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Comment on NCCN Guidelines for PET/CT Imaging in Prostate Cancer (Prostate Cancer PROS-8 and PROS-B page 3 of 3, Principles of Imaging)

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On behalf of MITA, I respectfully request that the NCCN Prostate Cancer Panel review the enclosed data describing the use of PET/CT imaging with 11C-choline, FDG, 18F NaF, and fluciclovine F 18 in men with suspected prostate cancer biochemical recurrence and **update the recommended list of imaging techniques accordingly.**

Approval status: ^{11}C-choline, FDG, ^{18}F NaF, and fluciclovine F 18 are FDA approved.

Rationale: In the United States and Western Europe, prostate cancer (PCa) afflicts 1 in 6 men, making it the most commonly diagnosed non-cutaneous malignancy in males.[1] Most of the approximately 35,000 men who die each year of PCa do so after the failure of either primary local or systemic therapy. The early and reliable identification of the sites of local, lymph node (LN) or distant recurrences of PCa is critical for determining the best course of treatment and for lowering the risk of death in these patients following primary failure.

Imaging modalities including CT, MRI, and nuclear bone scan are currently used in men with biochemical recurrence (BCR) after failure of primary treatment. However, these techniques cannot detect most PCa with acceptable sensitivity at early stages. The overall sensitivity for conventional imaging modalities is disappointingly low at 11%, with a mean cut-off PSA of 23 ng/mL.[2-4] Importantly, critical decisions regarding further management of relapsing PCa are often made at PSA levels that are significantly lower than this, where conventional imaging is least likely to be helpful in guiding subsequent management of patients with treatment-failure.

The collective literature describes improved detection of disease using PET/CT for BCR in this setting. The current NCCN recommendation (NCCN Guidelines Version 2.2016; Prostate Cancer) for the use of Choline PET/CT in the setting of biochemical recurrence to detect distant recurrence is appropriate, but should be expanded, as multiple PET/CT radiotracers that are FDA approved have been evaluated for this purpose.

Choline: Several studies show improved detection of BCR using PET/CT imaging with Choline labeled with C11 .[5-15] As an example, Giovacchini et al reviewed 2,124 PCa patients who received ^{11}C choline PET/CT. In the 358 who had undergone previous treatment by RP, and experienced BCR ($\geq$ 2 consecutive PSA measurements of >0.2 ng/mL), the sensitivity, specificity, PPV, NPV, and overall accuracy were, 85%, 93%, 91%, 87%, and 89%, respectively for detection of recurrent disease at all sites. On a lesion-based analysis other than a patient-based analysis, studies reported a sensitivity ranging between 39.7% and 90.9%, while the PPV ranged between 75.7% and 94.5%. Therefore, Choline PET/CT has a low-moderate sensitivity for the detection of individual LN disease on a lesion-based analysis and a moderate-high sensitivity for LN metastases in the pelvis and extra pelvic disease by sites.

FDG PET/CT has been evaluated for detection of recurrence PCa and is most effective in aggressive disease variants but it is less sensitive than other PET methods for detection of BCR. [8] Current recommendations by NCCN are appropriate in recommending use of FDG PET/CT in certain clinical situations but not routine use.

Sodium Fluoride PET/CT has high sensitivity of skeletal disease detection in the setting of biochemical recurrence but is challenged by low specificity. [16,17] Existing NCCN criteria include Sodium Fluoride PET/CT as an acceptable diagnostic test to detect bone metastases but appropriately, do not recommend it for initial assessment. The disadvantage of Sodium Fluoride PET/CT is the need for combined use with other soft tissue PET/CT methods to achieve acceptable disease detection sensitivity. [18]

Fluciclovine F-18 (also known as FACBC) recently received FDA approval for PET imaging in men with suspected PCa recurrence based on elevated PSA levels following prior treatment. [20] This approval was based on data from 877 subjects, including 797 males diagnosed with prostate cancer. [20] Odewole et al [19] found that recurrent PCa can be detected with significantly better accuracy using fluciclovine PET/CT than with CT. On a whole-body basis, in a patient population that was bone scan negative on inclusion, 41 of 53 fluciclovine PET/CT scans (77.4 %) were positive, but only 10 of 53 scans (18.9 %) were positive with CT. Of 33 patients with histological proof of disease, fluciclovine PET/CT detected disease in 31 (93.9 %) but CT detected disease in only 4 (12.1 %). Nanni et al compared to low-dose 11C choline (10 mCi) to fluciclovine F 18 (10 mCi) in 89 men with BCR post radical prostatectomy, with follow up at 1 year used as the reference standard. [25] Diagnostic performance was comparable for both agents at PSA values above 1 ng/mL, but fluciclovine F 18 imaging showed higher sensitivity in patients with low PSA levels (<1 ng/ml). Comparison of fluciclovine F 18 to standard-dose 11C choline (15-20 mCi) [13] has not been performed. **Existing NCCN criteria do not include fluciclovine PET/CT as an imaging tool but these results suggest that it should be considered as a useful imaging method for detection of BCR.**

Primary staging with 11C choline: Current NCCN recommendations do not include the use of ^{11}C choline PET/CT for initial staging assessment of prostate cancer. This appears to be appropriate. Choline PET/CT used to stage patients with prostate cancer yielded only incremental improvements in staging prior to definitive treatment. [22] Schiaviana et al evaluated ^{11}C choline PET for pre-operative staging of men with intermediate or high-risk prostate cancer and found that the sensitivity for detection of LN metastasis was quite low, with only marginal improvements over clinical nomograms. [23] Giovacchini et al examined the use of ^{11}C choline PET pre-operatively and concluded that it was not suitable for the initial diagnosis or staging of prostate cancer. [5] Because PET/CT can miss micrometastatic LNs, an extended secondary LND should be always performed to avoid an under-treatment. [24,25] Within in the context of initial staging, the incremental improvements in lesion detection provided by Choline PET/CT would not likely impact assignment of the patient to primary definitive therapy over and above that provided using NCCN standard clinical/pathologic predictive algorithms as well as current conventional modalities for imaging in a sufficient number of patients, although this remains to be tested.

Sincerely,

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