high-risk patients (PSA doubling time $\leq$ 12 months and a Gleason score > 8) in whom early ADT is recommended, two trials designs are proposed, both use MDT plus a short course of ADT for OMD identified on MIMs. Because there is no standard duration of ADT in combination with MTD, we postulate that 6 months could be used as a standard reference. In the first design, MDT is used to improve on present intermittent ADT (iADT) results in terms of time to CRPC, disease specific survival (DSS) or OS. An alternative endpoint is tCRPC whilst on ADT. In the second design, MIMs are used to offer surveillance to SIM negative patients.

Early CRPC (Figure 4)

SIMs are the standard of care for patients with a rising PSA and a testosterone level < 50 ng/dl. There is no widely accepted consensus on when to undertake SIMs in CRPC patients. The Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months for asymptomatic men [16]. Symptomatic patients should undergo relevant imaging investigations regardless of PSA level (Table 3).

Patients with a positive SIM require treatment with ARpI, based on the APCCC 2015 consensus [93]. In the APCCC 2017 consensus 76% of the panel members voted for PSMA as tracer, 10% voted for fluciclovine, 6% voted for choline and 4% for any of the three. Therefore, MIMs could

be used to confirm OMD and study the benefit of MDT. In patients with negative SIM (nmCRPC) with a PSA ≥ 2 ng/dl and a PSA DT ≤ 10 months, immediate ARpI are likely to become the standard of care [95]. In addition, patients with a negative MIM could be further randomized to surveillance *vs.* further local treatment if possible. MIMs could identify patients with OMD, and MDT used to either further increase metastasis free survival (MFS) or to test the hypothesis that MDT + a short course of ARpI is equivalent to long-term ARpI. In nmCRPC patients with a PSA < 2 ng/ml or a PSADT > 10 months, MIMs could identify candidates for MDT with the aim of delaying progression.

CONCLUSIONS

This consensus recommendation from the EORTC Imaging Group clarifies the role of MIMs for optimal identification of OMD at different stages of PCa. When MIMs are available, the residual role of SIMs is essentially either as a necessary step to define patient populations in agreement with current recommendations, or as a "triage" tool to identify patients with polymetastatic disease. Furthermore, it also sets out recommendations for the use of MIMs in patients in whom a precise metastatic count and lesion mapping is necessary. This paper finally highlights the imaging trial designs that should be implemented to demonstrate the benefit of incorporating MIMs into the care pathways at distinct stages of PCa: at ND, at BCR and in CRPC.

Bibliography

1 Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; **13**: 8–10.

2 Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM. Oligometastatic prostate cancer: Definitions, clinical outcomes, and treatment considerations. Nat. Rev. Urol. 2017; **14**: 15–25.

3 Tree AC, Khoo VS, Eeles RA, *et al.* Stereotactic body radiotherapy for oligometastases. Lancet Oncol. 2013; **14**. DOI:10.1016/S1470-2045(12)70510-7.

4 Heidenreich A, Moul JW, Shariat S, Jeffrey Karnes R. Role of salvage lymph node dissection in prostate cancer. Curr. Opin. Urol. 2016; **26**: 581–9.

5 Murphy DG, Sweeney CJ, Tombal B. "Gotta Catch 'em All", or Do We? Pokemet Approach to Metastatic Prostate Cancer. *Eur Urol* 2017; **72**: 1–3.

6 Shimoyama T, Katagiri H, Harada H, *et al.* Fracture after radiation therapy for femoral metastasis: Incidence, timing and clinical features. *J Radiat Res* 2017. DOI:10.1093/jrr/rrx038.

7 Boyce-Fappiano D, Elibe E, Schultz L, *et al.* Analysis of the Factors Contributing to Vertebral Compression Fractures After Spine Stereotactic Radiosurgery. *Int J Radiat Oncol* 2017. DOI:10.1016/j.ijrobp.2016.09.007.

8 Ost P, Reynders D, Decaestecker K, *et al.* Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* 2017; : JCO.2017.75.485.

9 Gillessen S, Attard G, Beer TM, *et al.* Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol* 2017; : 1–34.

10 Mottet N, Bellmunt J, Bolla M, *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017; **71**: 618–29.

11 deSouza NM, Liu Y, Chiti A, *et al.* Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer* 2018; **91**. DOI:10.1016/j.ejca.2017.12.012.

12 Larbi A, Dallaudière B, Pasoglou V, *et al.* Whole body MRI (WB-MRI) assessment of metastatic spread in prostate cancer: Therapeutic perspectives on targeted management of oligometastatic disease. *Prostate* 2016; **76**: 1024–33.

13 Ost P, Jereczek-Fossa BA, Van As N, *et al.* Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences. *Clin Oncol* 2016; **28**: e115–20.

14 Franklin JM, Sharma RA, Harris AL, Gleeson F V. Imaging oligometastatic cancer before local treatment. Lancet Oncol. 2016; **17**: e406–14.

15 ASCO. ASCO Educational Book. 2016 https://media4.asco.org/176/edbook/2016_edbook.pdf.

16 Crawford ED, Stone NN, Yu EY, *et al.* Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology* 2014; **83**: 664–9.

17 Conde-Moreno AJ, Herrando-Parreño G, Muelas-Soria R, *et al.* Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) vs choline-positron emission tomography-computed tomography (choline-PET/CT) for selecting treatments in recurrent prostate cancer. *Clin Transl Oncol* 2017; **19**: 553–61.

18 Hövels AM, Heesakkers RAM, Adang EM, *et al.* The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008; **63**: 387–95.

19 Gould MK, Kuschner WG, Rydzak CE, *et al.* Test Performance of Positron Emission Tomography and Computed Tomography for Mediastinal Staging in Patients with Non-Small-Cell Lung Cancer: A Meta-Analysis. *Ann Intern Med* 2003; **139**: 879–892+I18.

20 Zacho HD, Barsi T, Mortensen JC, *et al.* Prospective Multicenter Study of Bone Scintigraphy in Consecutive Patients With Newly Diagnosed Prostate Cancer. *Clin Nucl Med* 2014; **39**: 26–31.

21 Zacho HD, Manresa J a. B, Mortensen JC, Bertelsen H, Petersen LJ. Observer agreement and accuracy in the evaluation of bone scans in newly diagnosed prostate cancer. *Nucl Med Commun* 2015; : 1.

22 Fonager RF, Zacho HD, Albertsen S, *et al.* Observer agreement of treatment responses on planar bone scintigraphy in prostate cancer patients. *Nucl Med Commun* 2017; **38**: 215–21.

23 Zafeirakis A. Scoring systems of quantitative bone scanning in prostate cancer: Historical overview, current status and future perspectives. Hell. J. Nucl. Med. 2014; **17**: 136–44.

24 Messiou C, Cook G, Desouza N. Imaging metastatic bone disease from carcinoma of the prostate. *Br J Cancer* 2009; **101**: 1225–32.

25 Scher HI, Morris MJ, Stadler WM, *et al.* Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016; **34**: 1402–18.

26 Petersen LJ, Mortensen JC, Bertelsen H, Zacho HD. Computer-assisted interpretation of planar whole-body bone scintigraphy in patients with newly diagnosed prostate cancer. *Nucl Med Commun* 2015; **36**: 679–85.

27 Löfgren J, Mortensen J, Rasmussen SH, *et al.* A Prospective Study Comparing (99m)Tc-Hydroxyethylene-Diphosphonate Planar Bone Scintigraphy and Whole-Body SPECT/CT with (18)F-Fluoride PET/CT and (18)F-Fluoride PET/MRI for Diagnosing Bone Metastases. *J Nucl Med* 2017; **58**: 1778–85.

28 Schwarzenböck S, Souvatzoglou M, Krause BJ. Choline PET and PET/CT in primary diagnosis and staging of prostate cancer. Theranostics. 2012; **2**: 318–30.

29 Afshar-Oromieh A, Malcher A, Eder M, *et al.* PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging* 2013; **40**: 486–95.

30 Herrmann K, Bluemel C, Weineisen M, *et al.* Biodistribution and Radiation Dosimetry for a Probe Targeting Prostate-Specific Membrane Antigen for Imaging and Therapy. *J Nucl Med* 2015; **56**: 855–61.

31 Cho SY, Gage KL, Mease RC, *et al.* Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. *J Nucl Med* 2012; **53**: 1883–91.

32 Szabo Z, Mena E, Rowe SP, *et al.* Initial Evaluation of [(18)F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer. *Mol Imaging Biol* 2015; **17**: 565–74.

33 Giesel FL, Hadaschik B, Cardinale J, *et al.* F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Med Mol Imaging* 2017; **44**: 678–88.

34 Laidler P, Dulińska J, Lekka M, Lekki J. Expression of prostate specific membrane antigen in androgen-independent prostate cancer cell line PC-3. *Arch Biochem Biophys* 2005; **435**: 1–14.

35 Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. *Am J Clin Exp Urol* 2014; **2**: 273–85.

36 Yuan TC, Veeramani S, Lin MF. Neuroendocrine-like prostate cancer cells: Neuroendocrine transdifferentiation of prostate adenocarcinoma cells. Endocr. Relat. Cancer. 2007; **14**: 531–47.

37 Rowe S, Pienta K, Pomper MG, Gorin M. Proposal of a Structured Reporting System for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging: PSMA-RADS Version 1.0. *J Nucl Med* 2017; : jnumed.117.195255.

38 Maurer T, Gschwend JE, Rauscher I, *et al.* Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol* 2016; **195**: 1436–43.

39 Fendler WP, Calais J, Allen-Auerbach M, *et al.* (68)Ga-PSMA-11 PET/CT Interobserver Agreement for Prostate Cancer Assessments: An International Multicenter Prospective Study. *J Nucl Med* 2017; **58**: 1617–23.

40 Corfield J, Perera M, Bolton D, Lawrentschuk N. 68Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World J. Urol. 2018; : 1–9.

41 Perera M, Papa N, Christidis D, *et al.* Sensitivity, Specificity, and Predictors of Positive 68Ga–Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. Eur. Urol. 2016; **70**: 926–37.

42 von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G. 68Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. Eur. Urol. Focus. 2016. DOI:10.1016/j.euf.2016.11.002.

43 Lecouvet FE. Whole-Body MR Imaging: Musculoskeletal Applications. *Radiology* 2016; **279**: 345–65.

44 Padhani AR, Lecouvet FE, Tunariu N, *et al.* Rationale for Modernising Imaging in Advanced Prostate Cancer. Eur. Urol. Focus. 2017; **3**: 223–39.

45 Blackledge MD, Tunariu N, Orton MR, *et al.* Inter- and Intra-Observer Repeatability of Quantitative Whole-Body, Diffusion-Weighted Imaging (WBDWI) in Metastatic Bone Disease. *PLoS One* 2016. DOI:10.1371/journal.pone.0153840.

46 Lecouvet FE, El Mouedden J, Collette L, *et al.* Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? *Eur Urol* 2012; **62**: 68–75.

47 Pasoglou V, Michoux N, Tombal B, Jamar F, Lecouvet FE. wbMRI to detect bone metastases: critical review on diagnostic accuracy and comparison to other imaging modalities. Clin. Transl. Imaging. 2015; **3**: 141–57.

48 Messiou C, Collins DJ, Morgan VA, Desouza NM. Optimising diffusion weighted MRI for imaging metastatic and myeloma bone disease and assessing reproducibility. *Eur Radiol* 2011; **21**: 1713–8.

49 Lecouvet FE, Larbi A, Pasoglou V, *et al.* MRI for response assessment in metastatic bone disease. *Eur Radiol* 2013; **23**: 1986–97.

50 Tombal B, Rezazadeh A, Therasse P, Van Cangh PJ, Vande Berg B, Lecouvet FE. Magnetic resonance imaging of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases. *Prostate* 2005; **65**: 178–87.

51 Padhani AR, Lecouvet FE, Tunariu N, *et al.* METastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting of Whole-body Magnetic Resonance Imaging-based Evaluations of Multiorgan Involvement in Advanced Prostate Cancer [figure presente. *Eur Urol* 2017. DOI:10.1016/j.eururo.2016.05.033.

52 Schröder FH, Hugosson J, Carlsson S, *et al.* Screening for prostate cancer decreases the risk of developing metastatic disease: Findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2012. DOI:10.1016/j.eururo.2012.05.068.

53 Rydzewska LHM, Burdett S, Vale CL, *et al.* Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. *Eur J Cancer* 2017; **84**: 88–101.

54 Vale CL, Burdett S, Rydzewska LHM, *et al.* Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. *Lancet Oncol* 2016; **17**: 243–

56.

55 Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

56 Pasoglou V, Larbi A, Collette L, *et al.* One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified 'all-in-one' imaging approach? *Prostate* 2014; **74**: 469–77.

57 Heidenreich A, Bastian PJ, Bellmunt J, *et al.* EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent - Update 2013. *Eur Urol* 2014; **65**: 124–37.

58 Mohler J, Kantoff P, Armstrong A, *et al.* Prostate cancer, version 2.2014. J. Natl. Compr. Cancer Netw. 2014; **12**: 686–718.

59 Briganti A, Passoni N, Ferrari M, *et al.* When to Perform Bone Scan in Patients with Newly Diagnosed Prostate Cancer: External Validation of the Currently Available Guidelines and Proposal of a Novel Risk Stratification Tool. *Eur Urol* 2010; **57**: 551–8.

60 Shen C-T, Qiu Z-L, Han T-T, Luo Q-Y. Performance of 18F-Fluoride PET or PET/CT for the Detection of Bone Metastases. *Clin Nucl Med* 2015; **40**: 103–10.

61 Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skeletal Radiol. 2014; **43**: 1503–13.

62 Zacho HD, Manresa JAB, Aleksyniene R, *et al.* Three-minute SPECT/CT is sufficient for the assessment of bone metastasis as add-on to planar bone scintigraphy: prospective head-to-head comparison to 11-min SPECT/CT. *EJNMMI Res* 2017; **7**: 1.

63 Palmedo H, Marx C, Ebert A, *et al.* Whole-body SPECT/CT for bone scintigraphy: Diagnostic value and effect on patient management in oncological patients. *Eur J Nucl Med Mol Imaging* 2014; **41**: 59–67.

64 Evangelista L, Bertoldo F, Boccardo F, *et al.* Diagnostic imaging to detect and evaluate response to therapy in bone metastases from prostate cancer: current modalities and new horizons. Eur. J. Nucl. Med. Mol. Imaging. 2016; **43**: 1546–62.

65 Beheshti M, Vali R, Waldenberger P, *et al.* The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: correlation with morphological changes on CT.[Erratum appears in Mol Imaging Biol. 2010 Jun;12(3):360]. *Mol Imaging Biol* 2010; **12**: 98–107.

66 Beheshti M, Imamovic L, Broinger G, *et al.* 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. *Radiology* 2010; **254**: 925–33.

67 Maurer T, Gschwend JE, Rauscher I, *et al.* Diagnostic Efficacy of 68Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol* 2016; **195**: 1436–43.

68 Budäus L, Leyh-Bannurah S-R, Salomon G, *et al.* Initial Experience of 68Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. 2016 DOI:10.1016/j.eururo.2015.06.010.

69 van Leeuwen PJ, Emmett L, Ho B, *et al.* Prospective Evaluation of 68Gallium-PSMA Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Prostate Cancer. *BJU Int* 2016; : 209–15.

70 Barrio M, Fendler WP, Czernin J, Herrmann K. Prostate specific membrane antigen (PSMA) ligands for diagnosis and therapy of prostate cancer. Expert Rev. Mol. Diagn. 2016; **16**: 1177–88.

71 Pyka T, Okamoto S, Dahlbender M, *et al.* Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. *Eur J Nucl Med Mol Imaging* 2016; **43**: 2114–21.

72 Liu L-P, Cui L-B, Zhang X-X, *et al.* Diagnostic Performance of Diffusion-weighted Magnetic Resonance Imaging in Bone Malignancy:

Evidence From a Meta-Analysis. *Medicine (Baltimore)* 2015. DOI:10.1097/MD.0000000000001998.

73 Yang HL, Liu T, Wang XM, Xu Y, Deng SM. Diagnosis of bone metastases: A meta-analysis comparing 18FDG PET, CT, MRI and bone scintigraphy. *Eur Radiol* 2011; **21**: 2604–17.

74 Cornford P, Bellmunt J, Bolla M, *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol* 2017; **71**: 630–42.

75 Freitag MT, Radtke JP, Afshar-Oromieh A, *et al.* Local recurrence of prostate cancer after radical prostatectomy is at risk to be missed in 68Ga-PSMA-11-PET of PET/CT and PET/MRI: comparison with mpMRI integrated in simultaneous PET/MRI. *Eur J Nucl Med Mol Imaging* 2017; **44**: 776–87.

76 Robertson NL, Sala E, Benz M, *et al.* Combined Whole Body and Multiparametric Prostate Magnetic Resonance Imaging as a 1-Step Approach to the Simultaneous Assessment of Local Recurrence and Metastatic Disease after Radical Prostatectomy. *J Urol* 2017; **198**: 65–70.

77 Maurer T, Eiber M, Fanti S, Budäus L, Panebianco V. Imaging for Prostate Cancer Recurrence. *Eur Urol Focus* 2016; **2**: 139–50.

78 Sandgren K, Westerlinck P, Jonsson JH, *et al.* Imaging for the Detection of Locoregional Recurrences in Biochemical Progression After Radical Prostatectomy-A Systematic Review. Eur. Urol. Focus. 2017. DOI:10.1016/j.euf.2017.11.001.

79 Mottet N, Bellmunt J, Bolla M, *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017; **71**: 618–29.

80 Kane CJ, Amling CL, Johnstone PAS, *et al.* Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. *Urology* 2003; **61**: 607–11.

81 Lindenberg ML, Turkbey B, Mena E, Choyke PL. Imaging locally advanced, recurrent, and metastatic prostate cancer: A review. JAMA Oncol. 2017; **3**: 1415–22.

82 Umbehr MH, Muntener M, Hany T, Sulser T, Bachmann LM. The Role of 11C-Choline and 18F-Fluorocholine Positron Emission Tomography (PET) and PET/CT in Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol* 2013; **64**: 106–17.

83 Evangelista L, Zattoni F, Guttilla A, *et al.* Choline PET or PET/CT and biochemical relapse of prostate cancer: A systematic review and meta-analysis. Clin. Nucl. Med. 2013; **38**: 305–14.

84 Treglia G, Ceriani L, Sadeghi R, Giovacchini G, Giovanella L. Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: A meta-analysis. *Clin Chem Lab Med* 2014; **52**: 725–33.

85 Afshar-Oromieh A, Hetzheim H, Kratochwil C, *et al.* The Theranostic PSMA Ligand PSMA-617 in the Diagnosis of Prostate Cancer by PET/CT: Biodistribution in Humans, Radiation Dosimetry, and First Evaluation of Tumor Lesions. *J Nucl Med* 2015; **56**: 1697–705.

86 Eiber M, Maurer T, Souvatzoglou M, *et al.* Evaluation of hybrid 68Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med* 2015; **56**: 668–74.

87 Ceci F, Uprimny C, Nilica B, *et al.* 68Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging* 2015; **42**: 1284–94.

88 Montorsi F, Gandaglia G, Fossati N, *et al.* Robot-assisted Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer. *Eur Urol* 2017; **72**: 432–8.

89 Maurer T, Weirich G, Schottelius M, *et al.* Prostate-specific Membrane Antigen-radioguided Surgery for Metastatic Lymph Nodes in Prostate Cancer. *Eur Urol* 2015; **68**: 530–4.

90 Bandini M, Gandaglia G, Fossati N, Montorsi F, Briganti A. An Explanatory Case on the Limitations of Lymph Node Staging in Recurrent Prostate Cancer. *Urol Case Reports* 2017; **12**: 34–6.

91 Eschmann SM, Pfannenberg AC, Rieger A, *et al.* Comparison of 11C-choline-PET/CT and whole body-MRI for staging of prostate cancer. NuklearMedizin. 2007; **46**: 161–8.

92 Zacho HD, Nielsen JB, Afshar-Oromieh A, Haberkorn U, deSouza NM, De Paepe K, Dettmann K, Langkilde NC, Haarmark C, Fisker RV, Arp DT, Carl J, Jensen J PL. Prospective comparison of 68Ga-PSMA PET/CT, 18F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2018. DOI:10.1007/s00259-018-4058-4.

93 Gillessen S, Attard G, Beer TM, *et al.* Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol* 2017; : 1–34.

94 Smith MR, Saad F, Oudard S, *et al.* Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: Exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol* 2013; **31**: 3800–6.

95 Smith MR, Saad F, Chowdhury S, *et al.* Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med* 2018; : NEJMoa1715546.

96 Hussain M, Fizazi K, Saad F, *et al.* PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). *J Clin Oncol* 2018; **suppl 6S;**

97 De Bruycker A, Lambert B, Claeys T, *et al.* Prevalence and prognosis of low-volume, oligorecurrent, hormone-sensitive prostate cancer amenable to lesion ablative therapy. *BJU Int* 2017; **120**: 815–21.

98 Miyoshi Y, Yoneyama S, Kawahara T, *et al.* Prognostic value of the bone scan index using a computer-aided diagnosis system for bone

scans in hormone-naive prostate cancer patients with bone metastases. *BMC Cancer* 2016; : 1–7.

99 Poulsen MH, Rasmussen J, Edenbrandt L, *et al.* Bone Scan Index predicts outcome in patients with metastatic hormone-sensitive prostate cancer. *BJU Int* 2016; **117**: 748–53.

100 Reza M, Bjartell A, Ohlsson M, *et al.* Bone Scan Index as a prognostic imaging biomarker during androgen deprivation therapy. *EJNMMI Res* 2014; **4**: 58.

101 Armstrong AJ, Kaboteh R, Carducci MA, *et al.* Assessment of the bone scan index in a randomized placebo-controlled trial of tasquinimod in men with metastatic castration-resistant prostate cancer (mCRPC). *Urol Oncol* 2014; **32**: 1308–16.

102 Kaboteh R, Gjertsson P, Leek H, *et al.* Progression of bone metastases in patients with prostate cancer - automated detection of new lesions and calculation of bone scan index. *EJNMMI Res* 2013; **3**: 64.

103 Ulmert D, Kaboteh R, Fox JJ, *et al.* A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the bone scan index. *Eur Urol* 2012; **62**: 78–84.

104 Ceci F, Castellucci P, Nanni C, Fanti S. PET/CT imaging for evaluating response to therapy in castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging* 2016; **43**: 2103–4.

105 Schwarzenböck Sarah M., Eiber M, Kundt G, *et al.* Prospective evaluation of [11C]Choline PET/CT in therapy response assessment of standardized docetaxel first-line chemotherapy in patients with advanced castration refractory prostate cancer. *Eur J Nucl Med Mol Imaging* 2016; **43**: 2105–13.

106 Giorgi U De, Caroli P, Burgio SL, *et al.* Early outcome prediction on 18F-fluorocholine PET/CT in metastatic castration-resistant prostate cancer patients treated with abiraterone. *Oncotarget* 2014; **5**: 12448–58.

107 De Giorgi U, Caroli P, Scarpi E, *et al.* 18F-Fluorocholine PET/CT for early response assessment in patients with metastatic castration-resistant prostate cancer treated with enzalutamide. *Eur J Nucl Med Mol Imaging* 2015; **42**: 1276–83.

108 Sartor O, Vogelzang NJ, Sweeney C, *et al.* Radium-223 Safety, Efficacy, and Concurrent Use with Abiraterone or Enzalutamide: First U.S. Experience from an Expanded Access Program. *Oncologist* 2017; : theoncologist.2017-0413.

109 Verwer EE, Oprea-Lager DE, van den Eertwegh AJM, *et al.* Quantification of 18F-Fluorocholine Kinetics in Patients with Prostate Cancer. *J Nucl Med* 2015; **56**: 365–71.

110 Oprea-Lager DE, Kramer G, van de Ven PM, *et al.* Repeatability of Quantitative 18F-Fluoromethylcholine PET/CT Studies in Prostate Cancer. *J Nucl Med* 2016; **57**: 721–7.

111 Hope TA, Truillet C, Ehman EC, *et al.* 68Ga-PSMA-11 PET Imaging of Response to Androgen Receptor Inhibition: First Human Experience. *J Nucl Med* 2017; **58**: 81–4.

112 Perez-Lopez R, Mateo J, Mossop H, *et al.* Diffusion-weighted Imaging as a Treatment Response Biomarker for Evaluating Bone Metastases in Prostate Cancer: A Pilot Study. *Radiology* 2017. DOI:10.1148/radiol.2016160646.

113 Xie W, Regan MM, Buyse M, *et al.* Metastasis-free survival is a strong Surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017; **35**: 3097–104.

114 Afshar-Oromieh A, Zechmann CM, Malcher A, *et al.* Comparison of PET imaging with a 68Ga-labelled PSMA ligand and 18F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2014; **41**: 11–20.

115 Morigi JJ, Stricker PD, van Leeuwen PJ, *et al.* Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. *J Nucl Med* 2015; **56**: 1185–90.

Contributors

F.E.L., D.E.O-L., Y.L., P.O., B.T., N.M.DS. conceived and designed the study. All authors participated actively in the discussion and consensus meetings, wrote contributions in relation to their fields of expertise, and reviewed the paper.

Declaration of interests

CD reports grants and personal fees from Novartis, Terumo, AAA, Ipsen, Sirtex, Bayer, outside the submitted work.

KG reports grants and personal fees from Bayer, personal fees from Progenics Pharmaceutical and Blue Earth Diagnostics, outside the submitted work.

KH received personal fees from Endocyte, Ipsen, Adacap, personal fees and non-financial support from Siemens Healthineers, Curium and Bayer, non-financial support from ABX and Sofie, outside the submitted work.

EL received grants from AIRC, outside the submitted work.

BT has received personal fees from Amgen, Sanofi and Janssen, grants and personal fees from Ferring, Astellas and Bayer, outside the submitted work.
All other authors declare no competing interests.

Acknowledgements

This work was supported by Fonds Cancer (FOCA) from Belgium.

Figure 1: Consensus process on the definition, elaboration and validation of recommendations by the EORTC Imaging Group in oligometastatic prostate cancer.

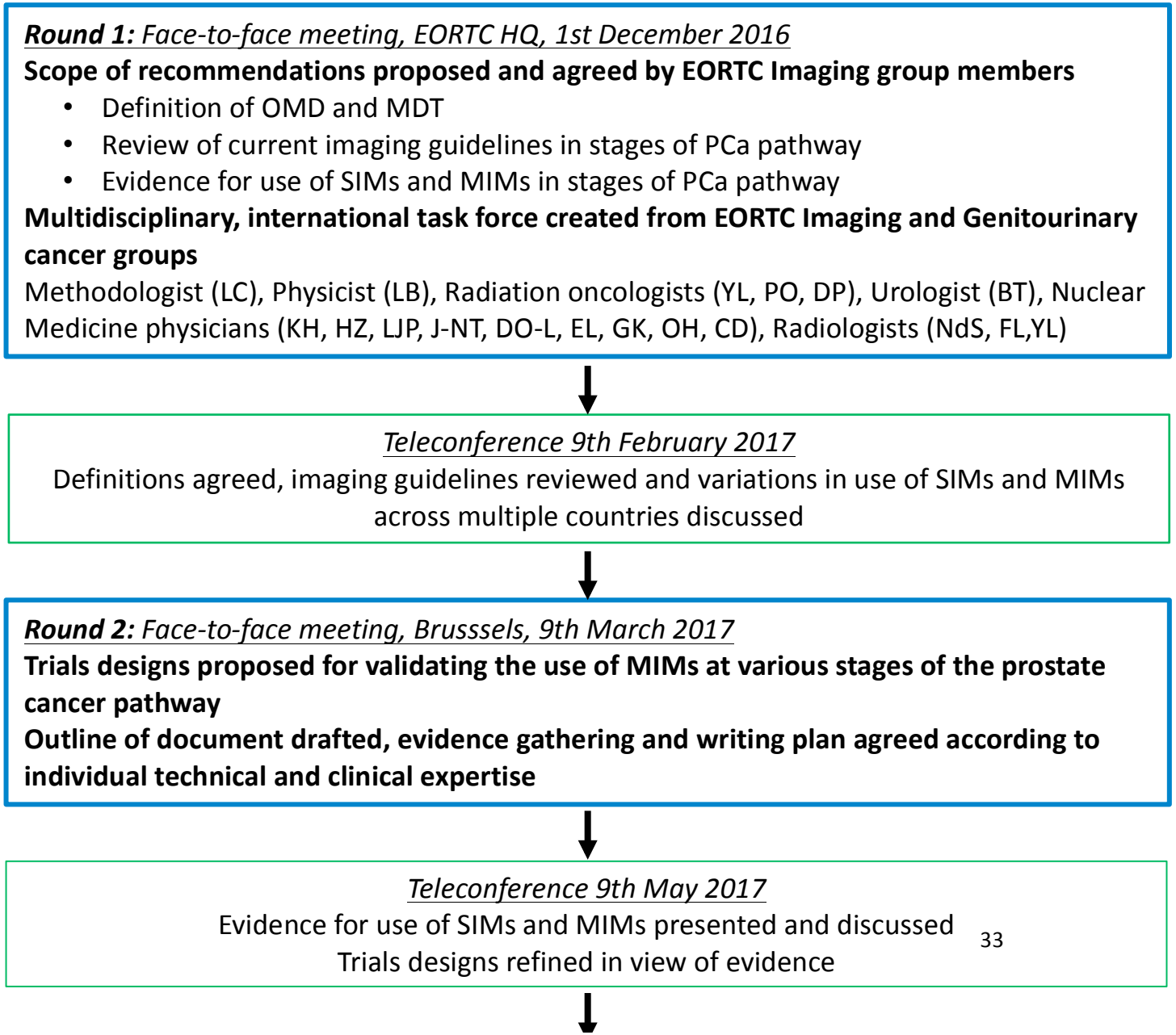
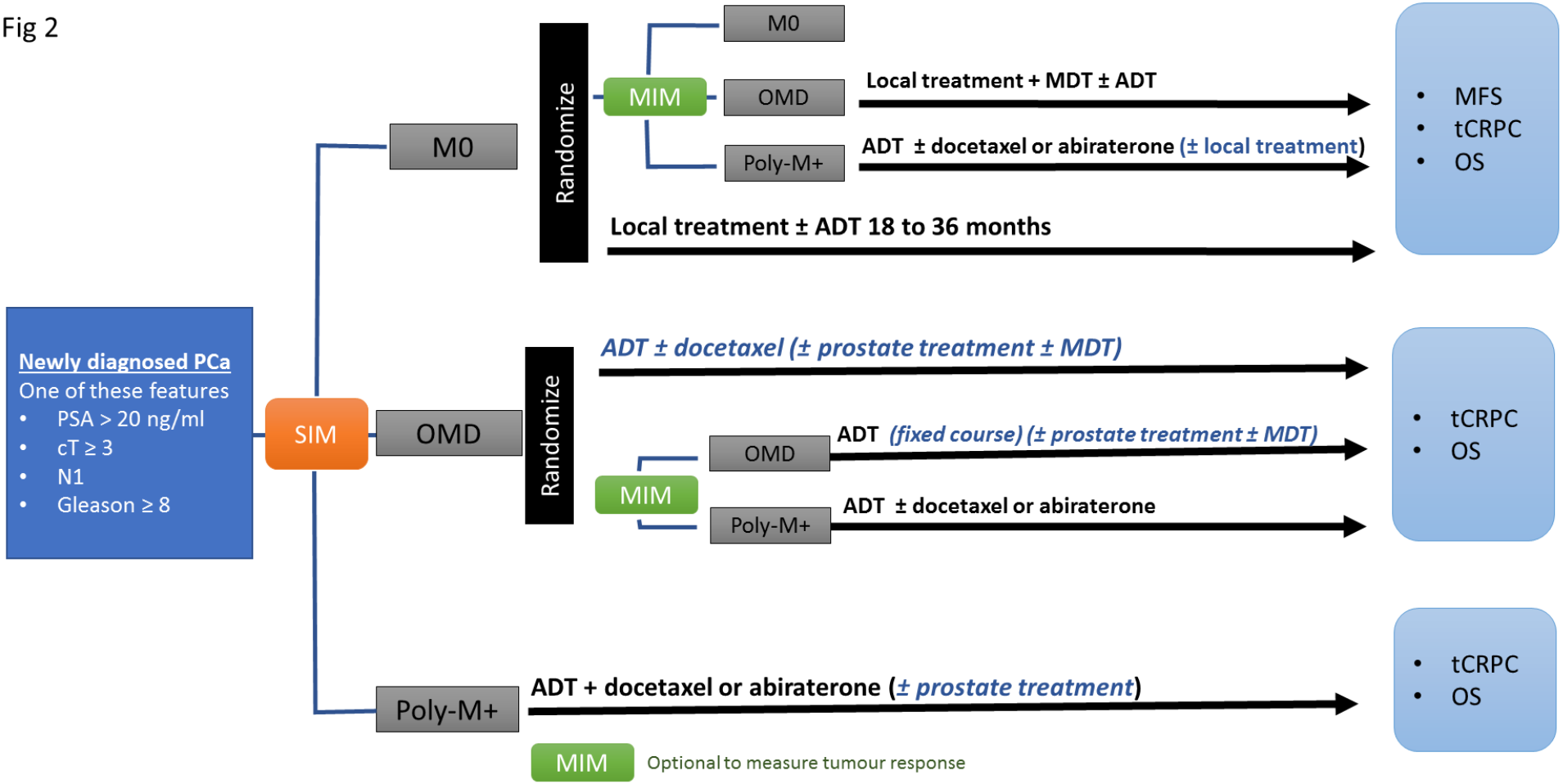


Fig 2

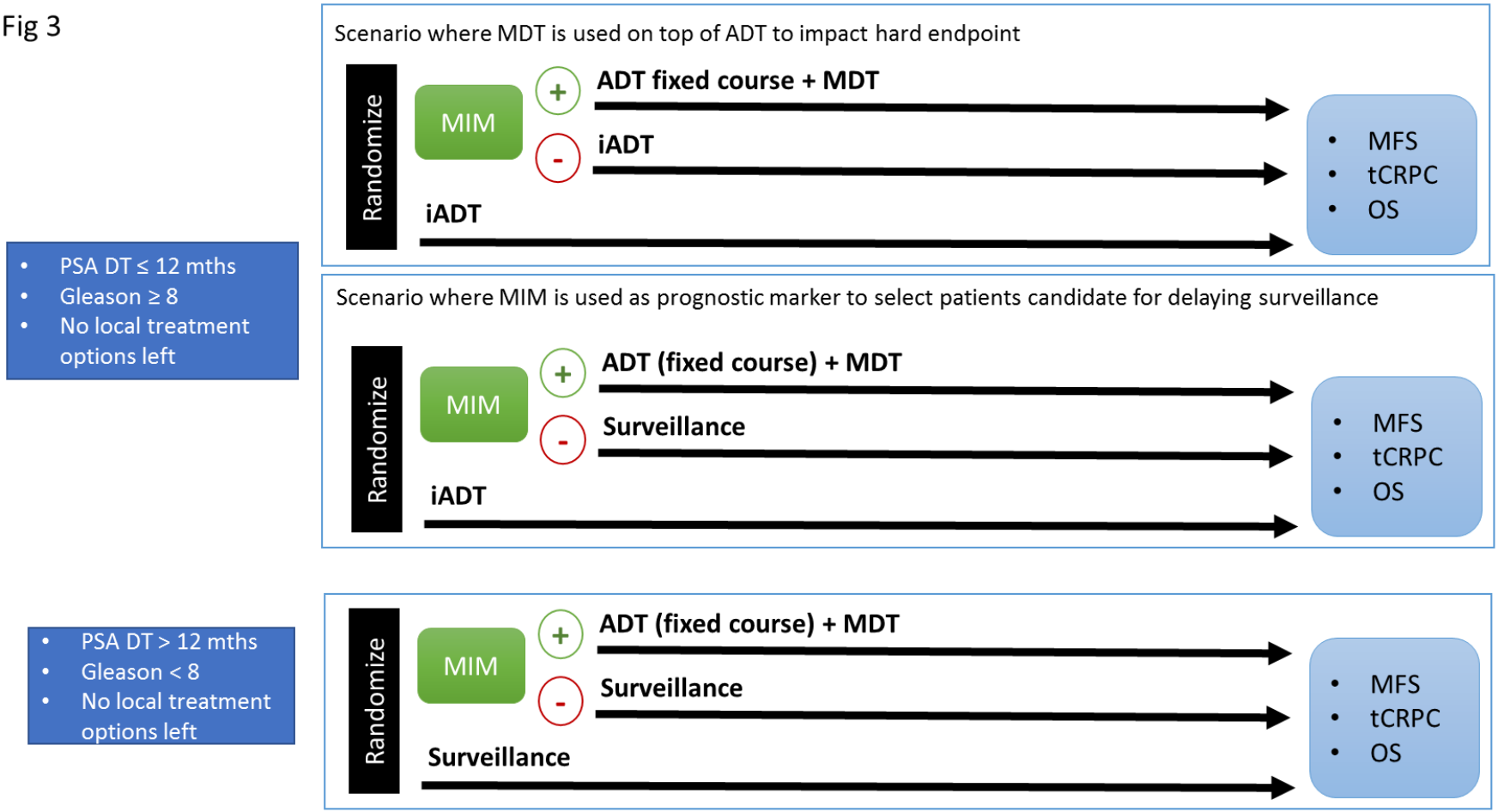


Investigational treatments are *in blue and italic.*

M0: non metastatic, OMD: oligometastatic disease, Poly-M+ Polymetastatic disease; ADT androgen deprivation therapy, MDT: metastasis directedtherapy; MFS: metastasis free survival (ICECAP), tCRPC time to CRPC (EAU definition); OS overall survival

Figure 2: Proposed clinical trials incorporating MIMs in newly diagnosed PCa and evaluating subsequent impact on care pathway, especially the role of MDT.

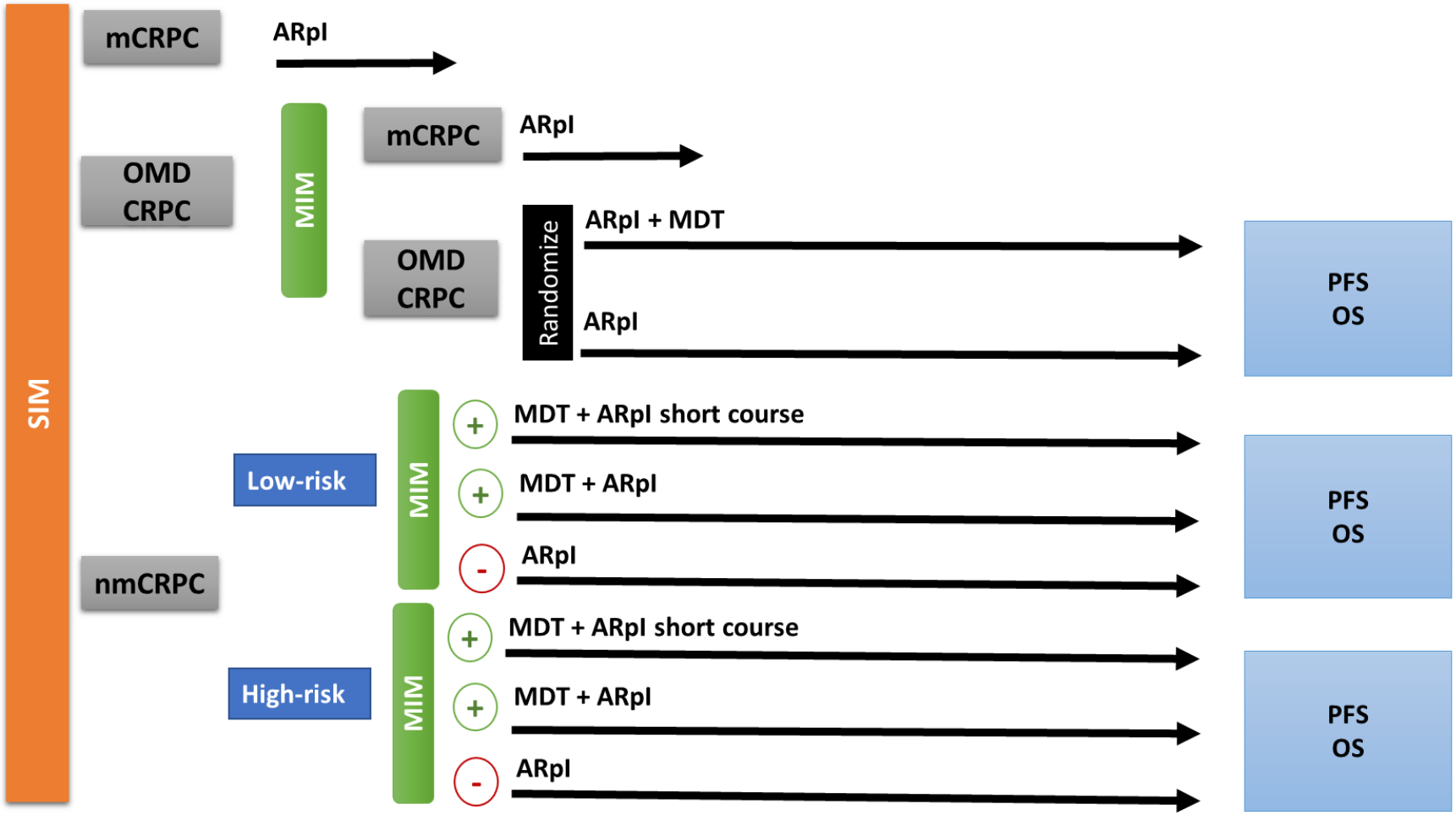
Fig 3



PSA DT: PSA doubling time, iADT intermittent androgen deprivation therapy, MDT: metastasis directed therapy; MFS: metastasis free survival (ICECAP), tCRPC time to CRPC (EAU definition); OS overall survival

Figure 3: Proposed clinical trials incorporating MIMs at BCR in PCa and evaluating subsequent impact on care pathway, especially the role of MDT

Fig 4



(n)mCRPC: (non)metastatic castration resistant PCa, ARpI:androgen receptor pathway inhibitor, MDT: metastasis directed therapy; PFS: progression free survival , OS : overall survival

Low risk: PSA ≤ 2ng/ml and PSAdt ≥ 10 months
Low risk: PSA > 2ng/ml and PSAdt < 10 months

Figure 4: Proposed clinical trials incorporating MIMs in CRPC and evaluating subsequent impact on care pathway, especially the role of MDT