

Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer

a consensus recommendation from the EORTC Imaging Group

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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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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 than 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 lesions¹⁰. Although recommended by most guidelines, these techniques have poor diagnostic accuracy, underestimating the number of metastatic deposits¹¹. 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 criteria¹⁴. 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)

¹⁸F-natriumfluoride (¹⁸F-NaF) PET, like ^{99m}Tc-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. ¹⁸F-NaF PET/CT does not offer a substantial clinical benefit compared to BS (including SPECT/CT) ²⁷.

PET with **¹⁸F- or ¹¹C radiolabeled choline** images cell membrane phospholipid synthesis and accordingly cell growth. ¹⁸F-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

¹⁸F) ²⁷. ¹⁸F-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 ⁶⁸Ga-PSMA-ligand matches well known cellular expression of PSMA across organs ^{29,30}. ¹⁸F-labeled PSMA-targeting imaging compounds, such as ¹⁸F-DCFBC, (a first generation low-molecular-weight inhibitor of PSMA), ¹⁸F-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 ¹⁸F-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. ⁶⁸Ga-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 ⁶⁸Ga-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 ⁶⁸Ga-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 metastatic⁵². 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 ≥ 10 mm but < 15 mm are considered pathological, although non-target lesions⁵⁵. Nodes > 15 mm 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 MRI⁵⁶. 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: ¹⁸F-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 specificity⁶⁴. 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, ¹⁸F-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 endpoints⁶⁵. For lymph node staging the sensitivity of ¹⁸F-choline PET/CT ranges between 33-100% and the specificity between 95-100%²⁸. In 912 lymph nodes sampled in high risk patients, ¹⁸F-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 ⁶⁸Ga-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 studies⁶⁹ and in literature reviews⁴⁰. Furthermore, comparative data suggests that ⁶⁸Ga-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 basis⁷². Meta-analyses have confirmed its superior diagnostic accuracy over ¹⁸F-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 ¹⁸F-/¹¹C-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 ¹¹C- and ¹⁸F-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 ¹⁸F-/¹¹C-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 ^{68}Ga -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 level⁷⁴. Registration of drugs for metastatic CRPC in the last ten years (two androgen-receptor pathway inhibitors (ARPI)- abiraterone and enzalutamide, two chemotherapies- docetaxel and cabazitaxel, three bone targeted agents- RA223, denosumab and zoledronic acid, and one vaccine, sipuleucel-T⁷⁴) demand imaging to justify their use and to monitor treatment response. ARPI are the treatment of choice where available⁹³. 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 months⁹⁴ 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 warranted⁹⁷.

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 RECIST⁵⁵. 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 measurable²⁵.

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 progression¹⁰⁴. As a change in choline uptake does not significantly correlate with PSA response¹⁰⁵, 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 ²²³radium ^{106,107,108}, early ¹⁸F-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 $\geq T3$, a PSA $> 20\text{ng/ml}$, or in presence of symptoms, current guidelines recommend BS and CT/MRI for the detection of bone, lymph node, and visceral metastases⁷⁴ (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 \pm 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 SIMs¹¹³. 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 ¹⁸F-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 care⁹⁵. 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.

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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.

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

Round 1: Face-to-face meeting, EORTC HQ, 1st December 2016

Scope of recommendations proposed and agreed by EORTC Imaging group members

- Definition of OMD and MDT
- Review of current imaging guidelines in stages of PCa pathway
- Evidence for use of SIMs and MIMs in stages of PCa pathway

Multidisciplinary, international task force created from EORTC Imaging and Genitourinary cancer groups

Methodologist (LC), Physicist (LB), Radiation oncologists (YL, PO, DP), Urologist (BT), Nuclear Medicine physicians (KH, HZ, LJP, J-NT, DO-L, EL, GK, OH, CD), Radiologists (NdS, FL,YL)



Teleconference 9th February 2017

Definitions agreed, imaging guidelines reviewed and variations in use of SIMs and MIMs across multiple countries discussed



Round 2: Face-to-face meeting, Brussels, 9th March 2017

Trials designs proposed for validating the use of MIMs at various stages of the prostate cancer pathway

Outline of document drafted, evidence gathering and writing plan agreed according to individual technical and clinical expertise

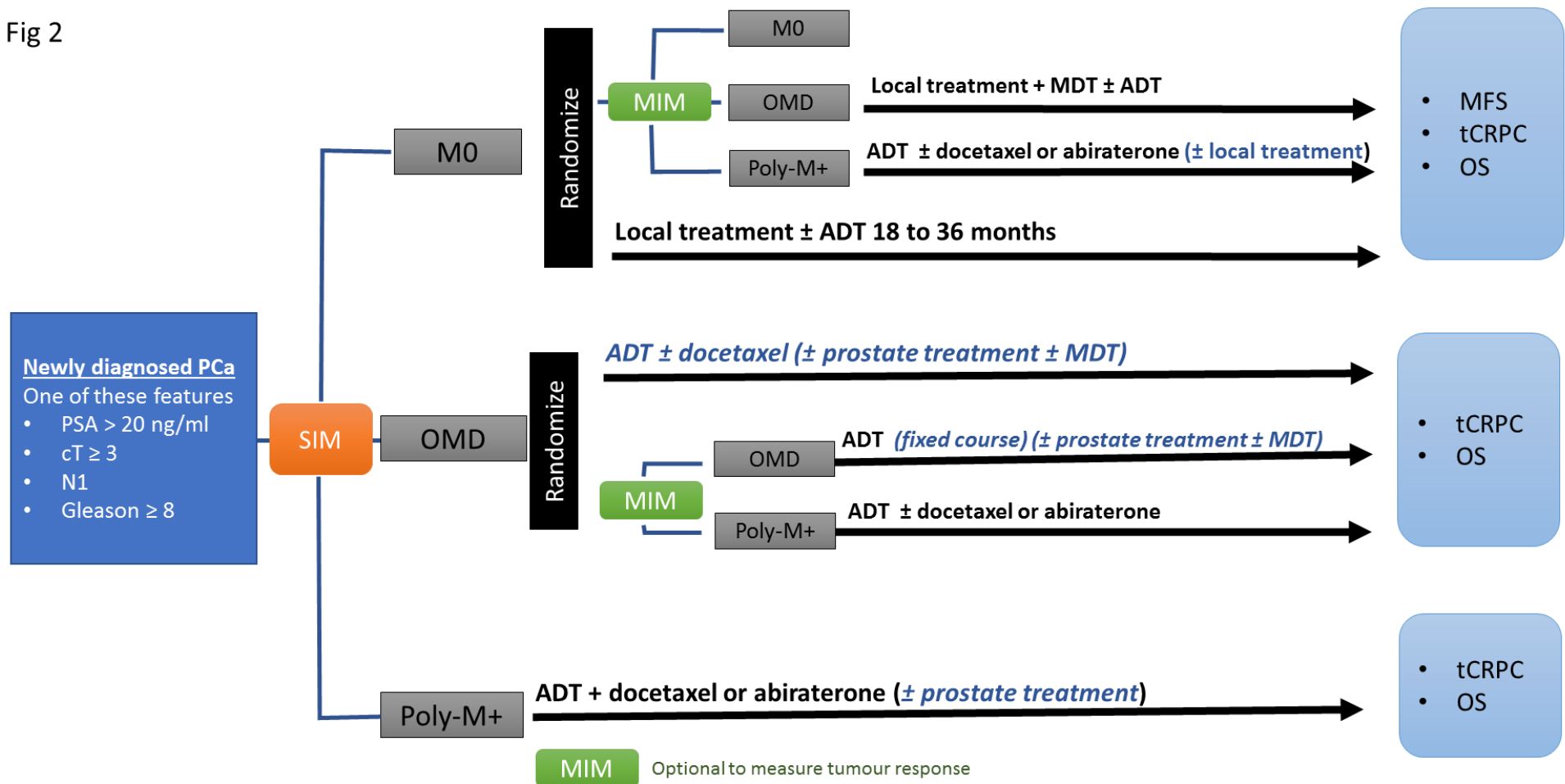


Teleconference 9th May 2017

Evidence for use of SIMs and MIMs presented and discussed
Trials designs refined in view of evidence



Fig 2

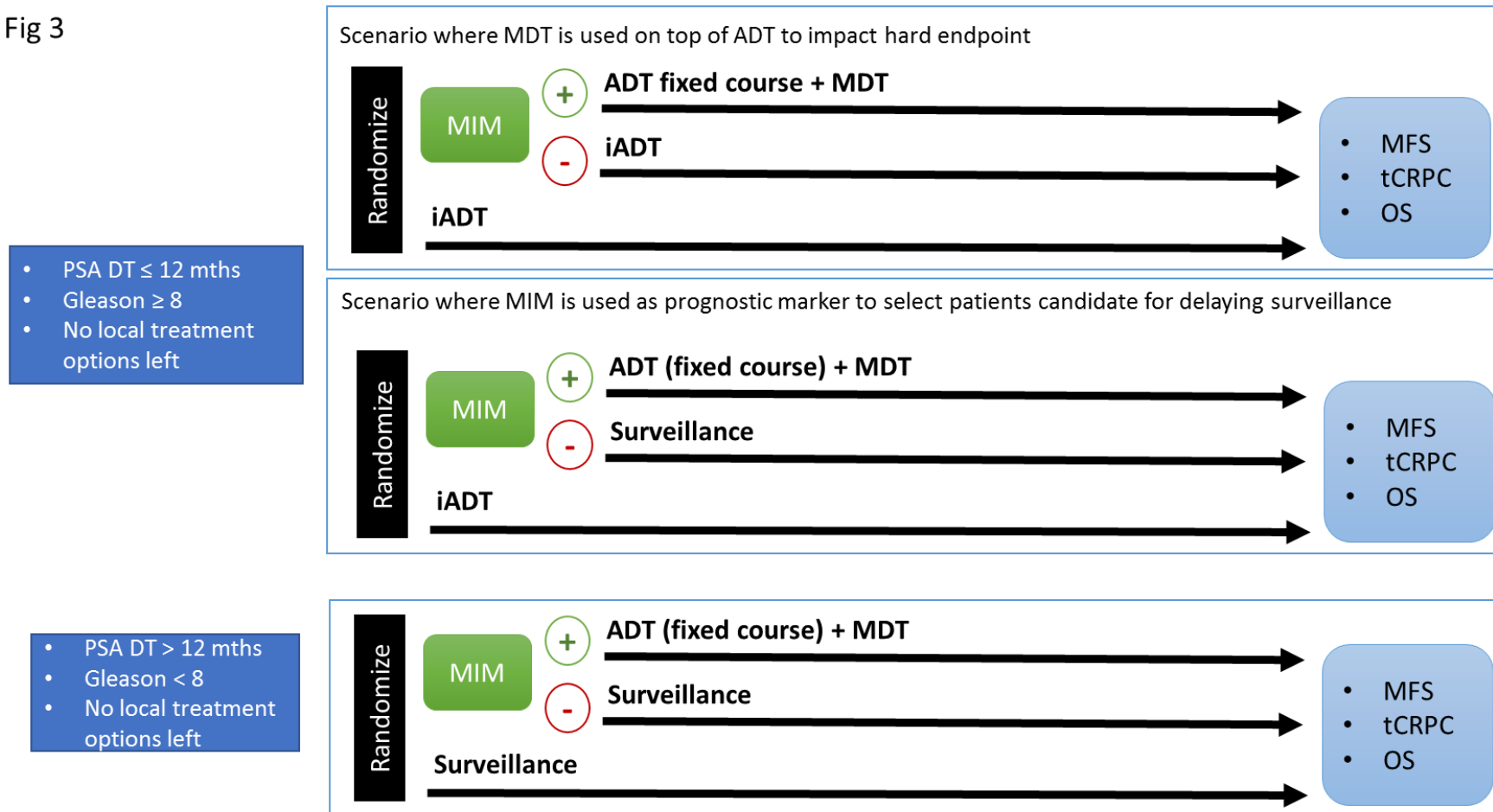


Investigational treatments are *in blue and italic*.

M0: non metastatic, OMD: oligometastatic disease, Poly-M+ Polymetastatic disease; ADT androgen deprivation therapy, MDT: metastasis directed therapy; 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.

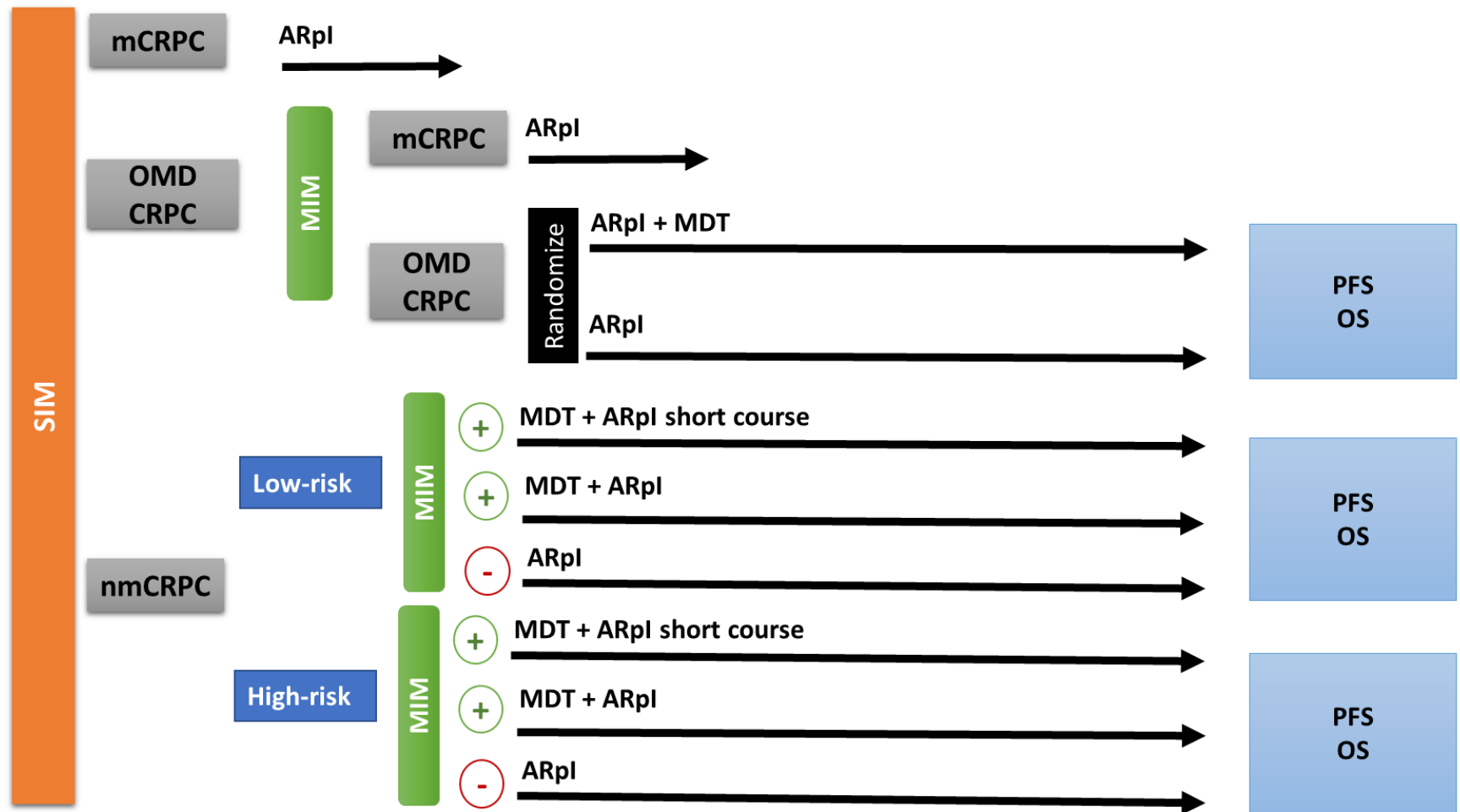
Fig 3



PSA DT: PSA doublingtime, iADT intermittent androgen deprivation therapy, MDT: metastasis directedtherapy; 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, ARpl: androgen receptor pathway inhibitor, MDT: metastasis directed therapy; PFS: progression free survival, OS: overall survival

Low risk: PSA ≤ 2ng/ml and PSA_{dt} ≥ 10 months

Low risk: PSA > 2ng/ml and PSA_{dt} < 10 months

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