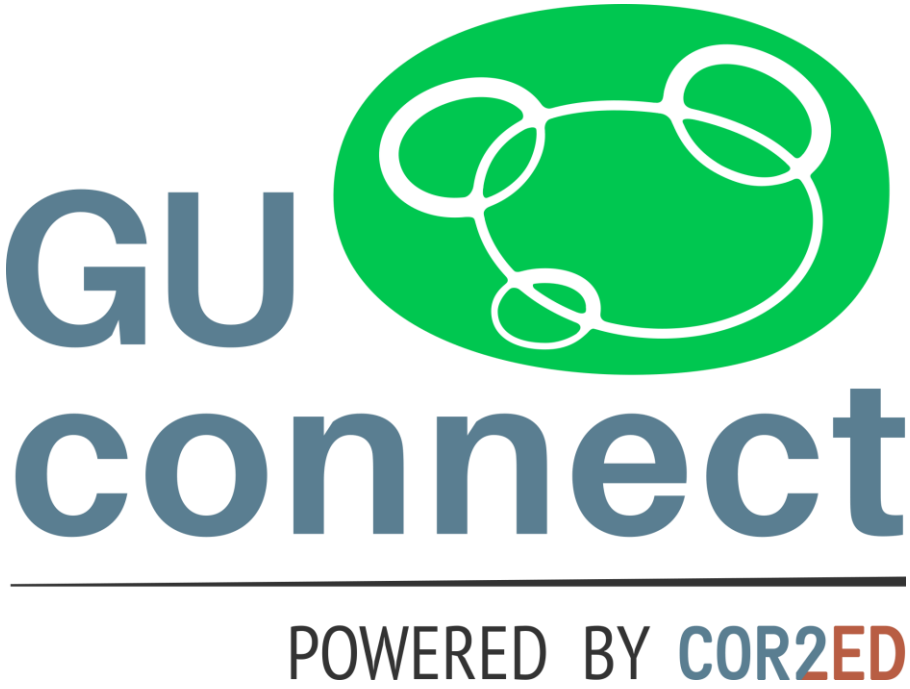
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ADVANCED PET IMAGING IN PROSTATE CANCER

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PET, positron-emission tomography

DISCLAIMER

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RADAR I RECOMMENDATIONS: CONVENTIONAL IMAGING FOR DETECTION OF METASTATIC DISEASE IN PROSTATE CANCER

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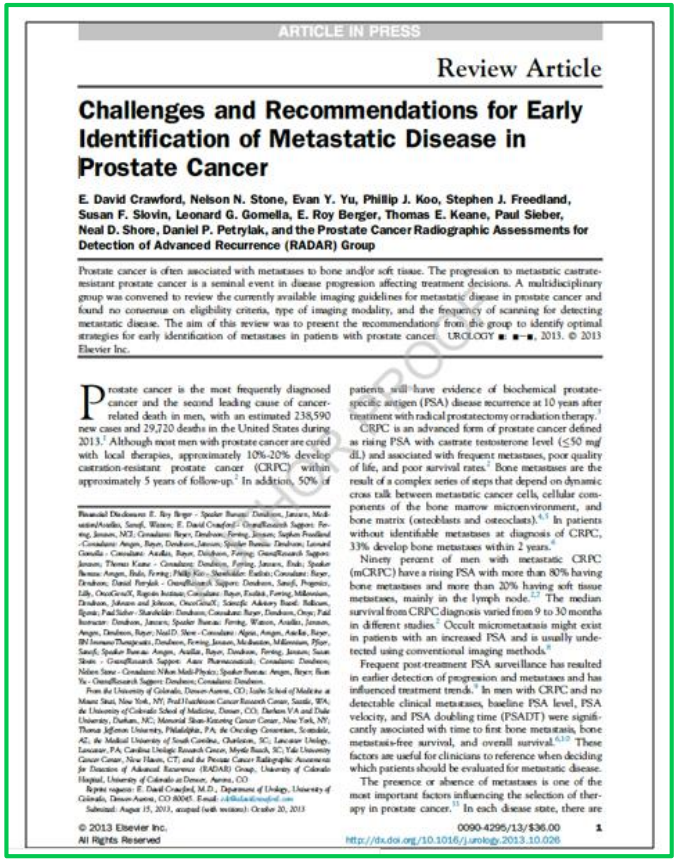

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Review Article

Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer

E. David Crawford, Nelson N. Stone, Evan Y. Yu, Phillip J. Koo, Stephen J. Freedland, Susan F. Slovin, Leonard G. Gomella, E. Roy Berger, Thomas E. Keane, Paul Sieber, Neal D. Shore, Daniel P. Petrylak, and the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group

Prostate cancer is often associated with metastases to bone and/or soft tissue. The progression to metastatic castrate-resistant prostate cancer is a seminal event in disease progression affecting treatment decisions. A multidisciplinary group was convened to review the currently available imaging guidelines for metastatic disease in prostate cancer and found no consensus on eligibility criteria, type of imaging modality, and the frequency of scanning for detecting metastatic disease. The aim of this review was to present the recommendations from the group to identify optimal strategies for early identification of metastases in patients with prostate cancer. UROLOGY ■, ■–■, 2013. © 2013 Elsevier Inc.

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer-related death in men, with an estimated 238,590 new cases and 29,720 deaths in the United States during 2013.[1] Although most men with prostate cancer are cured with local therapies, approximately 10%-20% develop castration-resistant prostate cancer (CRPC) within approximately 5 years of follow-up.[2] In addition, 50% of patients will have evidence of biochemical prostate-specific antigen (PSA) disease recurrence at 10 years after treatment with radical prostatectomy or radiation therapy.[3]

CRPC is an advanced form of prostate cancer defined as rising PSA with castrate testosterone level (≤50 mg/dL) and associated with frequent metastases, poor quality of life, and poor survival rates.[4] Bone metastases are the result of a complex series of steps that depend on dynamic cross talk between metastatic cancer cells, cellular components of the bone marrow microenvironment, and bone matrix (osteoblasts and osteoclasts).[4,5] In patients without identifiable metastases at diagnosis of CRPC, 33% develop bone metastases within 2 years.[6]

Ninety percent of men with metastatic CRPC (mCRPC) have a rising PSA with more than 80% having bone metastases and more than 20% having soft tissue metastases, mainly in the lymph node.[2,7] The median survival from CRPC diagnosis varied from 9 to 30 months in different studies.[2] Occult micrometastasis might exist in patients with an increased PSA and is usually undetected using conventional imaging methods.[8]

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression and metastases and has influenced treatment trends.[9] In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity, and PSA doubling time (PSADT) were significantly associated with time to first bone metastasis, bone metastasis-free survival, and overall survival.[6,10] These factors are useful for clinicians to reference when deciding which patients should be evaluated for metastatic disease.

The presence or absence of metastases is one of the most important factors influencing the selection of therapy in prostate cancer.[11] In each disease state, there are

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RADAR, radiographic Assessments for Detection of Advanced Recurrence

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RADAR III RECOMMENDATIONS: ADVANCED PET IMAGING FOR DETECTION OF METASTATIC DISEASE IN PROSTATE CANCER

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	Newly Diagnosed Patients	Biochemical Recurrent Patients	M0 Castrate-Resistant Patients	M1 Castrate-Resistant Patients*
RADAR I Conventional Scan Recommendations	Conventional scan high- and intermediate-risk patient with at least 2 of the following criteria positive: • PSA level >10 ng/ml • Gleason score ⩾7 • Palpable disease (⩾T2b)	1st conventional scan when PSA level between 5 and 10 ng/ml Imaging frequency if negative for previous conventional scan: 2nd scanning when PSA=20 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	1st conventional scan when PSA level ⩾2 ng/ml Imaging frequency if negative for previous conventional scan: 2nd conventional scan when PSA=5 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	Utilize conventional scans, and consider NGI only if conventional scans are negative and the clinician still suspects disease progression NGI based on at least one of the following: • With every doubling of PSA since the previous image • Every 6–9 months in the absence of PSA rise • Change in symptomatology • Change in performance status
RADAR III NGI Recommendations	If conventional imaging is equivocal or negative with continued high suspicion for metastatic disease, consider NGI	Consider NGI for PSA ⩾0.5 PSA <0.5 can be considered based on specific performance of various NGI techniques	Only consider NGI in the setting of PSADT <6 months, when M1 therapies would be appropriate	

*Limitations include lack of data and difficulty making comparisons to non-NGI techniques.

NGI, next generation imaging; M, metastasis; PET, positron-emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; T, tumour

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PROSTATE CANCER PET DETECTION RATES AS A FUNCTION OF PSA IN PATIENTS WITH BIOCHEMICAL RECURRENCE

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Study	PET Radiotracer	% of Patients with BCR	% of Patients with Positive PET/CT		
			PSA <1.0	PSA 1.0–2.0	PSA >2.0
Choline					
Mitchell	^{11}C-choline	100% (176/176)	44% (15/34)	67% (21/31)	86% (96/111)
Giovacchini	^{11}C-choline	100% (358/358)	19% (27/141)	46% (39/85)	72% (95/132)
Richter	^{11}C-choline	100% (73/73)	7% (1/5)	46% (6/13)	80% (36/45)
Krause	^{11}C-choline	100% (63/63)	36% (8/22)	43% (3/7)	71% (24/34)
Castellucci	^{11}C-choline	100% (190/190)	19% (10/51)	25% (10/39)	54% (54/100)
Nanni	^{11}C-choline	100% (89/89)	14% (4/28)	29% (8/28)	55% (18/33)
Schwenck	^{11}C-choline	100% (101/101)	44% (8/18)	81% (21/26)	89% (51/57)
Cimitan	^{18}F-choline	100% (1000/1000)	31% (66/211)	43% (66/153)	81% (513/636)
Schillaci	^{18}F-choline	100% (49/49)	20% (2/10)	56% (5/9)	83% (25/30)
Morigi	^{18}F-methchol	100% (38/38)	13% (2/16)	36% (5/14)	63% (5/8)
PSMA					
Schwenck	^{68}Ga-PSMA	100% (101/101)	61% (11/18)	76% (20/26)	93% (53/57)
Morigi	^{68}Ga-PSMA	100% (38/38)	50% (8/16)	71% (10/14)	88% (7/8)
Afshar-Oromieh	^{68}Ga-PSMA	100% (319/319)	53% (27/51)	72% (28/39)	92% (204/221)
Eber	^{68}Ga-PSMA	100% (248/248)	67% (35/52)	93% (67/72)	97% (120/124)
Bluemel	^{68}Ga-PSMA	100% (32/32)	29% (4/14)	46% (5/11)	71% (5/7)
Verburg	^{68}Ga-PSMA	100% (155/155)	44% (12/27)	79% (15/19)	89% (97/109)
Fluciclovine					
Nanni	^{18}F-FACBC	100% (89/89)	21% (6/28)	46% (13/28)	55% (18/33)
Odewole	^{18}F-FACBC	100% (53/53)	38% (3/8)	78% (7/9)	86% (31/36)
Bach-Gansmo	^{18}F-FACBC	100% (596/596)	41% (53/128)	58% (N?)	75%–85% (N?)
Schuster	^{18}F-FACBC	100% (93/93)		72% (N?)	

^{11}C, carbon-11; ^{18}F, fluorine-18; ^{68}Ga, gallium-68; BCR, biochemical recurrence; CT, computed tomography; FACBC, fluciclovine; PET, positron-emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen

RADIOTRACERS FOR NGI IMAGING OF PROSTATE CANCER

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Radiotracer	Sensitivity (%)	Specificity (%)	Action/Target	Pros	Cons	Indications
^{18}F-FACBC (fluciclovine)	89–100	67–70	Amino acid transport	Slow urinary excretion improving signal; more sensitive at lower PSA levels than acetate and choline	Moderate specificity and moderate performance at low PSA cut-offs; needs validation in larger studies	Detection of local and distant recurrence
^{11}C-choline	38–98	50–100	Cell membrane synthesis	Minimal bladder excretion	Short half-life; variable sensitivity and specificity for BCR particularly at low PSA cut-offs; only a few centers have cyclotron on-site	Detection of recurrent disease in lymph node and soft tissues
^{68}Ga-PSMA	63–86	95–100	Targets PSMA	High detection rates even at low PSA levels	Requirement of a ^{68}Ga generator, need more validation	High detection rate of local and distant sites of recurrence, also of metastatic disease in high-risk patients undergoing primary definitive therapy
^{18}F-DCFBC	92	88	Targets PSMA	Slightly longer half-life than ^{68}Ga	First generation of 18F-labeled urea; considerable blood pool activity, being investigated in clinical trials, need more validation	For better slection of primary definitive therapy, both hormone-sensitive and CRPC
^{18}F-DCFPyL	71	89	Binds PSMA	More sensitive to detect occult lymph nodes before primary definition therapy; higher tumor to background ratios due to high affinity	Still being investigated in phase 3 clinical study	Detection of occult lymph nodes before primary definitive treatment, early local and distant recurrence
^{11}C-acetate	42–90	64–96	Lipid Synthesis	Ability to image both soft tissue and skeletal mets; minimal bladder excretion	Short half-life few centers have a cyclotron on-site	Identification of metastatic disease

^{11}C, carbon-11; ^{18}F, fluorine-18; ^{18}F-DCFBC, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine; ^{18}F-DCFPyL, 2-(3-[1-carboxy-5-[(6-[^{18}F]fluoropyridine-3-carbonyl)amino]pentyl]-ureido)pentanedioic acid; ^{68}Ga, gallium-68; BCR, biochemical recurrence; CRPC, castration-resistant prostate cancer; FACBC, fluciclovine; NGI, next generation imaging; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen

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MEDICARE COVERAGE FOR SEVERAL NGI TECHNIQUES

Scan Type	Medicare Coverage
^{18}F-fluciclovine PET/CT	Yes
^{11}C-choline PET/CT	Yes (Limited[a])
^{18}F-NaF PET/CT	No
^{18}F-FDG PET/CT	Yes (STS)
^{68}Ga-PSMA PET/CT	No

[a]On-site cyclotron with site specific/ANDA

^{11}C, carbon-11; ^{18}F, fluorine-18; ^{68}Ga, gallium-68; ANDA, abbreviated new drug application; CT, computed tomography; FDG, fluorodeoxyglucose; NaF, sodium fluoride; NGI, next generation imaging; PET, positron-emission tomography; PSMA, prostate-specific membrane antigen; STS, subsequent treatment strategy

Crawford ED, et al. [published online ahead of print Aug 2, 2018]. J Urol. doi: 10.1016/j.juro.2018.05.164

SUMMARY

- Novel NGI techniques provide the ability to identify metastatic prostate cancer at an earlier stage in the disease course
- Advanced PET imaging is more accurate and detects disease at lower PSA levels than conventional imaging
- Current data regarding the use of advanced PET is most mature in patients with biochemically recurrent prostate cancer
- Access to and reimbursement for the various PET radiopharmaceuticals varies by region/country

NGI, next generation imaging; PET, positron-emission tomography; PSA, prostate-specific antigen

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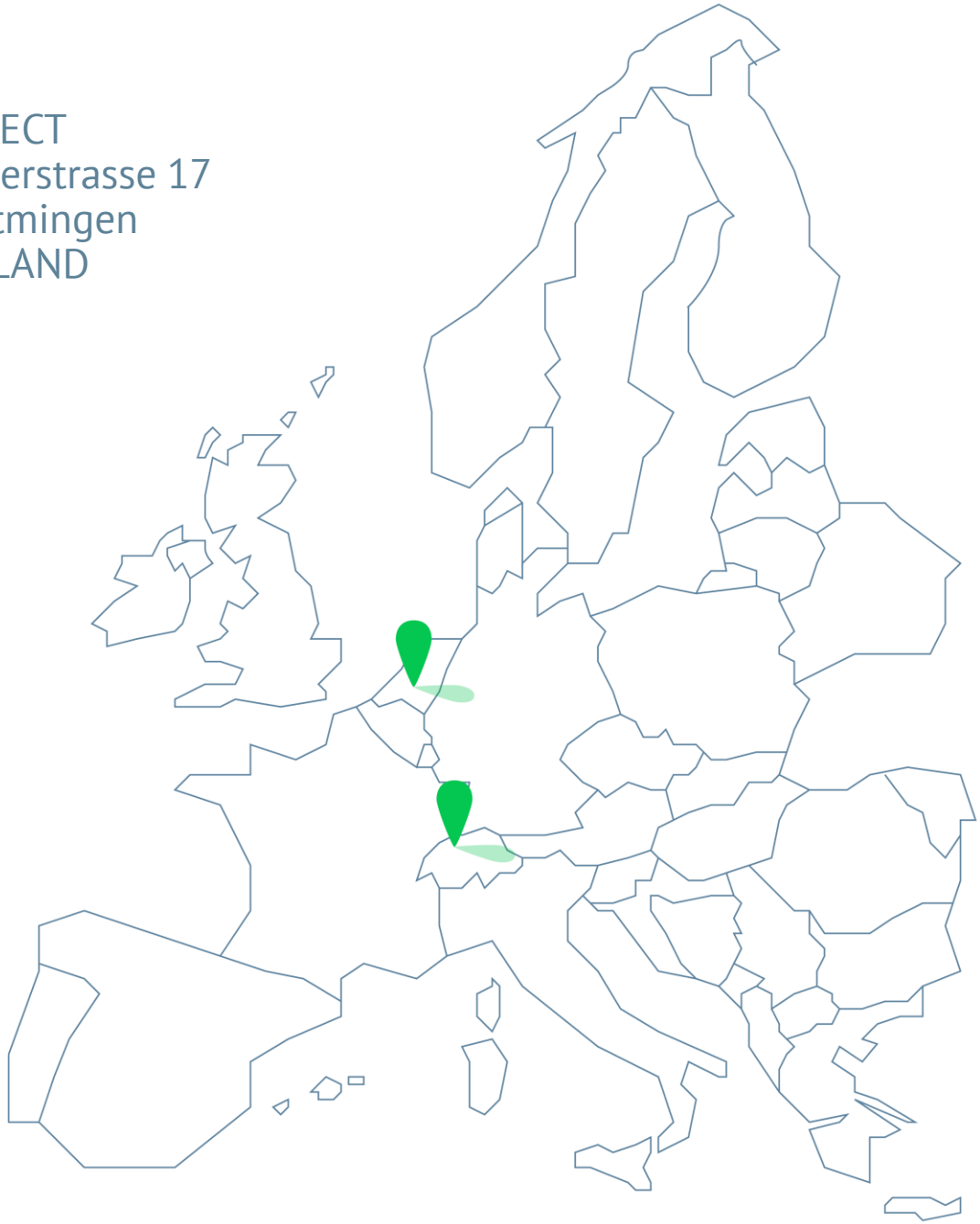

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