

Seduction by sensitivity; reality, illusion or delusion? The challenge of assessing outcomes following PSMA-imaging selection of patients for treatment

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Prostate specific membrane antigen (PSMA) has long been recognized to be an attractive target for evaluating prostate cancer (1). Over the past 2 decades, several groups have worked to develop imaging agents capable of leveraging the high expression of this target in most clinically-significant prostate cancer and its relatively low expression in most other pathological processes (2). These characteristics potentially provide the optimal conditions for both sensitive and specific prostate cancer imaging. Several groups have progressively refined synthesis of compounds that bind the extra-cellular domain of PSMA and are internalized through endocytosis. The most widely adopted and best validated of these agents has been ^{68}Ga -PSMA-11 (3). This agent is not currently approved by the FDA but its use in other jurisdictions, including Europe and Australia, has been enabled by extemporaneous compounding regulations that apply within hospital environments. ^{68}Ga -PSMA-11 is now the subject of investigational new drug applications at multiple institutions in the US, including a multi-Center Trial run by the Clinical Trials Network of SNMMI. Other PSMA radiotracers are now becoming available. These include ^{68}Ga -PSMA-I&T (4) and F-18 agents such as ^{18}F -DCFPyL (5) and ^{18}F -PSMA-1007 (6). Although data comparing these various agents that target PSMA are scarce, as a class, all seem to have a very high sensitivity compared to other competing imaging modalities, particularly including the conventional staging techniques of abdomino-pelvic CT and bone scintigraphy (7). Direct comparison of PSMA and other molecular imaging techniques has also suggested superiority. For example, Morigi *et al.* demonstrated the ^{68}Ga -PSMA-11 had a significantly higher detection rate than ^{18}F -fluoromethylcholine (FCH), especially at low PSA levels (8).

Despite our own long experience with ^{18}F -FCH PET/CT (9), with the very first ^{68}Ga -PSMA-11 PET/CT performed at the Peter MacCallum Centre in July 2014, we knew that our diagnostic and treatment paradigms for prostate cancer would never be the same. The scan detected a node measuring less than 5mm and an isolated rib metastasis that was not diagnostic on other imaging, thereby fundamentally changing the treatment plan for this patient. One of us (RJH) commented that it was like seeing the tide rushing out and knowing that a tsunami was coming. This prediction has been realized over the succeeding 3 years. Such has been the incredible appetite for these scans, almost every PET/CT facility in Australia now offers PSMA-imaging despite lack of Government reimbursement. In our own facility, the growth in demand has outstripped our ability to supply scans in a timely manner given the constraints of ^{68}Ga -generator-based radiopharmaceutical production. Consequently, we have migrated our program primarily to use of ^{18}F -DCFPyL. The ability to produce large activities of F-18 agents allows more efficient and convenient distribution and use of this agent as well as facilitating good manufacturing practice (GMP) compliance. Whether the lower positron energy of F-18 than Ga-68, which theoretically may enhance resolution, translates into higher sensitivity remains to be proven but preliminary evidence suggests at least comparable diagnostic performance compared to ^{68}Ga -PSMA-11 (10). Every day we are impressed by the performance of this technique in detecting otherwise occult sites of disease. The seduction of such sensitive imaging is pervasively felt in multidisciplinary meetings where an increasingly common retort to address diagnostic or management uncertainty is, "Let's get a PSMA scan".

PSMA imaging is probably the most accurate imaging technique that we have for detection of prostate cancer. The ability to detect involvement of small nodes is important since almost 80% of histopathologically-confirmed nodal metastases have been found to occur in nodes smaller than the morphological threshold of 8mm (11). This has specific relevance to the planning of salvage radiotherapy for biochemical failure. In a recent study involving 100 patients with low-level biochemical failure (median PSA 1.0ng/mL), tumor recurrence was detected in 76% of cases by PSMA PET/CT (12). Of these sites, 80% had no morphologic correlate on CT or MRI and their detection led to a change in stage in 43% of cases. Similarly, another recent study involving 31 patients found suspicious foci in 87% with negative conventional imaging with 58% of the sites detected being in locations that wouldn't have been covered in conventional radiotherapy fields (13). While these data are impressive, we should not succumb to the illusion that this technique is perfect. Clearly, all sites of disease are not detected. In a series of patients with pathological correlation, ⁶⁸Ga-PSMA-11 was false negative in just over 20% of cases (14). Although this was substantially superior to CT or MRI, which were false negative in more than 70% of the same cases, these findings have implications for management decisions that might flow from a negative scan and for scans that indicate limited sites of metastatic disease, which might be amenable to aggressive loco-regional therapies like stereotactic radiotherapy. With increasing use of PSMA PET/CT, we have become aware that oligometastatic prostate cancer is largely a delusion based on the insensitivity of conventional imaging. The whole concept of oligometastatic disease has its proponents and detractors (15). We need to ensure that we don't subscribe to wishful thinking in interpreting negative PSMA scans or selecting to treat or not treat patients based on such a result.

In the current edition of the *Journal of Nuclear Medicine*, Emmett et al. (Insert reference) report on outcomes in patients receiving salvage radiotherapy for PSA relapse and particularly on the prognostic significance of a negative ⁶⁸Ga-PSMA-11 scan in this setting. In this series, involving 164 men who were considered eligible for salvage radiotherapy (SRT) for biochemical failure after radical prostatectomy based on PSA readings between 0.05 and 1.0 ng/ml, almost 40% of patients had a negative scan. Indeed, in those with a PSA of <0.2 ng/ml, this rate increased to 50%. Following ⁶⁸Ga-PSMA-11 PET/CT, 24 patients were commenced on androgen-deprivation therapy, presumably for distant disease, leaving 140 men who apparently remained candidates for SRT. For reasons that are not clear from the paper, SRT seems to have been influenced by factors other than just the PSMA result. While all 36 men with disease confined to the prostate fossa on PSMA imaging were treated, most but not all those with involved nodes (88%) and a substantial proportion of those with distant disease (71%) were also treated. The latter group presumably had oligometastatic disease. Importantly, only 44% (n=27/60) of those with a negative PSMA PET went on to receive SRT. Although, this provided an opportunity to assess outcomes according to treatment delivered, the possibility that selection bias underlies the observed heterogeneity in treatment cannot be excluded. Nevertheless, in a novel finding alluded to in the title of the paper, they found an 85% PSA response rate in men with a negative PSMA who received SRT compared to further PSA increase in 65% of those not treated. At first glance, this suggests that a negative PSMA PET/CT identifies a group of men who particularly benefit from SRT and argues for use of SRT despite a negative PSMA.

Before accepting this premise, we need to consider reasons why PSMA might be negative in such patients and how these factors might influence prognosis independent of treatment or treatment response. First, it is evident that tumor burden, as reflected by PSA levels, seems to be an important predictor of PSMA scan positivity. In a large series of patients (n=248) with biochemical recurrence after radical prostatectomy, although close to 90% had a positive PSMA scan, when the PSA was 0.2-<0.5ng/ml, this rate fell to 58% (16). Similarly, in a Turkish multicenter study involving 31 patients, the mean diameter of nodes that were false negative of PSMA PET/CT was only 3.9mm (17), which confirmed earlier results indicating that those pathologically-involved nodes that were not detected were significantly smaller than nodes that were (18). Thus, it is likely that those patients with a negative scan have a smaller volume of disease than those with a positive scan. Consequently, their PSA levels may be more likely to fall back within the range specified for response by *Emmett et al.* (<0.1 ng/ml) even if some of their disease were to lie outside the treatment volume. Because of lag-time bias, a smaller volume of disease would likely take longer to manifest evidence of treatment failure. In this context, a median of follow-up of 10 months in their study is almost certainly too short to determine the overall survival benefit of SRT in such patients. The only robust means to determine outcome in prostate cancer treated with SRT is to prospectively assess the lack of failure over time, which in prostate cancer can mean a follow-up duration of years (or decades in the case of clinical failure endpoints). Short of this, use of a validated and widely accepted instrument (such as PSA \geq 0.4 and rising) is the only reliable contemporary indicator of outcome (19). The response criteria proposed in the current report must be considered exploratory, especially since a fall in PSA alone cannot be relied on to determine longer-term outcomes (20). As with patients with measurable but low-level thyroglobulin levels after thyroidectomy, it is possible that a low but measurable PSA level may reflect residual prostatic tissue despite prostatectomy (21). The likelihood of significant residual normal tissue appears to be greater with conventional than with robotic radical prostatectomy (22). Treatment of such tissue by SRT may serve to reduce PSA levels while regrowth from this remnant over time in the absence of treatment may contribute to rising PSA levels but, in neither situation, would this contribute to long-term outcome.

Second, tumor biology seems to be an important factor in determining PSMA expression. Studies suggest that tumor grade influences the likelihood of a positive scan with increasing Gleason score associated with higher PSMA expression (23). In the primary staging setting, the likelihood of a positive PSMA scan was related to both Gleason score and PSA levels (24). Further, preclinical studies indicate that folate may decrease the invasiveness of prostate cancer cells expressing PSMA (25), probably reflecting the function of PSMA as a folate hydrolase and suggesting that cases with high PSMA may be more likely to metastasize. Thus, a negative scan may indicate a lower grade of disease and a lower likelihood of disease existing beyond the prostate bed, the target of conventionally planned SRT. While this might influence the likelihood of response, it might also indicate a more indolent disease process in which an observational strategy may limit side-effects without adversely impacting survival. Consistent with this hypothesis, PSA doubling time has also been shown to be a predictive factor for a positive PSMA PET/CT (26,27). An exception to the general rule that a negative scan implies either small volume or low-grade prostate cancer is the observation that neuroendocrine

differentiation can be associated with low PSMA expression (28) and yet this is known to be an adverse prognostic group and can have low PSA levels (29). Because such disease may be missed on PSMA imaging, the likelihood of disease not being adequately included in a SRT treatment field would be increased and lead to treatment failure.

Finally, masking of disease close to urinary activity may serve to render PSMA imaging false-negative. This is a situation where multiparametric magnetic resonance imaging (mpMRI), particularly if performed on a hybrid PET-MRI, might improve sensitivity. A recent study of 119 patients with PSA relapse revealed that mpMRI improved detection of local recurrence close to the bladder base compared to ⁶⁸Ga-PSMA-11 (30). Recently described alternative approaches are to perform delayed imaging with or without diuretic administration (31) or by performing early imaging before urinary activity reaches the bladder (32). Low urinary clearance of ¹⁸F-PSMA-1007 may prove to be an advantage in this regard (6). Since this cause of false-negative PSMA relates to prostate bed recurrence, it would not be unexpected that such patients would have a PSA response to SRT but again the longer-term benefit of this likely to be determined by the likelihood of undetected disease beyond the treatment field and the biology of the disease.

As recently discussed in the *Journal of Nuclear Medicine* (33), the major challenge confronting oncologists managing prostate cancer is identifying which patients harbor significant and non-significant recurrence. With most current treatment having a rather low success in curing patients, avoiding toxicity and maintaining quality of life are important objectives in treatment selection. The paper by Emmett *et al.* reminds us that however sensitive a test appears to be, it is illusory. As Richard Feynman famously observed, there's plenty of room at the bottom. Neither should we delude ourselves that sensitive response criteria will necessarily translate into superior patient outcomes. We await with interest further studies that assess the long-term outcomes of patients with negative PSMA PET/CT studies on which clinicians elect not to treat and to the possibility of randomized trials of observation versus SRT in this setting. As Mark Twain posited, "“Supposing is good, but finding out is better.”"

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