Title: ^{18}F-rhPSMA-7 positron emission tomography to detect lymph node metastasis in patients with high-risk primary prostate cancer or suspicious lesions in patients with biochemical recurrence of prostate cancer

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Introduction and overall goal: For positron emission tomography (PET) scanning of prostate cancer, novel ^{18}F-labeled radiohybrid prostate-specific membrane antigen (rhPSMA) ligands offer longer half-life and potentially improved spatial resolution and image quality relative to ^{68}Ga-labeled PSMA ligands.
Specific aims: Compare the diagnostic performance of ^{18}F-rhPSMA-7 PET versus morphological imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) for N-staging men with high-risk primary prostate cancer; determine efficacy in detecting suspicious lesions, i.e., localizing recurrent disease, in men with biochemical recurrence (BCR), and assess association of detection rates with presence/absence of selected pre-analytical factors.
Rationale and background: In men with primary prostate cancer, accurate N-staging is important for treatment planning. In men experiencing BCR, early, accurate disease localization allows timely interventions, and aids in planning salvage or palliative therapies.
Methods and materials: Retrospective analysis of 58 consecutive men with D'Amico high-risk primary prostate cancer and 261 consecutive men with BCR after radical prostatectomy (RP)(Table 1). Men with primary prostate cancer were scanned with ^{18}F-rhPSMA-7 PET/CT (n=39) or PET/MRI (n=19), then had RP with extended pelvic lymph node dissection. Diagnostic performance was determined using histopathology as the gold standard. Men with BCR underwent ^{18}F-rhPSMA-7 PET a median [range] 56 [0–336] months post-RP.

Table 1. Patient characteristics		
Characteristic	***Patients with primary prostate cancer (N=58)***	***Patients with BCR of prostate cancer (N=261)***
Age, y, median [min.–max.]	68 [48–80]	72 [49–88]
PSA, ng/mL, median [min.–max.]	12.4 [1.2–81.6]	0.96 [0.01–400.0]
Gleason score category, % (n)		
≤6	0	5% (12)
7	62% (36)	42% (110)
≥8	38% (22)	33% (87)
Unknown	0	20% (52)

Results: Histologically-confirmed lymph node metastases were found in 31% of men with primary prostate cancer (18/58). ^{18}F-rhPSMA-7 PET performance in diagnosing N1 disease significantly surpassed that of morphologic imaging (p=0.01)(Table 2).

^{18}F-rhPSMA-7 detected suspicious lesions in 81% (211/261) of the BCR cohort, including bone lesions in 21% (54/261). Patient-level detection rates rose from 32% (7/22) at PSA <0.2 ng/mL to 71% (42/59) at PSA 0.2–0.5 ng/mL to 95% (76/80) at PSA ≥2 ng/mL; rates were unrelated to:

- Gleason score category (score ≤7, detection rate 78% [95/122], vs. score ≥8, 83% [72/87], p=0.38)
- Prior external beam radiotherapy (RT) (RT, 79% [83/105], vs. no RT, 82% [128/156], p=0.55)
- Androgen deprivation therapy (ADT) within 6 months pre-scan (ADT, 81% [54/67], vs. no ADT, 81% [157/194], p=0.54).

Table 2. Diagnostic performance to detect lymph node metastasis*, percentage (95% CI)*			
Variable	***^{18}F-rhPSMA-7 PET (N=58)***	***Morphologic imaging (CT, n=39, MRI, n=19)***	
Sensitivity	72.2% (46.5–90.3%)	50.0% (26.0–74.0.%)	
Specificity	92.5% (79.6–98.4%)	72.5% (56.1–85.4%)	
Accuracy	86.2% (74.6–93.9%)	65.5% (51.9–77.5%)	
Area under receiver-operating characteristics curve± std error	0.858±0.061 (0.742–0.936)	0.649±0.080 (0.512–0.769)	**p=0.01**

Discussion and conclusion: ^{18}F-rhPSMA-7 PET accurately identified N1 disease in men with high-risk primary prostate cancer, and detected suspicious lesions in >80% of a cohort with BCR and low median PSA levels. These data support continued clinical development of rhPSMA-7 PET in these prostate cancer settings, including prospective study of diagnostic performance and of impact on disease management and outcome.