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Title: Proposed Criteria Positions PSMA PET for the Future

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Kairos (καιρός) - an Ancient Greek word meaning the right, critical or opportune moment; a proper or opportune time for action.(*1*)

Prostate cancer is an oncologic disease that has been deprived of the benefits of molecular imaging in this era of oncologic FDG Positron Emission Tomography/Computed Tomography (PET/CT) compared to other tumor types due to its inherent biologic predilection for fatty acid rather than glucose metabolism. Due to this unmet clinical need, there has been an increased interest and development of emerging non-FDG PET radiotracers for prostate cancer including choline (^{11}C-Choline, ^{18}F-Fluorocholine, ^{18}F-fluoromethylcholine), acetate (^{11}C-Acetate, ^{18}F-Fluoroacetate), and amino acid-based (^{18}F-Fluciclovine) agents. Some of these radiotracers have successfully received United States Food and Drug Administration New Drug Application approval for clinical use (^{11}C-Choline, ^{18}F-Fluciclovine), which has been well received. However, recent developments and promising initial clinical studies with novel fluorine-18 and gallium-68 labeled low-molecular weight prostate specific membrane antigen (PSMA) PET radiotracers have generated increased excitement due to their very promising early results for improved detection and staging of prostate cancer beyond conventional imaging modalities and even other non-FDG PET radiotracers. (*2,3*) However, these new PSMA PET radiotracer will need to deliver on this initial promise in the next phase of its development for it to become a valuable tool for patient management and drug development for prostate cancer in forthcoming systematic multi-center clinical trials. The authors of two new proposed PSMA PET criteria to facilitate prostate cancer reporting and classification make important and needed first steps in the next phase of development of this class of molecular imaging agents for prostate cancer, also applicable to other non-PSMA PET agents. (*4,5*)

PSMA is a viable target for prostate cancer imaging due to its high expression on most prostate cancer cells and association with more aggressive prostate cancer biology. (*3*) The clinical relevance of PSMA PET for prostate cancer imaging includes a high signal-to-background signal for improved tumor detection, especially but not limited to localization of the sites of biochemical recurrence compared to conventional imaging and even to choline PET at low serum PSA levels. (*6,7*) Despite this high performance, false positive lesions have been reported and these pitfalls need to be taken into consideration in future criteria which includes PSMA PET uptake in normal physiologic distribution (example: ureter, sympathetic chain ganglion), inflammatory processes (example: sarcoidosis), benign osseous processes (example: Paget's disease) and tumor neovasculature of non-prostate malignancies (example: renal cell carcinoma). (*8*)

A standardized reporting system for incorporation of PSMA PET imaging to meet upcoming clinical diagnostic and clinical research needs requires an efficient but accurate method to meet the needs for the imager, referring treating clinicians and multi-center clinical trials. These clinical and research needs, while overlapping, each have unique requirements. Clinical diagnostic reporting tools need to be simple, efficient and clinical action directed, while adaptable to unique clinical situations.

Incorporation of PSMA PET findings into current anatomic imaging-based diagnosis staging criteria is also needed to efficiently communicate these findings to support clinician therapeutic management decisions. Research reporting tools need to be reproducible and accurately allow for stratification of patient cohorts as well as provide the structure for pooling of patient data for multi-center trials. Both reporting tools need to be adaptable to allow for incorporation of updates and changes as we learn more about PSMA PET imaging with new research findings and clinical experience. The reporting and Data System (RADS), is a quality assurance tool applied to pre-therapy initial diagnosis of primary prostate cancer. The TNM classification of malignant tumors (TNM) is a notation system that describes the stage and anatomical extent of a solid tumor. Both PSMA-RADS and PROMISE classifications propose incorporation of PSMA PET into existing systems of tumor diagnosis and staging classifications, albeit with complementary proposals based on the RADS and TNM classification, respectively.

PSMA-RADS Version 1.0 proposes a standardized method to "allow for an accurate and efficient means of relaying findings to referring providers" and "facilitate the collection of data for large prospective trials". (*4*) They propose reporting an imager's level of certainty regarding PSMA PET findings using a five-point scale (ranging from PSMA-RADS-1: benign, PSMA-RADS-2: likely benign, PSMA-RADS-3: equivocal, PSMA-RADS-4: prostate cancer highly likely, PSMA-RADS-5: prostate cancer almost certainly present), with additional sub-levels for each category. PSMA-RADS is proposed for categorization of findings outside of the prostate in pelvic or distant metastatic disease and does not address primary prostate cancer. An individual lesion and patient based PSMA-RADS report is also proposed, an important perspective requiring simplification of complex imaging findings in patients with widespread metastatic disease. A strength of this proposed method is the incorporation of clearly defined levels of confidence in imaging findings with actionable recommendations, ranging from benign, equivocal (requiring confirmatory workup or follow-up imaging) or positive disease not requiring confirmatory biopsy. This criteria also importantly adds required reporting guidelines (example: PSA level, date of last treatment, dose of radiotracer injection, etc.) and addresses the oligometastatic disease setting (state of disease with ≤ 5 metastatic sites) proposing a PSMA-RADS score for each site of suspected metastasis given emerging focal ablative therapy options for individual sites of metastasis in this disease setting. However, the interpretation of PET imaging findings in PSMA-RADS termed "typical" or "atypical" for prostate cancer is an issue that will require clarification and further refinement with more research studies and development of PSMA PET interpretation guidelines.

PROMISE incorporates PSMA PET-based molecular imaging (although the authors propose this criteria can also be used for non-PSMA radiotracers) also with the goal of adopting a "unified language…for organizing findings in comprehensible categories" to allow for efficient communication of findings among "physicians and institutions". (*5*) Their proposal provides a first step for a molecular imaging-based tumor, node and metastasis TNM reporting system (miTNM version 1.0) for PSMA PET/CT and

PET/magnetic resonance (MR). An important aspect of this criteria incorporates PSMA PET findings with current anatomic imaging based clinical reporting criteria to report the location and extent of sites of disease including primary prostate (adopting and layering in Prostate Imaging Reporting and Data System (PI-RADS) for primary prostate cancer), pelvic and extrapelvic sites of tumor spread. A uniform adoption of this anatomic localization system using the same locations and terminology agreed upon amongst both the imager and treating clinician is critical for effective communication as well as comparing results across clinical studies, especially for studies involving pathological lymph node dissection and radiation therapy planning. This proposal also incorporates a diagnostic confidence score based on incorporation of relevant clinical and conventional anatomic imaging. A unique contribution of this criteria is primary prostate cancer reporting with a proposed six segment (sextant) schema for use with PSMA PET/MR. An issue is that future clinical applications may need more localized anatomic definition (from 6 to 12 segments incorporating an anterior/posterior segments) or adopt use of a magnetic resonance imaging (MRI) sector segmentation map used in PI-RADS version 2 for MRI (39 sectors/regions: thirty-six for the prostate, two for the seminal vesicles and one for the external urethral sphincter). Another important issue that will need further clarification and discussion is the anatomic definition of pelvic and extra-pelvic region amongst imagers, radiation oncologists and surgeons as this anatomic boundary will be critical in correlating imaging findings with surgical nodal dissection or pelvic radiation fields.

Visual criteria to define whether there is PSMA PET positive or negative findings for prostate cancer was proposed in PROMISE but not discussed in PSMA-RADS. PROMISE proposes the molecular imaging PSMA (miPSMA) score using internal organ reference PET uptake. This similar to the visual PET classification criteria incorporated in both clinical and research by the current lymphoma Lugano criteria utilizing a five-point FDG PET Deauville visual scale using normal liver and mediastinal blood-pool as reference regions (*9*). The proposed miPSMA criteria uses blood pool, liver and parotid gland for reference regions (with spleen replacing liver in radiotracers with liver dominant excretion PET agents such as ^{18}F-PSMA 1007), with a miPSMA score of 0 (<blood pool), 1 (≥ BP, < liver), 2 (≥ liver, < parotid gland), 3 (≥ parotid gland). However, the use of this proposed miPSMA score would need adapting and verification with some concern that PSMA uptake in these reference regions may vary amongst patients and different PSMA PET radiotracers resulting in variability of reporting and poor reproducibility. There is also concern that certain lesions, especially small subcentimeter lymph nodes at sites of tumor recurrence, may have a miPSMA score of 0 require any visually discernible activity to be considered metastatic disease depending on our threshold for sensitivity in our interpretation needed for certain clinical setting such as biochemical recurrence with low serum PSA levels.

Important issues relevant to future versions of PSMA PET criteria but too premature to be addressed at this time with available scientific data includes the use of a semi-quantitative standardized uptake value-based PSMA PET metric for prostate cancer

detection and response assessment. The effect of androgen therapy and its modulation and effect on PSMA expression and therefore the PSMA PET signal in castration-sensitive or castration-resistant disease setting will also need to be addressed in future criteria. (*10*)

Prospective multi-center studies with PSMA PET can be best served by incorporating the important complementary information proposed in PSMA-RAD (table 1 from PSMA-RADS) and PROMISE (figure 2 from PROMISE) in a combined reporting system. PROMISE addresses the anatomic regional definition of primary disease and recurrence, whereas PSMA-RADS delineates an imager's level of certainty regarding PSMA PET findings for metastatic disease. A multi-disciplinary PSMA PET working group, similar to the international working group for lymphoma, could help better consolidate and update PSMA PET imaging criteria based on available scientific data and adapt to the changing landscape and needs of prostate cancer therapies. Future trials can prospectively test and validate these proposed criteria in initial studies by assessing the predictive value for detection of primary and metastatic disease with reference histopathology correlation, clinical outcome in PSMA-directed ablative therapies and change in clinical management. A standardized criteria can also be adapted to compare PSMA PET with other emerging imaging modalities, including novel PET and SPECT imaging agents, to select the best modality for particular prostate cancer clinical scenarios. We cannot lose this momentum and opportunity presented to us in the molecular imaging community to lay the proper groundwork to deliver on the promise of PSMA PET molecular imaging for the sake of our current and future patients afflicted with this disease.

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