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 represents a clinical and anatomical manifestation between localised and polymetastatic disease. In prostate cancer, as with other cancers, recognition of oligometastatic disease enables focal, metastasis-directed therapies. These therapies potentially shorten or postpone the use of systemic treatment and can delay further metastatic progression, thus increasing overall survival. Metastasis-directed therapies require imaging methods that definitively recognise oligometastatic disease to validate their efficacy and reliably monitor response, particularly so that morbidity associated with inappropriately treating disease subsequently recognised as polymetastatic can be avoided. In this Review, we assess imaging methods used to identify metastatic prostate cancer at first diagnosis, at biochemical recurrence, or at the castration-resistant stage. Standard imaging methods recommended by guidelines have insufficient diagnostic accuracy for reliably diagnosing oligometastatic disease. Modern imaging methods that use PET-CT with tumour-specific radiotracers (choline or prostate-specific membrane antigen ligand), and increasingly whole-body MRI with diffusion-weighted imaging, allow earlier and more precise identification of metastases. The European Organisation for Research and Treatment of Cancer (EORTC) Imaging Group suggests clinical algorithms to integrate modern imaging methods into the care pathway at the various stages of prostate cancer to identify oligometastatic disease. The EORTC proposes clinical trials that use modern imaging methods to evaluate the benefits of metastasis-directed therapies.

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Introduction

Oligometastatic disease represents a clinical and anatomical manifestation between localised and polymetastatic disease, and has been described in prostate cancer.[1,2] Its importance is increasingly acknowledged, as evidence grows for the treatment of limited metastatic lesions with focal ablative therapies, such as stereotactic body radiation therapy, surgery, or focal thermal ablation, rather than with systemic therapies.[3,4] In oligometastatic disease, these metastasis-directed therapies 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 metastasis-directed therapies have become increasingly popular among physicians, their delivery relies more on conventional wisdom than on robust evidence.[5] Implementation of these treatments in patients in whom the underlying disease is polymetastatic (a particular problem in prostate cancer, in which there is a long lead time in metastasis development) is undesirable because it merely results in unnecessary morbidity. If disease is polymetastatic, stereotactic radiotherapy and salvage surgery can cause specific toxicity (eg, increased femoral fractures[6] and vertebral compression fractures[7] after focal radiation therapy), delay systemic treatment, and, in rapidly progressing patients, might even be counterproductive, by leaving non-detectable, aggressive disease untreated. Metastasis-directed therapies in prostate cancer, therefore, remain largely investigational; only one phase 2 trial has shown that metastasis-directed therapies delay the onset of androgen deprivation therapy (ADT) in patients with biochemical recurrence after local treatment.[8] Demonstration of the efficacy of metastasis-directed therapies relies on a definitive diagnosis of oligometastatic disease at the outset.

Imaging has a key role in identifying metastases at various points in the prostate cancer care pathway—eg, at new diagnosis, biochemical recurrence, or in the setting of castration-resistant prostate cancer. No standard definition of oligometastatic disease exists and experts still debate on the maximum number of metastatic deposits and their locations. At the 2017 Advanced Prostate Cancer Consensus Conference (APCCC) consensus meeting, oligometastatic disease was defined as the presence of three or fewer bone or lymph node metastases.[9] Such an anatomical definition implies that the imaging technique used to define lesions is accurate for detection of metastasis. For prostate cancer, the standard imaging methods are technetium medronic acid (^{99m}Tc-MDP) bone scintigraphy to detect bone metastases and contrast-enhanced thoraco-abdomino-pelvic CT or morphological 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, such as PET-CT with tumour-specific tracers and increasingly whole-body MRI (WB-MRI) with diffusion-weighted

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imaging (DWI) sequences, allow earlier and more precise identification of metastases.[12,13]

No consensus regarding the use of modern imaging methods in prostate cancer exists, nor do comprehensive recommendations of clinical trials that evaluate the benefits of treating oligometastatic disease recognised with these methods. In this Review, we assess the evidence for using modern imaging methods to identify oligometastatic disease in patients with prostate cancer at the various stages of the disease pathway. We then outline several clinical trial designs for the evaluation of the potential benefit of delivering metastasis-directed therapy to oligometastatic disease on the basis of the use of modern imaging methods (figure 1). We do not address specific drug or ablative technologies, sample size, or endpoints for these trials.

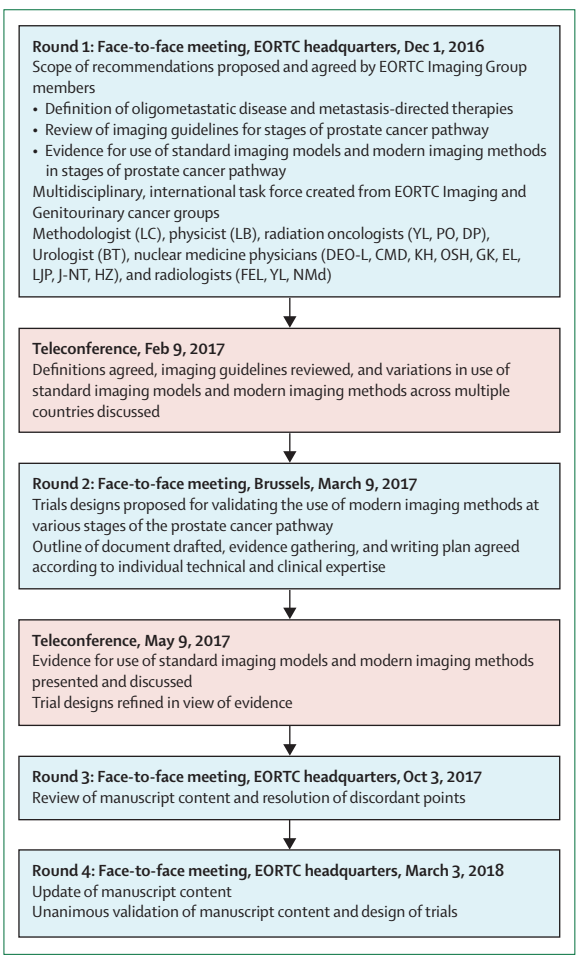

Figure 1: **Consensus process on the definition, elaboration, and validation of recommendations by the EORTC Imaging Group in oligometastatic prostate cancer**
Illustrates the methodology, participants, and procedures used for agreeing the imaging recommendations for diagnosis of oligometastatic disease in prostate cancer: definition of oligometastatic disease and metastasis-directed therapy, review of guidelines and of evidence for the use of modern imaging methods, determination of the stages of prostate cancer to consider. At each structured round, results of the findings were submitted to controlled feedback, reiteration and validation of content, finally integrating them into our trial designs. EORTC=European Organisation for Research and Treatment for Cancer.

Validity of imaging methods

The main imaging requirements for efficient oligometastatic disease screening include high sensitivity and high specificity, and also high negative predictive value at the patient, region, and lesion levels. Standardised acquisition, validated repeatability and reproducibility, reading recommendations, and response measurement criteria are also essential.[14] Comparisons of standard and modern imaging methods have repeatedly shown the superiority of modern approaches, with results particularly showing the failure of standard imaging approaches to meet the requirements for precision medicine.[15,16] Modern imaging methods are, therefore, preferred for optimal diagnosis and therapeutic planning in oligometastatic disease. Some modern imaging methods might only partially meet the requisite criteria for detecting oligometastatic disease, so a combinatorial approach might be required.[17] Therefore, despite their cost implications, modern imaging methods can help us to rethink the care pathways of patients with prostate cancer, by providing information that facilitates selection of targeted curative therapy in the presence of a limited metastatic burden.[16] Nevertheless, modern imaging methods are poorly represented in guidelines (tables 1–3).

Standard imaging methods

CT and ^{99m}Tc-MDP bone scintigraphy have a low sensitivity to detect oligometastatic disease (appendix pp 1–3).[15,16] CT allows for whole-body imaging. It is widely available and affordable, but has poor sensitivity and specificity for detection of lymph nodes metastases and is suboptimal for the detection of bone metastases.[18,19] Bone scintigraphy offers reader consistency for classification of M1 versus M0 disease in prostate cancer, but misses metastatic lesions.[20–22] By use of standardised reporting tools, the classification of progression versus non-progression with these standard imaging methods is excellent, but responses are not easily detected.[23] Intervals of 2–3 months between examinations are needed for bone scintigraphy and it can be affected by the flare phenomenon;[24] therefore, additional confirmatory examinations are needed and diagnosis can be delayed.[22,25] Computer-aided analysis has been proposed to improve classification of the presence and extent of M1 status, but evaluation of the diagnostic performance of software by experts masked to the software shows notable variation.[26]

Modern imaging methods

^{18}F-sodium fluoride (^{18}F-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 insufficient (appendix pp 1–3).[27] ^{18}F-NaF PET/CT does not offer a

substantial clinical benefit compared with bone scintigraphy (including SPECT/CT).[27]

PET with ^{18}F or ^{11}C radiolabelled choline can be used for the imaging of cell membrane phospholipid synthesis and consequently cell growth. ^{18}F-labelling is more widely available and more convenient because of its longer half-life (110 min *vs* 20 min) and better spatial resolution (shorter positron range of ^{18}F).[27] ^{18}F-choline PET/CT is mainly used for restaging patients at biochemical recurrence (appendix p 4). Use of choline PET is recommended by guidelines when prostate-specific antigen (PSA) concentrations are more than 1 ng/mL.[10,28]

Well known cellular expression of prostate-specific membrane antigen (PSMA) across organs can be matched by PET with ^{68}Ga-PSMA-ligand.[29,30] ^{18}F-labelled PSMA-targeting imaging compounds, such as ^{18}F-DCFBC (a first generation low molecular weight inhibitor of PSMA), ^{18}F-DCFPyL (second generation ^{18}F-labelled 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.[31–33] Metastases usually appear as focally increased tracer uptake contrasting with the background. High background activity obscures disease detection in the liver and is compounded by the loss of PSMA expression in advanced liver metastases.[34–36] Absent or low expression of PSMA on the tumour cells can result in false negatives, although the exact proportion of patients is unknown; therefore, strict criteria for visual interpretation remain to be established.[37] Maurer and colleagues[38] compared PSMA-ligand PET-CT with pelvic lymph node dissection and found that 11 (8%) of 130 patients had no or very faint PSMA uptake in the primary tumour. ^{68}Ga-PSMA-ligand PET is recommended at biochemical recurrence in patients with PSA concentrations more than 1 ng/ml (appendix p 5).[10] A high level of interobserver 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 emphasise the potential added value of ^{68}Ga-PSMA-ligand PET/CT for primary staging and for biochemical recurrence detection with a PSA concentration of lower than 1 ng/mL.[39–42]

WB-MRI (with T1, T2, short tau inversion recovery, and DWI sequences) allows mapping of the full extent of the disease and 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 (95% CI 0·89–0·99) for the median global apparent diffusion coefficient (ADC) and 0·97 (0·83–0·99) for the mean ADC.[45] In other studies, WB-MRI has outperformed bone scintigraphy (κ=0·87, 95% CI 0·66–1·00 for ADC, 0·60, 0·26–0·78 for bone scintigraphy).[46,47] The variability of ADC measurements is less than 15%, making it sensitive to treatment-induced changes, thus allowing response to be quantifiable and measurable.[48–50] This capability to assess response is particularly helpful in late stage disease (ie, castration-resistant prostate cancer).[44] International guidelines have been published for harmonisation in acquisition, interpretation, and reporting of WB-MRI, and response assessment criteria have been defined.[51]

Methodology for reaching consensus recommendations

The Imaging Group of the European Organisation for Research and Treatment of Cancer (EORTC) comprises radiologists and nuclear medicine physicians from trial centres throughout Europe who actively participate in multicentre, EORTC-sponsored trials. The group has 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 three face-to-face meetings at the main Imaging Group meetings occurred, as well as two teleconferences to refine the final recommendations. A procedure of discussion and re-iteration between experts was followed, which 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

In countries where PSA testing is available, less than 10% of the newly diagnosed prostate cancers are metastatic.[52] Based on five randomised controlled trials, the standard treatment of patients metastatic at diagnosis has shifted from ADT alone to ADT plus chemotherapy or abiraterone acetate.[53,54] These drugs have shown a clear benefit in patients with high-volume disease (defined as the presence of visceral metastases, or four or more bone lesions with one or more beyond the vertebral bodies and pelvis), but their effect on lower volume disease is unclear. For patients with oligometastatic disease, intense research is ongoing to assess the potential benefit of combining ADT with locoregional metastasis-directed therapy. Imaging at new diagnosis should, therefore, include recognition of metastatic disease in high-risk patients (table 1).

Standard imaging methods detect abnormal lymph nodes on the basis of a size threshold. According to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, nodes with a short axis of 10 mm or longer but smaller than 15 mm are considered pathological, although non-target, lesions.[55] Nodes longer than 15 mm in short axis are considered pathological and measurable by both RECIST and Prostate Cancer Working Group 3 (PCWG3) criteria.[25,55] Despite its high spatial resolution

	Imaging recommendation
European Association of Urology	
Low risk (PSA <10 ng/mL, Gleason score <7 [ISUP grade 1], clinical stage T1–2a)	No imaging
Intermediate risk (PSA 10–20 ng/mL, Gleason score 7 [ISUP grade 2 or 3] or clinical stage T2b); predominantly gastrointestinal 4	Multiparametric MRI for local staging, abdominal and pelvic CT, bone scintigraphy
High risk (PSA >20 ng/mL, Gleason score >7 [ISUP grade 4 or 5]), or locally advanced)	Multiparametric MRI for local staging, abdominal and pelvic CT, bone scintigraphy
Any risk	No CT or TRUS for local staging, no choline-PET for detection of lymph node metastases, no final recommendation on Ga-PSMA or F-PSMA ligand PET, no final recommendation on WB-MRI
National Comprehensive Cancer Network (version 2.2017)	
If life expectancy >5 years or asymptomatic and: T1 and PSA >20 ng/mL, T2 and PSA >10 ng/mL, Gleason score 9, T3 or T4	Bone scintigraphy
Symptomatic and T3 or T4, T1–T2 and nomogram >10% risk of lymph node metastases	CT and MRI
American Urological Association, American Society for Radiation Oncology, Society of Urologic Oncology 2017	
Very low risk (PSA <10 ng/mL, and grade group 1, and clinical stage T1–T2a, and <34% of biopsy cores positive, and no core with >50% involved, and PSA density <0·15 ng/mL per cm^3)	No abdominal and pelvic CT or bone scintigraphy
Low risk (PSA <10 ng/mL, and grade group 1, and clinical stage T1–T2a)	No abdominal and pelvic CT or bone scintigraphy
Unfavourable intermediate risk (grade group 2 [with either PSA 10–20 or clinical stage T2b-c] or grade group 3 [with PSA <20 ng/mL])	CT and MRI, bone scintigraphy
High risk (PSA >20 ng/mL, or grade group 4–5, or clinical stage >T3, or locally advanced)	CT and MRI, bone scintigraphy
Integraal Kankercentrum Nederland (guideline prostate cancer, version 2.1)	
PSA >20ng/mL, clinical stage T3, Gleason score 8, symptomatic	Bone scintigraphy or choline PET
Any risk	Multiparametric MRI for primary diagnosis (if available), multiparametric MRI for staging (only if relevant for therapy), no CT for staging, no routine choline-PET for primary staging

PSA=prostate-specific antigen. ISUP=International Society of Urologic Pathologists. TRUS=transrectal ultrasound. PSMA=prostate-specific membrane antigen. WB-MRI=whole-body MRI.

Table 1: **Imaging guidelines for newly diagnosed prostate cancer**

and even when additional contrast agents are used, CT has poor soft tissue contrast resolution, resulting in inferior performance compared with MRI.[56] An inability to detect architectural changes in lymph nodes smaller than 10 mm results in very low sensitivity (40%) for CT and reactive or inflammatory changes can result in false-positive observations, which explains its low specificity (80%). Although widely used for bone metastases screening at staging of prostate cancer,[10,57,58] the proportion of equivocal planar bone scintigraphy in large trials ranges from 15% to 25%.[20,59] The proportion of falsely negative examinations is even more problematic, because radical treatments to the prostate are probably ultimately futile. At a lesion level, a patient with polymetastatic disease might be falsely identified as having oligo-metastatic disease. For bone scintigraphy, results from meta-analyses[60,61] show a sensitivity ranging from 79% to 88% and a specificity ranging from 75% to 82%. The use of SPECT/CT reduces the proportion of equivocal findings.[62,63]

The modern imaging method ^{18}F-NaF PET is superior to bone scintigraphy, but is similarly limited to bone screening alone. In a review[64] of 318 patients from eight studies, sensitivity was 95·5% (range 81–100), specificity was 77·4% (54–100), positive predictive value was 85·2% (74–100), negative predictive value was 94·9% (77·9–100), and accuracy was 78·5% (65·4–100). The sensitivity of ^{18}F-NaF PET to minimal degenerative changes reduces its specificity.[64] Its higher cost and lower availability mean that it has not replaced bone scintigraphy.

Radiolabelled choline PET/CT has the advantage of being tumour specific. For bone metastases, ^{18}F-choline PET/CT has a sensitivity of 79%, specificity of 97%, and diagnostic accuracy of 84%, 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% and 100% and the specificity between 95% and 100%.[28] In 912 lymph nodes sampled in high-risk patients, ^{18}F-choline PET/CT proved better than CT, particularly for metastases larger than 5 mm in size (sensitivity of 66%, specificity of 96%, positive predictive value of 82%, and negative predictive value of 92%).[66]

Tumour specificity is further improved by use of ^{68}Ga-PSMA PET/CT, for which 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 suggest that ^{68}Ga-PSMA PET/CT is more accurate than bone scintigraphy and CT for the detection of bone and visceral metastases.[70,71] Formal prospective assessment is needed before translation into clinical routine.

Another validated approach to detect both bone and lymph node metastases at staging of first diagnosed prostate cancer is the use of WB-MRI. A meta-analysis study on bone metastasis showed a pooled sensitivity of 95% (95% CI 90–97), specificity of 92% (88–95), and area under the curve for DWI of 0·98 on both a per-patient and per-lesion basis.[72] Meta-analyses have confirmed the superior diagnostic accuracy of WB-MRI over ^{18}F-choline PET/CT, CT, and bone scintigraphy in prostate cancer.[61,73]

Optimal methods for imaging metastases in patients with biochemical recurrence

About 30% of patients treated radically for high or very-high risk prostate cancer have biochemical recurrence.[74] In those patients with previous radical prostatectomy, salvage external beam radiotherapy is recommended.[74] After previous external beam or interstitial radiotherapy, salvage surgery, high-intensity focused ultrasound, or cryotherapy can be used.[74] These treatment methods 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 indispensable. Imaging should be used to rule out polymetastatic disease not amenable to cure by local treatment alone, and to detect oligometastatic disease that could benefit from regional salvage therapies.[75–77] The detection of oligometastatic disease at biochemical recurrence is important, because results from at least one trial have shown that metastasis-directed therapy could delay initiation of ADT. Imaging at biochemical recurrence can also rule in and confirm locoregional recurrence to plan salvage local treatment; multi-parametric MRI is the technique of choice.[77,78] However, even when imaging is negative, pelvic bed external beam radiation therapy is administered on the assumption that local recurrence is undetected at imaging, a strategy supported by several trials of salvage external beam radiation therapy. Imaging is recommended in biochemical recurrence when PSA concentrations are more than 0·2 ng/mL–1 ng/mL after surgery and more than 2 ng/mL above the nadir after radiotherapy (table 2).[79]

CT and bone scintigraphy are not recommended in patients with biochemical recurrence, although bone scintigraphy can be used if the PSA has reached a concentration of 10 ng/mL or higher (table 2).[80,81]

With regards to modern imaging methods, findings from a meta-analysis of 12 studies in 1055 patients with biochemical recurrence showed that ^{18}F-choline or ^{11}C-choline PET-CT on a per-patient basis had a pooled sensitivity of 85% (95% CI 79–89), specificity of 88% (73–95), and diagnostic odds ratio of 41·4 (19·7–86·8).[82] Comparable results were described in a meta-analysis of 19 studies in 1555 patients that showed that the pooled sensitivity for all sites of disease (prostatic fossa, lymph nodes, and bone) was 85·6% (95% CI 82·9–88·1) for ^{11}C-choline and 92·6% (90·1–94·6) for ^{18}F-choline PET/CT.[83] However, in another meta-analysis of 14 studies in 1869 patients, a pooled detection of 58% was reported for ^{18}F-choline and ^{11}C-choline PET/CT in a restaging setting.[84] A PSA doubling time of less than 6 months and PSA velocity of more than 1 ng/mL per year or higher than 2 ng/mL per year 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 amount of PSA.

The most studied modern imaging method in the setting of biochemical recurrence is ^{68}Ga-PSMA-ligand PET/CT.[29,85–87] In patients with biochemical recurrence after radical prostatectomy, the technique was reported to detect pathological findings in 90% of cases, with at least one positive lesion in 83% of cases.[85,86] Results from a meta-analysis showed that the proportion of positive ^{68}Ga-PSMA-ligand PET-CT scans increases with pre-PET PSA (42% positive scans for PSA 0–0·2 ng/mL, 58% for 0·2–1 ng/mL, 76% for 1–2 ng/mL, and 95% for >2 ng/mL).[41] Shorter PSA doubling times also increase detection of ^{68}Ga-PSMA-ligand PET/CT on per-patient and per-lesion analyses.[41] However, the limitations of the previous studies must be emphasised, including no histological proof for tumoural involvement in detected foci, heterogeneity in patient populations, and uneven validation. False-positive PET scans, mostly based on PSMA, showed no lymph node involvement on pathology in 32% at salvage surgery and only 30% of patients had a PSA drop.[88] However, because no post-surgery imaging was done, the wrong lymph node could have been taken out, underlining the need for PSMA-directed radioguided surgery.[89] One case report study also emphasised the problem of false-negative findings of modern imaging methods, with both PSMA PET/CT and ultrasmall superparamagnetic iron oxide-enhanced MRI underestimating the number of involved nodes.[90]

WB-MRI can detect metastases at biochemical recurrence even at very low PSA values (median 0·36 ng/mL; appendix p 5).[76] 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 biochemical recurrence.[12] Although it is potentially a reliable alternative to choline PET/CT in these patients,[91] results from a single-centre study,[92] in which a direct comparison was made between WB-MRI (done with the suboptimal high b value of 600 mm²/s as per

	Imaging recommendation
European Association of Urology	
After prostatectomy with PSA <1 ng/mL	No imaging
After prostatectomy with PSA >1 ng/mL	Choline or PSMA-ligand PET
After radiotherapy (if fit enough for curative salvage)	Multiparametric MRI, and choline-PET, no standard tool for Ga-PSMA-ligand PET, but should be considered if available
General (only if PSA >10 ng/mL, PSA doubling time <6 months, and PSA velocity >0·5 ng/mL per month)	Abdominal and pelvic CT, bone scintigraphy, no final recommendation on WB-MRI
National Comprehensive Cancer Network (version 2.2017)	
After prostatectomy	Bone scintigraphy
After radiotherapy, if candidate for local therapy (T1–2, Nx, or N0, Life expectancy >10 years, and PSA >10 ng/mL)	Chest X-ray, bone scintigraphy, and prostate MRI; abdominal and pelvic CT and MRI and ^{11}C-choline PET should also be considered
Integraal Kankercentrum Nederland (guideline prostate cancer, version 2.1)	
PSA >5 ng/mL, PSA >1 ng/mL and PSA doubling time <3 months, Gleason score 8	Choline PET, bone scintigraphy only if PSA >20 ng/mL
Any risk	No CT for staging, multiparametric MRI should be considered for local recurrence

PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

Table 2: **Imaging guidelines for biochemical recurrence of prostate cancer**

	Imaging recommendation	Notes
European Association of Urology		
PSA >2 ng/mL, symptomatic	Bone scan, CT	If negative repeat when PSA >5 ng/mL and after PSA doubling time
Metastatic castration-resistant prostate cancer, monitoring of treatment	Chest CT, abdominal and pelvic CT, bone scan	Repeated every 6 months
National Comprehensive Cancer Network (version 2.2017)		
Castration naive	Bone scan, chest X-ray, abdominal and pelvic CT and MRI with and without contrast; choline PET should be considered	..
Monitoring metastatic castration-resistant prostate cancer	CT and MRI, bone scan	CT and MRI every 6–12 months, bone scan every 8–12 weeks
APCCC 2017 (Delphi method >75% agreement)		
Oligometastatic castration-naive prostate cancer	No abdominal and pelvic CT or bone scan	..
Staging and monitoring metastatic castration-resistant prostate cancer when treating with radium-223	Thoracoabdominal CT, bone scan	..
APCCC 2015		
Metastatic castration-resistant prostate cancer	Chest CT, abdominal and pelvic CT, bone scan, no routine WB-MRI or PET/CT for staging	Before start of treatment
Prostate Cancer Working Group 3		
If locally persistent or recurrent	Multiparametric MRI	..
All patients	Chest CT (<5 mm slices), abdominal and pelvic CT (<5 mm slices), bone scan, WB-MRI and PET/CT (all tracers) not recommended	..

PSA=prostate-specific antigen. APCCC=Advanced Prostate Cancer Consensus Conference. WB-MRI=whole-body MRI.

Table 3: **Imaging guidelines for castration-resistant prostate cancer**

European Society of Urogenital Radiology guidelines) and ^{68}Ga-PSMA PET/CT, showed WB-MRI to be inferior.

Optimal methods for imaging metastases in early castration-resistant prostate cancer

Castration resistance is defined by a PSA rise or a radiological progression in a patient with testosterone in the castrate level.[74] Registration of drugs for metastatic castration-resistant prostate cancer in the past 10 years (two androgen-receptor pathways inhibitors [ARPIs]—abiraterone acetate and enzalutamide, two chemotherapies—docetaxel and cabazitaxel, three bone-targeted drugs—radium-223, denosumab, and zoledronic acid, and one vaccine—sipuleucel-T)[74] demands imaging to justify their use and to monitor treatment response. ARPIs are the treatment of choice when available.[93] The progression to metastatic castration-resistant prostate cancer (identifiable lesions on imaging) from non-metastatic castration-resistant prostate cancer (PSA increase without detectable metastases on standard imaging methods) is usually slow, except in patients with a short PSA doubling time of 6 months or less.[94] In those with a PSA doubling time 10 months or less, the ARPIs apalutamide and enzalutamide have been shown to significantly extend metastatic-free survival.[95,96] Therefore, in patients with castration-resistant prostate cancer, modern imaging methods can help identify early metastatic progression, resulting in an earlier initiation of abiraterone acetate and enzalutamide. Because up to 30% of patients with progressive disease have oligometastatic disease, addition of metastasis-directed therapy to further increase metastasis-free survival might be warranted.[97]

The standard imaging method of bone scintigraphy is the reference diagnostic tool (table 3) for defining progression of bone metastases, as defined by the PCWG3 criteria.[25] The bone scan index has a prognostic value for estimating survival and the PCWG3 criteria (two new confirmed lesions define progressive disease) predict overall survival.[98–103] The low sensitivity of bone scintigraphy to treatment response, however, exposes patients with short life expectancy to futile and potentially toxic treatment.

Contrast-enhanced CT and MRI are recommended (PCWG3) 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 more than 5 mm increase in the short axis from baseline or nadir in a previously normal lymph node to more than 10 mm is considered progressive for RECIST. For PCWG3, nodes between 10 mm and 15 mm in short axis are considered pathological and subject to clinical discretion but non-measurable; an increase in size in short axis to more than 15 mm is considered progressive and measurable.[25]

The modern imaging method of choline PET/CT has been suggested to assess treatment response in patients treated with docetaxel and decreasing PSA concentrations but with clinical signs of disease progression.[104] Because a change in choline uptake does not significantly correlate with PSA response,[105] use of choline PET/CT in patients with castration-resistant prostate cancer is limited to the detection of resistant tumour lesions during the course of treatment (positive predictive value of 99% and negative predictive value of 81%).[104] Furthermore, in patients with castration-resistant prostate cancer undergoing dedicated therapy with abiraterone acetate, enzalutamide, or radium-223,[106–108] 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] By contrast with its value in biochemical recurrence, PSMA PET/CT is not used for response assessment, owing to the scarcity of knowledge on the temporal association (early overexpression and later decrease) between treatment and PSMA expression.[111]

WB-MRI has the potential to allow for early categorisation of lesions into response categories to define disease response, stability, or progression. Examination protocols and both qualitative (eg, lesion

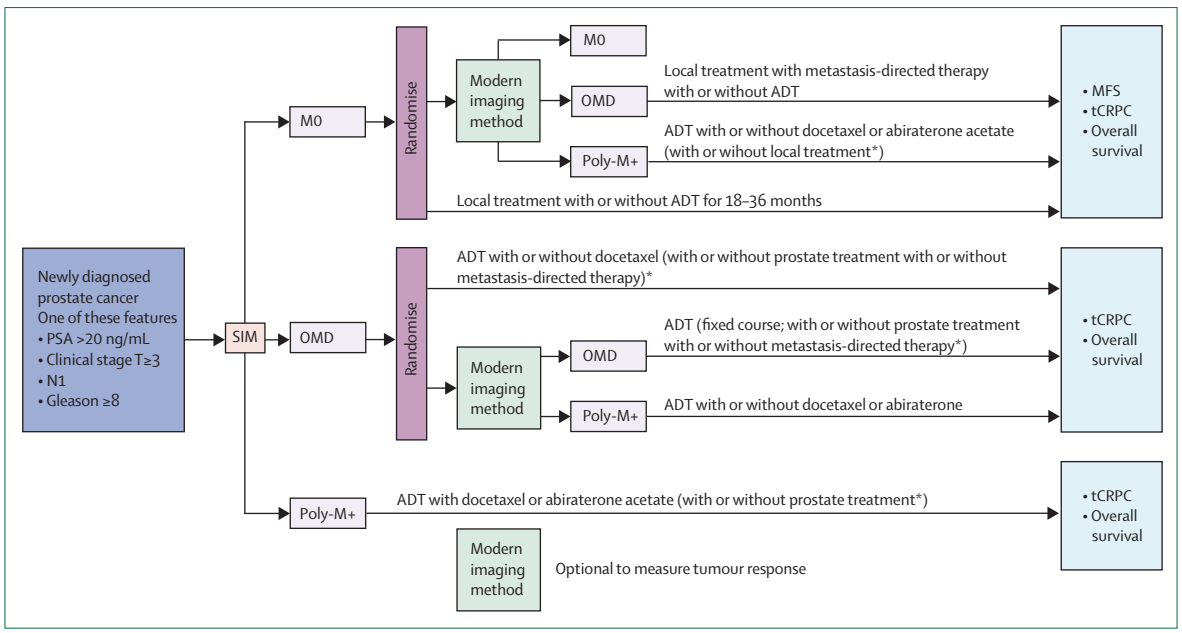

Figure 2: **Proposed clinical trials incorporating modern imaging methods in newly diagnosed prostate cancer and impact on care pathway**
*Investigational treatments. PSA=prostate-specific antigen. N1=regional (pelvic) lymph nodes. SIM=standard imaging methods. MFS=metastasis-free survival. M0=non-metastatic. OMD=oligometastatic disease. Poly-M+=Polymetastatic disease. ADT=androgen deprivation therapy. tCRPC=time to castration-resistant prostate cancer (European Association of Urology definition).

signal and soft tissue extension) and quantitative (eg, number, size, and average diffusion coefficients [ADC]) response criteria have been defined, harmonised, and reported in the published literature.[44,49,50] 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 concentrations and circulating tumoural cell counts.[112] The available data are derived from single-centre, non-randomised studies with small patient numbers, so should be interpreted with caution. Larger-scale multicentre trials are necessary.

Proposed clinical trial designs incorporating modern imaging methods

The study of modern imaging methods has focused primarily on assessing their diagnostic performance, not their effect on care pathways. A study in which patients are stratified by modern versus standard imaging methods for subsequent care would show the difference between a modern and a standard imaging method-driven care pathway. We anticipate that the detection of oligometastatic disease on modern imaging methods would trigger metastasis-directed therapy whenever deliverable. The alternative would be to test a care pathway in which everybody receives modern imaging methods and a decision is taken to use or ignore the results. Based on these general hypotheses, the EORTC Imaging Group has proposed clinical trial designs to validate the use of modern imaging methods for defining treatment options in oligometastatic disease at various stages of prostate cancer, namely at new diagnosis, at biochemical recurrence, and at the castration-resistant prostate cancer stage. Trials of metastasis- directed therapy to the prostate itself in these cases are not included. Endpoints and sample size are not addressed in these simulated trials. Modern imaging methods are referred to generically. Each study could, therefore, use the most appropriate modern imaging method (eg, choline *vs* PSMA-ligand PET/CT, or WB-MRI).

Newly diagnosed prostate cancer

In patients with a Gleason score of more than 7 (4+3), a T stage of T3 or higher, or a PSA of more than 20 ng/mL, or in presence of symptoms, guidelines recommend bone scintigraphy and CT and MRI for the detection of bone, lymph node, and visceral metastases (table 1).[74] In patients with a negative metastatic investigation on these standard imaging methods, modern imaging methods 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 or complementing radical treatment with ADT or metastasis-directed therapy when metastatic disease is of low volume. In patients with low-volume metastatic disease on standard imaging methods, modern imaging methods also might be useful to exclude polymetastases. Modern imaging methods have no role in patients designated polymetastatic on standard imaging methods.

High-risk patients with newly diagnosed prostate cancer with a negative standard imaging method should be randomly assigned to receive a modern imaging

method or not (figure 2). The standard of care when modern imaging method is not done is local treatment of the prostate and the pelvic lymph nodes and ADT for 18–36 months. If the modern imaging method is negative, the standard of care remains unchanged. If the modern imaging method reveals oligometastatic disease, patients could also receive metastasis-directed therapy in an investigational setting. Patients with polymetastatic disease in a modern imaging method group could be treated with ADT with or without docetaxel or abiraterone acetate, local treatment being investigational.

Based on the Intermediate Clinical Endpoints in Cancer of the Prostate working group, the endpoint for patients with localised disease on standard imaging methods is metastasis-free survival.[113] For patients with metastases, no validated endpoint other than overall survival exists. Time to castration-resistant prostate cancer could be captured as an earlier endpoint compared with overall survival.

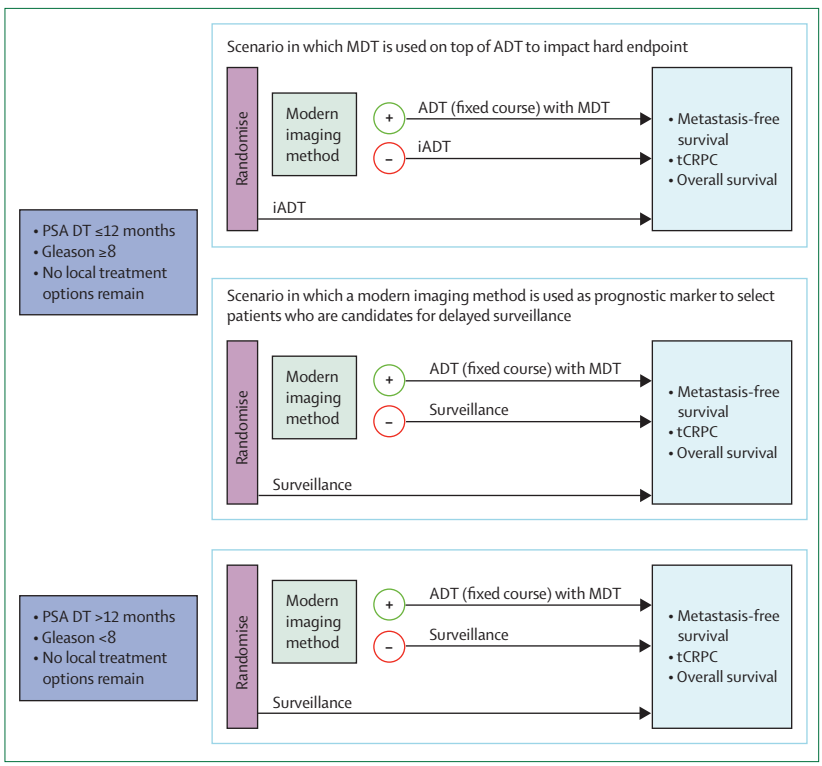

Figure 3: **Proposed clinical trials incorporating modern imaging methods at biochemical recurrence in prostate cancer and impact on care pathway**
PSA DT=prostate-specific antigen doubling time. iADT=intermittent androgen deprivation therapy. tCRPC=time to castration-resistant prostate cancer (European Association of Urology definition). MDT=metastasis-directed therapy.

Biochemical recurrence without locoregional salvage options

Patients with biochemical recurrence can be stratified into two categories, those at low-risk and those at high-risk of metastasis and death (figure 3). Patients at high risk are candidates for early ADT (indicated if PSA doubling time ≤12 months, or a high initial Gleason score [≥8], and a long-life expectancy).[10] European Association of Urology guidelines already recommend choline-PET/CT and PSMA-PET/CT at biochemical recurrence at a PSA threshold of 1 ng/mL. PSMA-PET/CT is preferred, if available, based on findings from several studies proving its superiority over choline-PET and because of lower production costs.[114,115] Based on results from individual studies and meta-analyses, WB-MRI also appears to be superior to ^{18}F-choline PET/CT and could be considered at this stage.[44,61]

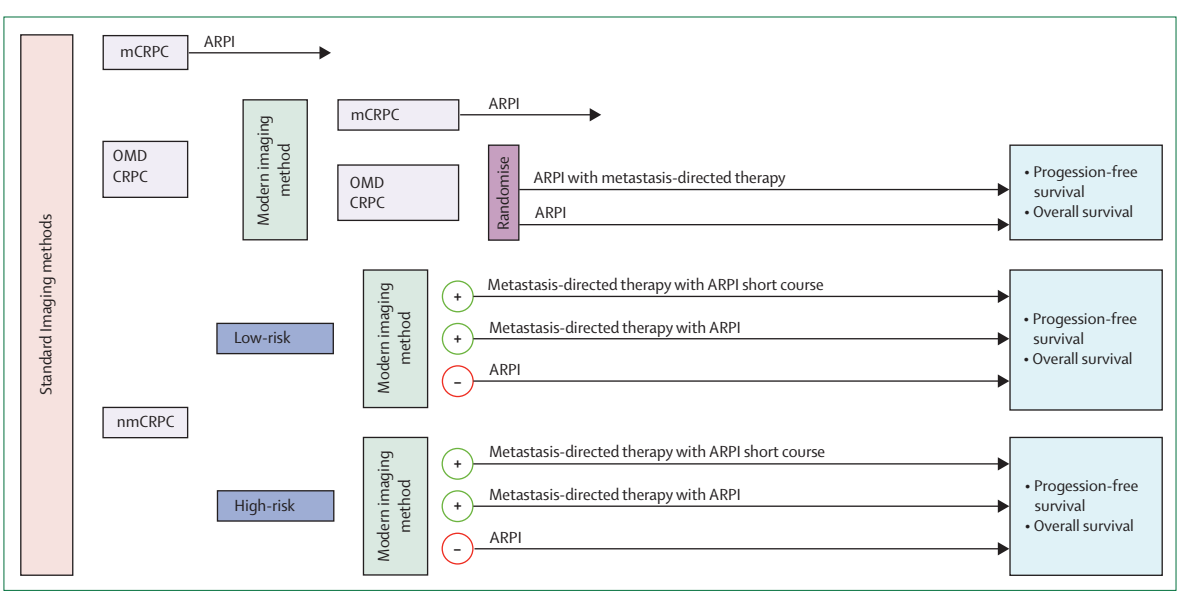

Figure 4: **Proposed clinical trials incorporating modern imaging methods in castration-resistant prostate cancer and their impact on care pathways**
Low-risk: PSA 2 ng/mL or less and PSA doubling time 10 months or more. High-risk: PSA 2 ng/mL or higher and PSA doubling 10 months or less. mCRPC=metastatic castration-resistant prostate cancer. nmCRPC=non-metastatic castration-resistant prostate cancer. ARPI=androgen receptor pathway inhibitor. OMD=oligometastatic disease.

In high-risk patients (PSA doubling time ≤12 months and a Gleason score ≥8) in whom early ADT is recommended, two trials designs are proposed (figure 3). Both trials use metastasis-directed therapy plus a short course of ADT for oligometastatic disease identified on modern imaging methods. Because there is no standard duration of ADT in combination with metastasis-directed therapy, we suggest that 6 months could be used as a standard reference. In the first trial design, metastasis-directed therapy is used to improve on present intermittent ADT results in terms of time to castration-resistant prostate cancer, disease-specific survival, or overall survival. An alternative endpoint is time to castration-resistant prostate cancer while on ADT. In the second design, modern imaging methods are used to offer surveillance to patients with a negative standard imaging method.

Early castration-resistant prostate cancer

Standard imaging methods are the standard of care for patients with a rising PSA and a testosterone concentration of lower than 50 ng/dL. No widely accepted consensus exists for when to undertake standard imaging methods in patients with castration-resistant prostate cancer. The Assessments for Detection of Advanced Recurrence group suggested a bone scan and a CT scan when the PSA reaches 2 ng/mL and, if the scan was negative, it should be repeated when the PSA reaches 5 ng/mL, and again after every doubling of the PSA on the basis of PSA testing every 3 months for asymptomatic men.[16] Symptomatic patients should undergo relevant imaging investigations regardless of PSA concentration (table 3).

Patients with a positive standard imaging method require treatment with ARPIs , 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, modern imaging methods could be used to confirm oligometastatic disease and study the benefit of metastasis-directed therapy (figure 4). In patients with negative standard imaging method (non-metastatic castration-resistant prostate cancer) with a PSA of 2 ng/dL or higher and a PSA doubling time of 10 months or less, immediate ARPIs are likely to become the standard of care.[95] Additionally, patients with a negative modern imaging method could be further randomised to surveillance versus further local treatment, if possible. Modern imaging methods could identify patients with oligometastatic disease, and metastasis-directed therapy used to either further increase metastasis-free survival or to test the hypothesis that metastasis-directed therapy plus a short course of an ARPI is equivalent to long-term treatment with an ARPI. In patients with non-metastatic castration-resistant prostate cancer with a PSA of lower than 2 ng/mL or a PSA doubling time of more than 10 months, modern imaging methods could identify candidates for metastasis-directed therapy with the aim of delaying progression.

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". We imposed no language restrictions. We excluded preclinical and animal studies. The type of study, source of data, and important findings were noted.

Conclusion

This consensus recommendation from the EORTC Imaging Group clarifies the role of modern imaging methods for optimal identification of oligometastatic disease at different stages of prostate cancer. When modern imaging methods are available, the role of standard imaging methods should be either as a necessary step in defining patient populations, in agreement with current recommendations, or as a triage tool to identify patients with polymetastatic disease. Furthermore, we also set out recommendations for the use of modern imaging methods in patients in whom a precise metastatic count and lesion mapping is necessary. We finally highlight the imaging trial designs that should be implemented to show the benefit of incorporating modern imaging methods into the care pathways at distinct stages of prostate cancer: at new diagnosis, at biochemical recurrence, and in castration-resistant prostate cancer.

Contributors

FEL, DEO-L, YL, PO, BT, and NMd 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

CMD reports grants and personal fees from Novartis, Terumo, Advanced Acceleration Applications, Ipsen, Sirtex, and Bayer, outside the submitted work. KG reports grants and personal fees from Bayer, and personal fees from Progenics Pharmaceutical and Blue Earth Diagnostics, outside the submitted work. KH received personal fees from Endocyte, Ipsen, and Adacap, personal fees and non-financial support from Siemens Healthineers, Curium, and Bayer, and non-financial support from Advanced Biochemical Compounds and Sofie, outside the submitted work. EL received grants from Associaziome Italiana per la Ricerca sul Cancro, outside the submitted work. BT has received personal fees from Amgen, Sanofi, and Janssen, and grants and personal fees from Ferring, Astellas, and Bayer, outside the submitted work. All other authors declare no competing interests.

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