Letter to the Editor

Prostate-specific Membrane Antigen Positron Emission Tomography Scans Before Curative Treatment: Ready for Prime Time?

In order to understand which management plan is appropriate for an individual patient, we must first understand the stage and grade of their disease to allow instigation of the most effective intervention and avoid side effects from unnecessary treatments. However, investigations come with risks and costs that can only be justified if they change the treatment decision and improve the final outcome by avoiding undertreatment and overtreatment. For men with prostate cancer (PCa), local stage is currently most commonly assessed using multiparametric magnetic resonance imaging (mpMRI), with nodal or metastatic spread evaluated via a combination of computed tomography (CT) and bone scans. However, positron emission tomography (PET)/CT with $^{68}$Ga- or $^{18}$F-labelled ligands for prostate-specific membrane antigen (PSMA) is increasingly favoured because it provides a better contrast-to-noise ratio and thus increases the detectability of lesions. PSMA is also an attractive target because of its specificity for prostate tissue, even if expression in other nonprostatic malignancies, sarcoidosis, or benign bone diseases may cause incidental false-positive findings [1,2]. Established with a role in assessing biochemical recurrence (BCR) or persistent prostate-specific antigen (PSA) after radical treatment [3], PSMA-based PET/CT is also increasingly reported as an investigation before definitive therapy. A recent meta-analysis included a subgroup analysis of studies presenting data for PSMA PET/CT performed before definitive therapy and using histological correlation as a reference standard. The pooled sensitivity and specificity were 75% and 99% on a per lymph node (LN) basis and 77% and 97%, respectively, on a per patient basis [4]. A separate systematic review and meta-analysis [5] also found that $^{68}$Ga-PSMA had higher sensitivity and comparable specificity for staging preoperative LN metastases in intermediate- and high-risk PCa when compared with mpMRI. Indeed, this approach appears to be a more effective and appropriate imaging modality when compared to conventional imaging for predicting LN metastasis before surgery, as indicated by the area under the symmetric receiver-operating characteristic curve. Beyond LN assessment, a prospective multicentre study evaluated 108 intermediate- and high-risk patients referred for primary staging. In comparison to conventional staging, PSMA PET detected additional LNs and bone/visceral metastases in 39% and 16% of patients, respectively [6]. A recent retrospective review investigated the risk of metastases identified by $^{68}$Ga-PSMA at initial staging in 1253 patients [7]. LN metastases were identified by PSMA PET in 107 men (8.5%). Advanced local stage increased the risk of LN metastasis from 5.3% for T2 lesions to 33.9% for T3b lesions on mpMRI, many of which were seen outside the boundaries of an extended pelvic LN dissection. Skeletal metastases were also identified in 59 men, which is uncommon among men with mpMRI-confined (T2) lesion (3.3%) but more common among men with T3b tumours (14.4%). Bone metastases were also more common among men with grade group 4–5 tumours (7.5%), and visceral metastases were also seen in four men in this group. These largely retrospective data from a single-arm study have recently been confirmed in a prospective randomised study [8] showing superior diagnostic accuracy (92% vs 65%) of PSMA PET over CT and bone scans for both LN involvement and metastatic disease among 302 men with high-risk PCa. Although the results are promising, there are significant issues regarding the data and how they should be interpreted in terms of their impact on clinical practice. Although a test suggesting localised disease may reassure patients, such findings are subject to some uncertainty because false-negative results have been observed, in part because metastatic deposits below the spatial resolution of PET (~5 mm) may still be missed. The real uncertainty concerns the best treatment if PSMA PET/CT reveals metastatic disease. All the available data on treatment selection are based on defining N1 and M1 status using bone and CT scans. PSMA PET will result in stage migration as men with high-risk localised disease are found to have locally advanced or metastatic disease. Data from STAMPEDE showed that men with clinical high-risk disease (at least two of cT3–4, grade group ≥ 4, or PSA ≥ 40 ng/ml), many of whom are likely to have disease outside the prostate on PSMA PET, gained the same improvement in relative risk of death as patients with M1 disease when treated with systemic therapy [9]. There was a survival benefit with the addition of radiotherapy to long-term androgen deprivation therapy (ADT) in men with the same high-risk criteria [10] and failure-free survival for those with low-volume metastatic disease [11]. It is unclear if we can extrapolate these results to PSMA PET/CT–defined M1

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disease, especially if we find multiple spots on bone or nodes. Indeed, how would we define the cutoff for local treatment? Our main concern is that the rapid introduction of PSMA PET/CT into clinical pathways without robust data that compare outcomes with standard imaging might alter the paradigm of patient management from data-driven protocols to one driven by tentative and exploratory data (summarised in Table 1). The concern is that greater numbers of men will be subjected to life-long ADT, particularly when PSMA PET/CT is applied to a standard high-risk definition (one of PSA >20 ng/ml, grade group ≥3, or cT3+) [8] without evidence of a survival benefit. Authors have reported a change in management after PSMA PET/CT findings [6] but although it is clear this will happen we do not have any outcome data for this new subgroup to justify these choices.

PSMA PET/CT has the advantage of providing significantly more accurate staging information than bone and CT scans. However, prospective studies on survival outcomes when using PSMA PET for staging need to be conducted. Until then, caution must be used when PSMA PET/CT detects LN involvement or metastases that are not visible on bone or CT scans. In these cases, doctors should advise patients that treatment decisions cannot be based on direct evidence of better outcomes because PSMA PET/CT has not yet been used in such studies. As a consequence, patients with positive PSMA PET/CT findings can be confident they are basing their decision on the most accurate imaging information but are left with greater uncertainty about what is the correct treatment for their condition.

**Conflicts of interest:**

Erik Briers has received grant and research support from IPSEN and the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring; has received company speaker honoraria from Astellas, Janssen, Ipsen, and Pfizer; has participated in trials run by Ferring; and has received fellowships and travel grants from Astellas and Janssen. Maria De Santis is a company consultant for Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthony, Takeda, Teva, OncoGenex, and Sandoz; receives speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, GSK, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, Synthon, and Takeda; participates in trials run by Technical University Munich, Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SOTIO, and Cancer Research UK; and as a member of the EORTC GU group participates in various trials. She has received research grants from Pierre Fabre Oncologie and travel grants from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthony, Takeda, and Teva/OncoGenex. Stefano Fanti is a company consultant for Bayer and ANMI; has received speaker honoraria from Bayer, Genzyme, ANMI, and GE Healthcare; and participates in trials by Amgen, Bayer, BMS, Genzyme, Janssen, Merck, and Novartis. Jeremy Grummet has received a speaker honorarium from Mundipharma, a travel grant from Astellas, and a research grant from Cancer Australia. He is the owner of MRI PRO Pty Ltd., an online training platform. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and IPSEN. Malcolm D. Mason is a company consultant for Ellipses Pharma and Oncotherics. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received

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**Table 1 – Clinical scenarios**

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Standard imaging</th>
<th>Standard Tx</th>
<th>PET/CT</th>
<th>Uncertainties in Tx due to PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk localised disease</td>
<td>Bone + CT scans</td>
<td>RP or RT + 2yr of ADT</td>
<td>2 spots inside the pelvis</td>
<td>• Is RP still valid?</td>
</tr>
<tr>
<td></td>
<td>show N0M0</td>
<td></td>
<td></td>
<td>• Should patients be offered lifelong ADT?</td>
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<td></td>
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<td>• Should we offer targeted directed therapy?</td>
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<td></td>
<td></td>
<td>• Will we deny local Tx on top of ADT if N0M0 on standard imaging (undertreatment)?</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Will we combine ADT + ARTA + local Tx (overtreatment)?</td>
</tr>
<tr>
<td>Locally advanced disease</td>
<td>Bone + CT scans</td>
<td>Local Tx + long-term systemic ADT (at least when EBRT is considered)</td>
<td>3 spots outside the pelvis</td>
<td>Additional targeted Tx to the visualised lesion but no proven impact on outcome</td>
</tr>
<tr>
<td></td>
<td>show N0M0</td>
<td></td>
<td></td>
<td>• Will we deny local Tx on top of ADT if N0M0 on standard imaging (undertreatment)?</td>
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<td></td>
<td>• Will we combine ADT + ARTA + local Tx (overtreatment)?</td>
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<td>• What is the evidence for such an approach?</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; ARTA = androgen receptor–targeted agents; CT = computed tomography; EBRT = external beam radiation therapy; PSMA PET = prostate-specific membrane antigen positron emission tomography; RP = radical prostatectomy; RT = radiotherapy; Tx = treatment.
Appendix

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References

